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# Overview and Perspectives on Automation Strategies in $^{68}\text{Ga}$ Radiopharmaceutical Preparations

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## Abstract

The renaissance of  $^{68}\text{Ga}$  radiopharmacy has led to great advances in automation technology. The availability of a highly efficient, reliable, long-lived  $^{68}\text{Ge}/^{68}\text{Ga}$  generator system along with a well-established coordination chemistry based on bifunctional chelating agents have been the bases of this development in  $^{68}\text{Ga}$  radiopharmacy. Syntheses of  $^{68}\text{Ga}$  peptides were originally performed by manual or semiautomated systems, but increasing clinical demand, radioprotection, and regulatory issues have driven extensive automation of their production process. Several automated systems, based on different post-processing of the  $^{68}\text{Ga}$  generator eluate, on different engineering, and on fixed tubing or disposable cassette approaches, have been developed and are discussed in this chapter. Since automatic systems for preparation of radiopharmaceuticals should comply with qualification and validation protocols established by regulations current Good Manufacturing Practices (cGMP) and local regulations, some regulatory issues and the more relevant qualification protocols are also discussed.

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## 1 Introduction

Positron emission tomography (PET) is an imaging modality which provides quantitative images of biological processes in vivo at molecular level. It provides clinically important information for tumor diagnosis and staging as well as for neurological applications.

Most of the PET radiopharmaceuticals are labeled with radionuclides ( $^{18}\text{F}$ ,  $^{11}\text{C}$ ,  $^{15}\text{O}$ ,  $^{13}\text{N}$ ) which are produced by medical cyclotrons, thus limiting the availability of these short-lived tracers. Generator-produced radionuclides such as  $^{68}\text{Ga}$  represent an important and interesting alternative to cyclotron-produced radionuclides because of some important advantages.

$^{68}\text{Ga}$  decays 89% by positron emission, with  $E_{\text{max}}$  of 1.92 MeV, and 11% via electron capture. Its physical half-life of 67.71 min is compatible with the pharmacokinetics of most radiopharmaceuticals of low molecular weight.

In the early 1990s, Deutsch (1993) proposed the use of  $^{68}\text{Ga}$  for PET, even if  $^{68}\text{Ga}$  had been used since the early 1960s in nuclear medicine (Shealy et al. 1964; Hayes et al. 1965). Many reasons, however, underlie the enormous development of  $^{68}\text{Ga}$  in the last seven years.

First of all, PET has become a routine clinical imaging modality in the last decade. Second,  $^{68}\text{Ge}/^{68}\text{Ga}$  generators approached a reliable level of robustness, adequate for modern requirements of radiometal labeling chemistry in a clinical environment. Third, more favorable chemistry was developed, substituting open-chain complexing agents by macrocyclic 1,4,7,10,-tetraazacyclododecane-1,4,7,10 tetraacetic acid (DOTA)- and 1,4,7-triazacyclononane- $\text{N},\text{N}',\text{N}''$ -triacetic acid (NOTA)- derived conjugates.

These complexing agents provide outstanding characteristics to the radiopharmaceuticals, by shielding the Ga core effectively under physiological conditions, thus avoiding ligand exchange with the blood serum protein transferrin, which has very high affinity for  $\text{Ga}^{3+}$  ( $K_{\text{ST}} = 20.3$ ) (Harris and Pecoraro 1983).

Optimization of these chelating structures in terms of thermodynamic stability and kinetic inertness as well as in terms of labeling efficiency and options for bifunctionality opens brilliant research and clinical perspectives.

One of the most important drivers for development of  $^{68}\text{Ga}$  radiopharmacy has been the development of small tumor-affine peptides, most notably those targeting somatostatin receptors (Maecke et al. 2005).  $^{68}\text{Ga}$ -DOTA-octreotide derivatives were the breakthrough vector molecules and fundamental to the development of present-day  $^{68}\text{Ga}$  radiopharmacy and  $^{68}\text{Ge}/^{68}\text{Ga}$  generators.

PET with  $^{68}\text{Ga}$ -DOTA-conjugated peptides has brought about dramatic improvements in spatial resolution and is increasingly being used in many specialized centers. In particular, PET clearly offers higher resolution and improved pharmacokinetics as compared with somatostatin (SST) receptor scintigraphy, with promising results for detection of SST receptor-expressing tumors (Kowalski et al. 2003; Buchman et al. 2007), as well as providing prognostic information (Campana et al. 2010).

Syntheses of  $^{68}\text{Ga}$  peptides were originally performed by manual or semiautomated systems. Radioprotection considerations and increasing regulatory demands may hamper wider clinical application of such systems. Extensive automation of the process is therefore needed to fulfill radioprotection as well as increasing regulatory requirements for hospital-based preparation of PET radiopharmaceuticals.

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## 2 Approach to Automation: Considerations on $^{68}\text{Ga}$ Radiolabeling Process

The availability of a highly efficient, reliable, long-lived  $^{68}\text{Ge}/^{68}\text{Ga}$  generator system has been the basis of the development in  $^{68}\text{Ga}$  radiopharmacy. A very comprehensive review on  $^{68}\text{Ge}/^{68}\text{Ga}$  generators and coordination chemistry is available in the literature (Roesch and Riss 2010). Different types of  $^{68}\text{Ge}/^{68}\text{Ga}$  generator are described, with absorption of the parent radionuclide  $^{68}\text{Ge}$  ( $t_{1/2} = 270.8$  days) onto different solid column materials, such as organic pyrogallol-formaldehyde resins and metal oxides (mainly  $\text{SnO}_2$  or  $\text{TiO}_2$ ). Most of them are commercially available, and considerable efforts towards sterile, pharmaceutical-grade, cGMP-compliant generators are underway.

However, there are still some drawbacks to direct use of  $^{68}\text{Ga}$  eluate for radiolabeling of peptides in clinical PET.

The most relevant issues are measurable activities of the long-lived parent radionuclide  $^{68}\text{Ge}$  (i.e.,  $^{68}\text{Ge}$  breakthrough), the high eluate volume, and the high HCl concentration (0.1–1 M). In addition, metallic impurities such as  $\text{Zn}^{2+}$ , generated from the decay of  $^{68}\text{Ga}$ ,  $\text{Ti}^{4+}$  or other potential impurities from the column material, as well as  $\text{Fe}^{3+}$  could be present in the eluate. All these metallic impurities may adversely affect the  $^{68}\text{Ga}$  yield as well as the specific activity of the labeled product.

It is important to underline that the concept of specific activity in this context is more related to the coformation of metal complex with the same ligand than to the presence of stable gallium isotopes.

Several approaches for processing generator-derived  $^{68}\text{Ga}$  eluates have recently been described, each with a markedly different impact on the development of automatic systems for  $^{68}\text{Ga}$  radiolabeling.

Processing of  $^{68}\text{Ga}$  eluates by using strong anion exchange resins was introduced first (Meyer et al. 2004; Velikyan et al. 2004).  $^{68}\text{Ga}$  is retained in 5.5 N HCl by forming an anionic tetrachloro complex  $[\text{}^{68}\text{GaCl}_4]^-$  to remove cationic impurities and concentrate the generator eluate. This strategy separates  $^{68}\text{Ge}$ , but does not allow direct loading of  $^{68}\text{Ga}$  onto the anion exchange resin from 0.1 N HCl eluate.

Another approach to overcome these problems is to fractionate the initial generator eluate (Breeman et al. 2005). The rationale resides in the fact that about two-thirds of the total  $^{68}\text{Ga}$  activity elutes within a  $\sim 1\text{--}2$  mL activity peak. However,  $^{68}\text{Ge}$  and metallic impurities are only minimized, because of the lower eluate volume, rather than being chemically removed.

Zhernosekov et al. (2007) reported an efficient and simplified method for preparation of  $^{68}\text{Ga}$ -labeled radiopharmaceuticals based on the different affinities of  $^{68}\text{Ga}$  and other metals toward cation exchange resin in acetone/HCl solutions. This method combines volume reduction with almost complete removal of metallic contaminants as well as  $^{68}\text{Ge}$ , thus providing concentrated  $^{68}\text{Ga}$  in a useful form for direct radiolabeling.

Gallium possesses a well-established coordination chemistry. DOTA and NOTA bifunctional derivatives are easy to label with  $^{68}\text{Ga}$  in a reproducible manner and with high yield in water or, most frequently, in buffers such as acetate or 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES).

NOTA derivatives have the advantage of room-temperature labeling, while DOTA requires elevated temperatures and longer reaction times. Differences in the chelator system may also influence the pharmacokinetics, the affinity, and the tumor uptake of some new somatostatin antagonists (Fani et al. 2011).

Microwave heating was found to be efficient to accelerate and improve the complexation reaction of  $^{68}\text{Ga}$  with bifunctional chelators, DOTA and NOTA, conjugated to peptides and oligonucleotides and to increase specific radioactivity (Velikyan et al. 2004).

The final part of the radiolabeling process is purification of the  $^{68}\text{Ga}$ -DOTA-conjugated peptides. This is generally accomplished by solid-phase extraction (SPE). This step increases the radiochemical purity by removing free  $^{68}\text{Ga}$  ions and acetate complex as well as colloidal  $^{68}\text{Ga}$ , which is formed especially at higher pH.

The increasing clinical demand for such tracers has motivated automation of the radiolabeling process to facilitate the transition from manual or semiautomated systems to full automation. Drivers for this transition can be summarized as follows:

- **Radioprotection.** A fully automated synthesis process, including post-processing of the eluate, without user intervention leads to much lower hand doses to the operator.
- **Higher reproducibility and robustness.** A prevalidated process increases standardization robustness and synthesis reproducibility.

- **Better cGMP compliance.** Traceability of the complete process, including documentation of all process parameters and functions, is mandatory for fulfilling the requirements for patient application in clinical settings.
- **Better control on sterility.** A fully automated and validated cleaning routine after each process or use of the sterile disposable cassette approach can guarantee better control of sterility and apyrogenicity of the radiopharmaceutical.
- **Dissemination.** Standardized and fully validated technologies are easy to transfer to new institutions, thus increasing the number of patients studied.

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### 3 Modules for $^{68}\text{Ga}$ Radiopharmaceuticals

A renaissance in  $^{68}\text{Ga}$  radiopharmacy has resulted from the huge demand for  $^{68}\text{Ga}$ -DOTA somatostatin analogs. Manual systems have been described (Meyer et al. 2004; Zhernosekov et al. 2007) and have definitely boosted the diffusion of such radiopharmaceuticals in clinical centers. Many of them are still in use, especially in countries with lower regulatory impact.

An example (Zhernosekov et al. 2007) is shown in Fig. 1. This manual system has been used for years in our laboratory, with some modification to improve operator radioprotection (Di Pierro et al. 2008), with excellent results in terms of radiochemical yield and robustness.

A manual, easy-to-use, self-shielded system including an organic-based  $^{68}\text{Ge}/^{68}\text{Ga}$  generator is available on the market from ITG (ITG Isotope Technologies Garching GmbH, Garching, Germany). The system is equipped with a sterile single-use kit, no post-processing of  $^{68}\text{Ga}$  eluate is needed, and it has a built-in filter integrity test device (Fig. 2).

Supply of automatic systems has considerably increased in the last few years. Several automated systems are commercially available, combining generator elution, post-processing,  $^{68}\text{Ga}$  labeling reactions, and purification of  $^{68}\text{Ga}$ -labeled peptide with pharmaceutical characteristics.

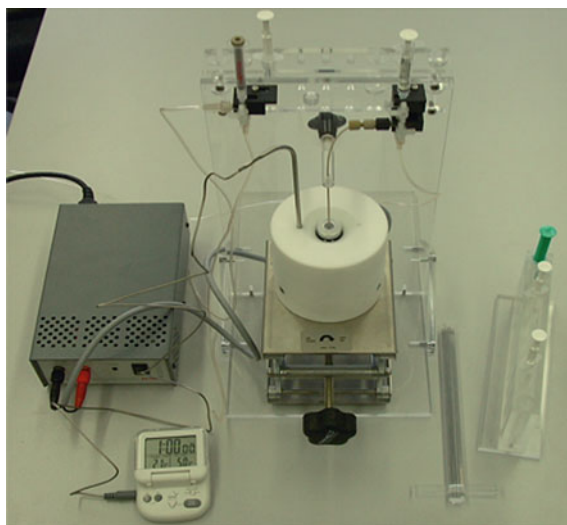
#### 3.1 Classification and Characteristics of Automated Systems

A tentative classification of the available automated systems could be based on:

- **Post-processing approach:** anionic, fractionation, cationic
- **System engineering:** fully equipped compact system, modular system
- **Fluid path:** fixed tubing system, disposable sterile cassette.

All the post-processing approaches mentioned in Sect. 2 have been adopted in developing and engineering automatic systems. The choice of post-processing approach is based on scientific considerations which fall outside the scope of this chapter.

There are, however, commercial reasons often based on collaborations and spin-offs between academia and companies which have actually led to preferential implementation of one of the post-processing approaches.



**Fig. 1** Manual system for  $^{68}\text{Ga}$  radiolabeling (Zhernosekov et al. 2007)



**Fig. 2** Manual self-shielded system

Moreover, fractionation was widely used, at least in the early years, because it is intrinsically easy to use and cost effective, and it shortens synthesis time.

Some companies still offer a choice of systems adopting different post-processing approaches.

Data from the literature evidence differences in the radiochemical yield of the whole  $^{68}\text{Ga}$ -DOTA-peptide labeling process among different post-processing approaches.

The 60% decay corrected (d.c.) radiochemical yield was reported using a fully automated system with a fractionation protocol (Decristoforo et al. 2007) and 30  $\mu\text{g}$  DOTA-D-Phe<sup>1</sup>-Tyr<sup>3</sup>-octreotide (DOTATOC) in acetate buffer. Different amount of peptide used, strong influence of the type of buffer (Bauwens et al. 2010), and incubation parameters make comparison among automatic systems using different post-processing approaches extremely difficult.

A radiochemical yield of 95% was reported by cation exchange-based post-processing because of the high purity of the  $^{68}\text{Ga}$  eluted from AG50 X8 resin (Zhernosekov et al. 2007). Since this method requires manual interference in the labeling procedure, this protocol was completely automated by using a miniaturized multi-use column with a cation exchange resin (AG 50 W-X4) similar to that described by Zhernosekov and, successively, using a commercial, disposable cation exchange cartridge (Ocak et al. 2010).

Replacement of a multiple-use resin by a single-use cartridge has led to better cGMP compliance and simplification of the process, as cleaning and reconditioning of the column for multiple uses is avoided. Better microbiological safety with respect to sterility and pyrogens should also be considered. Inactive metal impurities, except Zn, are less reduced than with a permanent cation exchanger but without problems for synthesis.

Comparative decay/non-decay corrected yields of  $^{68}\text{Ga}$ -DOTATOC, with using different post-processing approach synthesis methods were reported by the same author (Ocak et al. 2010). These values ranged from 67% d.c. for the fractionation method to 77–84% d.c. using different cationic post-processing and different buffer. The longer overall synthesis time with fully automated prepurification as compared with a fractionated system (Decristoforo et al. 2007) was compensated by the advantage of using all available activity of  $^{68}\text{Ga}$  by concentration on the cation exchanger, thus balancing the radiochemical yield.

Commercial automatic systems based on fractionation, anionic, and cationic post-processing are shown in Figs. 3, 4, 5.

Fully equipped, ready-to-use, compact systems are available from companies such as Iason, Veenstra, Comecer, and Raytest (Figs. 3, 4, 5). These systems represent turnkey solutions, suitable for cGMP pharmaceutical environments, but, at least in principle, with limited flexibility.

Increasing flexibility can be achieved by “modular” systems or systems based on expandable platforms (Eckert and Ziegler, Scintomics). Automation of a broad spectrum of procedures for radiolabeling, isotope purification, routine tracer production, and other radiopharmaceutical processes is possible with such systems.



**Fig. 3** Fractionation-based automatic systems

System integrated components, such as handling parts, sensors, pumps, valves, regulators, heaters, high-performance liquid chromatography (HPLC) equipment, etc., allow for a high level of flexibility in the construction of customized modules.

It is important to underline that the need for flexibility and regulatory requirements are often conflicting, since regulations pose some hurdles to the production of radiopharmaceuticals for clinical use. The different chemistry approaches used, the many types of PET tracer required for research and clinical studies, and the limited resources in production facilities call for flexible systems. On the other hand, regulations for small-scale hospital radiopharmaceutical preparation are based on risk analysis-based validation plans, extensive qualification/validation protocols, and full documentation and traceability, thus reducing the possibility of implementing flexible processes.

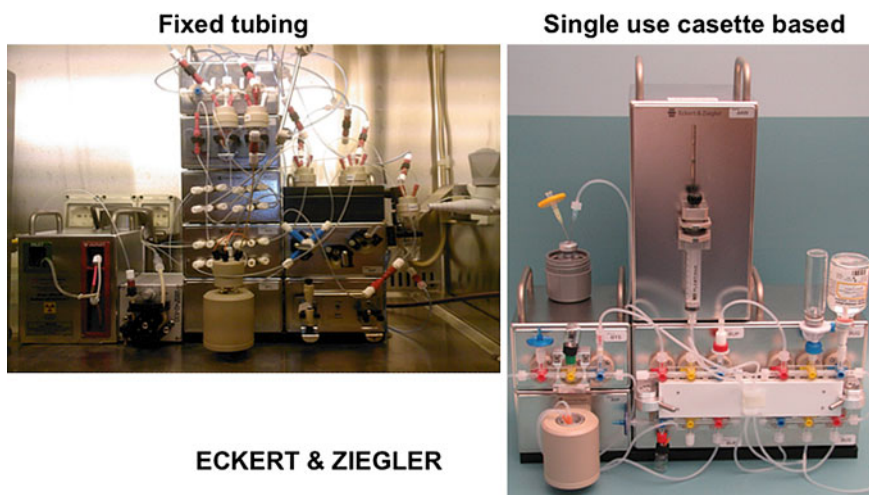
Since regulations (cGMP or local, national pharmacopoeia regulations) are becoming mandatory for radiopharmaceutical preparations, a current trend in engineering of automatic systems is to move from fixed tubing to cassette systems.

Single-use sterile cassettes avoid time-consuming cleaning validation procedures as well as intense cleaning and sanitation routines. By changing the cassette, multiple syntheses can be easily performed even for various tracers and with different radionuclides.





**Fig. 4** Anionic exchange-based automatic systems



**Fig. 5** Cationic exchange-based automatic systems

This is particularly attractive for management of neuroendocrine tumors, since radiolabeling of DOTA-somatostatin analogs with  $^{68}\text{Ga}$  for tumor staging and labeling of the same compound with a radionuclide such as  $^{177}\text{Lu}$  or  $^{90}\text{Y}$  for therapy become feasible. By simply changing the cassette, it is possible to avoid the delicate cleaning validation process to guarantee complete removal of  $^{90}\text{Y}$  or  $^{177}\text{Lu}$ .

$^{68}\text{Ga}/^{177}\text{Lu}/^{90}\text{Y}/^{111}\text{In}$ -DOTA peptides have been synthesized with high purity, high radiochemical yield (>80% d.c. for  $^{68}\text{Ga}$ -DOTA peptides and 90% d.c. for  $^{177}\text{Lu}/^{90}\text{Y}/^{111}\text{In}$ -DOTA peptides), and acceptable synthesis time (Petrik et al. 2011). Sterile, single-use, disposable cassettes assembled under cGMP-compliant clean-room conditions guarantee better control of sterility and apyrogenicity of the radiopharmaceutical preparation, even if complete control of these parameters relies only on a fully validated process.

Eckert and Ziegler engineered a self-shielded cassette-based solution for routine production, becoming an integral part of the synthesis system. Only single-use cassettes are located inside the shielded area, allowing weight reduction to one-tenth of that of a conventional hot cell. The system can be placed in virtually any laboratory, without any reinforcement of the floor, thus facilitating dissemination of the methodology.

Many companies are moving toward single-use disposable kits or a cassette approach. GE Healthcare has drawn up the Gallea project for development of a cassette system for  $^{68}\text{Ga}$  radiopharmaceutical preparations based on the Fastlab platform.

Cassette systems have also some drawbacks if compared with fixed tubing systems: first, the high cassette cost and the reliance on the cassette manufacturer; second, reduced flexibility. Optimized and fully validated cassettes for each radiopharmaceutical are needed, and the development of new cassette systems strongly relies only on marketing considerations. Third, the fluid path of the cassette is often engineered by commercially available disposable medical devices (tubes, stopcock valves, kits for intravenous injection). Leaks and bubbles are then possible, and special care should be taken to assess all components and connections to avoid malfunctioning resulting in low radiochemical yield.

A comprehensive comparison between tubing and cassette systems is presented in Table 1.

Since the majority of these systems have been developed and/or upgraded in the second part of the 2000s, the various software packages are generally characterized by intuitive user interfaces that comply with cGMP and good laboratory practices (GLP) requirements. Some software complies also with GAMP5 guidelines, or with more extensive requirements such as FDA 21CFR part 11.

The software controls all aspects of the synthesis, many of them being easy to program by simple drag-and-drop operations of graphical symbols, and provides complete traceability of the process through audit trails and extensive documentation of the radiopharmaceutical preparation.

**Table 1** Comparison between cassette and tubing systems

	Cassette	Tubing
Synthesis pathways	Fractionated, precleaning with disposable cation exchange cartridge	Fractionated, precleaning with one-way, permanent cation exchange cartridge
Handling	Very easy	Easy
Cleaning	None	Fully automatic cleaning procedure, validation of cleaning procedure needed
Sterility	All parts in contact with media are sterile	System needs cleaning and disinfection to maintain sterility
Costs	Costs for cassette, reliance on manufacturer	Tubing replacement (min. yearly), personnel cost because of time for cleaning and handling
Flexibility	Only limited	Full
Cross-contamination	None, various tracers and nuclides such as $^{90}\text{Y}$ , $^{111}\text{In}$ , and $^{177}\text{Lu}$ on the same system with different cassettes	Cannot be excluded, use of various nuclides not tolerated by authorities
GMP	Fully compliant	

### 3.2 Automation and Regulatory Aspects

As with any other medicinal products, it is mandatory to ensure that quality and safety of  $^{68}\text{Ga}$  radiopharmaceuticals are adequate for their intended use.

Substantial differences between US and EU regulation for preparation of radiopharmaceuticals are still evident, in spite of efforts towards worldwide harmonized regulation in the field of medicinal products for human use. Furthermore, different interpretation of European regulations among EU countries as well as local, specific GMP-like regulations generates differences in the requirements demanded by national regulatory authorities.

In recent years, the trend has been for implementation of cGMP regulation for PET radiopharmaceutical preparations, even if the cost and difficulty of cGMP enforcement in academic and hospital environments could hamper the development of clinical and research applications of these medicinal products. Besides cGMP, there are several guidelines such as [GAMP<sup>®</sup> 5](#) which provide guidance to achieve compliant GxP computerized systems using a flexible risk-based approach.

To achieve the quality objective, however, a comprehensively designed and correctly implemented quality assurance system is of utmost importance. Accordingly, all equipment, instruments, and technologies which may affect the quality of the product should undergo proper qualification protocols. Written and approved protocols specifying critical steps, acceptance criteria, and how qualification will be conducted should be established.

Automatic systems for synthesis of radiopharmaceuticals which will be installed in radiopharmacies should therefore comply with qualification and validation protocols which are established by regulations (cGMP, GMP-like, or local regulations).

Annex 15 of the EU Guide to Good Manufacturing Practice (cGMP) provides important definitions of the qualification protocols that should be implemented. They are derived from the validation master plan, which includes all the strategies and protocols for the entire validation plan and can be listed as follows:

**Design qualification (DQ):** documented verification that the proposed design of the facilities, systems, and equipment is suitable for the intended purpose.

**Installation qualification (IQ):** documented verification that the system is installed according to the specifications and complies with approved design and manufacturer's recommendations.

**Operational qualification (OQ):** documented verification that the system performs as intended throughout the established operating ranges.

**Performance qualification (PQ):** documented verification that the system performs according to the process specifications, assuring reproducibility, robustness, and product quality.

Successful OQ should allow the finalization of calibration, operating, and cleaning procedures, operator training, and preventative maintenance requirements. It should permit formal "release" of the system.

The qualification protocols described above should be derived from well-established specification protocols implemented by the manufacturer, starting from the user requirement, through functional and design specifications. The protocols and the documents derived from them are the prerequisite for complete and successful IQ, OQ, and PQ.

Continuous interaction between users and manufacturers could be extremely helpful to better define the requirements and, consequently, specifications. Manufacturers should definitely provide documental and technical support for qualification plans to be implemented at sites.

A risk-based approach to a compliant system is shown in Fig. 6.

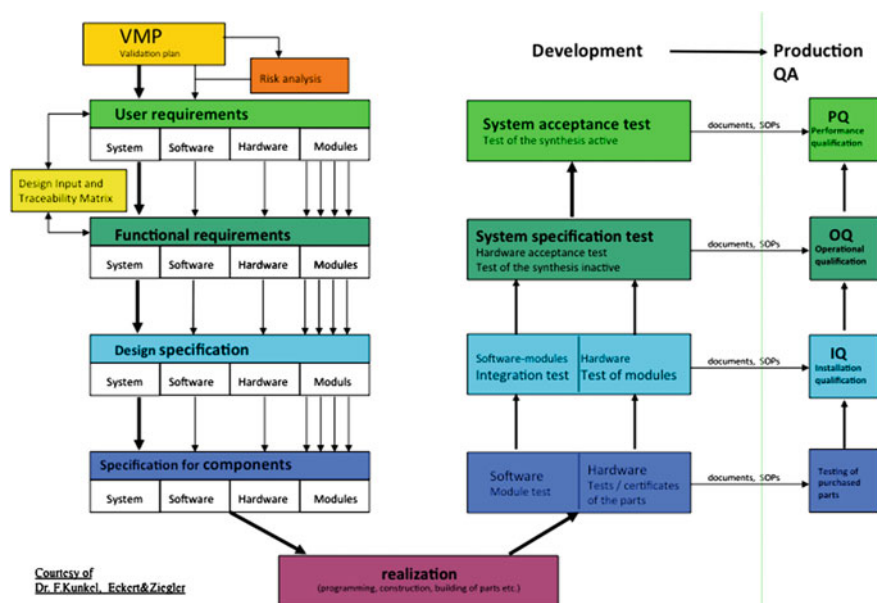
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## 4 Perspectives

The renaissance of  $^{68}\text{Ga}$  radiopharmacy has led to great advances in automation technology in the last five years. Different automation strategies are now available, which can also be tailored to different needs. Also, sites with no experience can receive a turnkey system and adequate training.

Automation technologies have implemented different prepurification approaches leading to increased chemical and radionuclidic purity (minimizing  $^{68}\text{Ge}$  breakthrough) as well as high specific radioactivity of the final preparation.

The fundamental advantages of using automated systems reside in their improved reproducibility, higher throughput, easier handling, improved response to clinical demand, and cGMP-compliant production.



**Fig. 6** A risk-based approach to a compliant system

Available systems are well established, and many centers have already performed hundreds of syntheses in a reproducible and robust manner.

Preloaded cassette-based modules, manufactured under cGMP standards, could represent a further improvement in terms of safety and compliance with regulations, but huge investments are needed, and the clinical demand is not as great as for  $^{18}\text{F}$ -fluorodeoxyglucose (FDG).

Further development toward miniaturization is possible. Microfluidic approaches could open interesting perspectives, at least for  $^{68}\text{Ga}$  labeling. Major concerns are, however, radiolysis due to the high concentration of radionuclide and surface effects.

Development of  $^{68}\text{Ga}$  radiopharmaceuticals as freeze-dried kits, similar to  $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ -generator-based  $^{99\text{m}}\text{Tc}$  radiopharmaceuticals, may indeed be an alternative to cyclotron-based radiopharmaceuticals. Use of bifunctional chelating agents based on NOTA scaffold might allow for simple kit-based radiopharmaceuticals (Velikyan et al. 2008).

Detailed discussion on kit development issues lies beyond the scope of this chapter. Anyway, moving towards kit-based preparations will require simplified post-processing technology. Remaining differences between generators and eluates should be overcome by new generator concepts which avoid metal-base matrixes and utilize HCl at less than 0.1 M to achieve optimum conditions for high yield and quick, room-temperature labeling. More effort is needed on generators themselves than on automation technology.

The availability of a commercial  $^{68}\text{Ge}/^{68}\text{Ga}$  generator with potential for routine application and a favorable chemistry using DOTA- and NOTA-derived bifunctional chelators has opened a brilliant future for almost unlimited application of  $^{68}\text{Ga}$  in all fields of noninvasive molecular imaging with radioactive probes.

Automation technology has grown together with the huge clinical demand for  $^{68}\text{Ga}$ -DOTA somatostatin receptor agonists, which have become the golden standard for PET/CT imaging of neuroendocrine tumors, to become one of the most important tools for bridging the development and application of new  $^{68}\text{Ga}$ -radiolabeled molecules into clinical practice.

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Theranostics, Gallium-68, and Other Radionuclides  
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