Chapter 14

Automation of PET Radiopharmaceutical Quality Control

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14.1 OVERVIEW

The US Pharmacopeia (USP) is a compendium of drug quality standards. According to the definition offered in USP General Chapter <823>, "Positron Emission Tomography Drugs for Compounding, Investigational, and Research Uses" [1], quality assurance (**QA**) and quality control (**QC**) are important elements in the process of making positron emission tomography (**PET**) drugs. QA is a broad concept that covers all matters that influence the identity, strength, quality, and purity of a PET drug. QC is a subset of QA that deals with testing materials and PET drugs to determine if they meet acceptance criteria. QC functions include the following: (i) evaluate each lot of incoming material to ensure that it meets its established specifications before use in the preparation or testing of PET drugs; (ii) evaluate each batch of a PET drug to ensure the batch meets its established specifications before authorizing the final release or rejection of the batch. It is important to clarify in this context that the scope of QC automation discussed in this chapter relates mostly to pre-release testing required for each batch of a PET drug. It will not cover testing of incoming materials, periodic testing of a PET drug that is not required for release of each batch, or post-release sterility testing.

QC procedures differ between PET tracers and between countries. Therefore, in order to offer a context for meaningful comparison, most of the solutions presented in this chapter will be discussed as they relate to the US environment and clearly distinguishing 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG). Other tracers will be discussed as a group only in

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aspects of QC that cannot be demonstrated with FDG. It is expected that a discussion in such a narrow context provides the most concise story, which the reader should be able to easily extrapolate to their tracer of interest and local regulatory environment.

While the development of automated systems for radiosynthesis dates back to the 1970s [2, 3] and was immediately fueled by the early success of PET [4, 5], automation of QC has not received much attention until recent years despite its complexity being comparable to or exceeding that of manual radiosynthesis.

In the early days of PET, QC procedures differed among tracer manufacturers and relied mostly on scientific judgment. Mechanisms used to confirm that such judgment was sound included (i) state-regulated practice of medicine and compounding pharmacies [6], putting the liability on the pharmacist; as well as review of procedures via (ii) Radioactive Drug Research Committee (**RDRC**) [7] or (iii) investigational new drug (**IND**) [8] applications. Such mechanisms yielded a variety of QC procedures [9–11], acceptance criteria, and no uniform standards. In such an environment, with diverse QC approaches, there was little structure for the development of QC automation. Furthermore, when most PET was supported only by FDG [12–14], once QC procedures matured, there was no pressure to modify them. However, the evolution of PET in the past decade has catalyzed a wave of QC automation developments across the world, indicating both the need for and feasibility of such innovation.

This chapter will first identify the most important milestones in the PET industry that have led to QC standardization and set the stage for automated solutions. It will then introduce the progression of approaches to automation undertaken by different organizations. Discussion of these approaches, drivers, barriers, and opportunities should put the reader in a position to compare the automated QC solutions available today or arising in the future. It will offer a structure for assessing the value of QC automation for the reader's goals. This discussion will be followed by a regulatory framework and mechanisms available for practical transition from traditional to automated QC. The outlook section at the end will offer the author's perspective on continued innovation and welcome readers to formulate their own.

14.2 PET MILESTONES RELEVANT TO QC AUTOMATION

14.2.1 Milestone 1 – Standardization of PET Tracer QC Requirements

The development of automated solutions can only be justified if they can be applied across a broad set of users. A uniform solution would not be possible in a situation where each manufacturer defined its own QC processes. Thus, standardization of QC procedures was an important prerequisite for QC automation.

The first PET tracer to set a precedent for QC standards was sodium fluoride, [F-18]NaF [15]. Its new drug application (**NDA**) was approved by the US Food and Drug Administration (**FDA**) in 1972. The corresponding USP monograph was published in

1979 [16]. This first published PET tracer monograph required the following QC tests: pyrogens (endotoxins), radionuclidic identification, pH, radiochemical purity, assay, and sterility (post-release). This monograph was omitted in 1980 as [F-18]NaF production stopped. Then, until the publication of the 1990 Fludeoxyglucose F 18 Injection (FDG) USP monograph [17], there was no centralized guidance on QC for any PET tracer. Thus, the systematic evolution of standardized QC requirements that we know today practically starts with the latter document.

In 1998, the USP published the first version of General Chapter <823> – "Radiopharmaceuticals for Positron Emission Tomography (PET) – Compounding, Investigational, and Research Uses" – which provided general QA standards for PET drugs [18]. Specifically, it required pH, appearance, radiochemical purity and identity, radionuclidic identity, filter integrity, endotoxin, and sterility (post-release) tests to be performed on each batch for all PET products. Specific activity was required for products with mass-dependent toxicity concerns. Concentrations of residual solvents [19] and other toxic chemical constituents of the final product had to be compliant with the acceptance criteria for each of these compounds. Contaminants needed to be defined based on synthesis and purification processes used to prepare the drug. Products with half-lives under 20 minutes had a special definition of a *batch* where all batches of product made on a given day were to be considered sub-batches of one batch, for which full QC would be performed only once per day.

The requirements defined in the USP are not static. They change based on new developments and risks. For example, when the nucleophilic FDG production method [20] introduced Kryptofix 222 (4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane) as a phase transfer reagent, a test for Kryptofix 222 became necessary, considering the molecule's toxicity profile [21]. Similar logic applies to new tracers. If their syntheses or formulations involve toxic substances not relevant to FDG, the QC requirements need to be amended accordingly. Current FDG QC requirements based on the 2018 updates to General Chapter <823> [1] and USP Monograph on Fludeoxyglucose F 18 Injection [22] are summarized in Table 14.1. The tests are presented in three groups corresponding to the reasons behind them. The purpose of the tests in the "Identity and Strength" group is to demonstrate the presence of the desired product in the amount needed. Tests in the "Purity" group are performed to confirm that all contaminants that may be reasonably expected in the given tracer formulation are less than the predetermined thresholds. Finally, the "Safety" group of tests confirms that the product is acceptable for parenteral administration to patients.

Sterility is the riskiest factor, since injecting bacterially contaminated drugs may cause serious disease, especially in ill patients. However, the tracers must be injected into patients before the culture test result is known, since the half-life of PET tracers is much shorter than the 14 days needed for microbial colony growth in the sterility test [23]. Therefore, there is always a risk of non-sterile injection. As a result, substantial effort is placed on sterility assurance during drug product preparation. The only pre-release indication of sterility is the final product being filtered through a membrane filter followed by confirming the integrity of that filter.

Table 14.1 The most common QC procedures for PET tracers produced in the US.

	<823> pre-release tests	Method	Example tracer	Specification (for example tracer)	Detection technology
Identity and strength	Radionuclidic identity	Half-life	FDG	105–115 min	Dose calibrator
	Radiochemical identity	TLC	FDG	R_f = 90–110% of USP standard R_f	TLC scanner
		HPLC	FMISO	Retention time = standard ± 10 s	HPLC radiation detector
	Radioactivity concentration	Radioactivity/volume correlation	FDG	4–300 mCi ml^{-1}	Dose calibrator
Purity	Visual inspection	Appearance	FDG	Clear, colorless, free from visible particulates	Human eye
	Radiochemical purity	TLC	FDG	>90%	TLC scanner
		HPLC	FMISO	>95%	HPLC UV and radiation detectors
	Chemical purity and residual compounds used in synthesis	HPLC	FMISO	<35 μg per dose of UV-absorbing impurities	HPLC UV detector
		Spot test	FDG	<50 μg ml^{-1} (Kryptofix 222)	Human eye
	Specific activity	HPLC	FMISO	>125 Ci mmol^{-1}	HPLC UV and radiation detectors
	Residual solvents used in synthesis or purification	GC	FDG	<0.5% (ethanol)	Flame ionization detector
			FDG	<0.041% (acetonitrile)	
Safety	pH	pH strip	FDG	4.5–7.5	Human eye
	Bacterial endotoxin	Endosafe PTS	FDG	<175 EU per dose	PTS reader
	Filter integrity test	Bubble point	FDG	>344.8 kPa	Human eye
	<823> post-release test				
	Sterility (post-release)	14-day culture test	FDG	0 colony forming units	Human eye
	<823> periodic tests				
Purity	Radionuclidic purity	Gamma ray spectrometry	FDG	F-18 > 99.5% of radionuclides	Multi-channel analyzer (MCA)
	Low-level non-toxic impurities	HPLC	FDG	<1 mg per dose (ClDG)	HPLC pulsed amperometric detector
	Class 3 residual solvents	GC	FMISO	<0.5% (acetone)	Flame ionization detector

Pharmacopeial requirements differ among the USP, European Pharmacopeia (**EP**) [24], British Pharmacopeia (**BP**) [25], and International Pharmacopeia overseen by the World Health Organization (**WHO**) [26]. There are detailed reviews summarizing relevant QC procedures [27] and offering a comparison of various pharmacopeial monographs [28]. There is also draft guidance published by the FDA [29] that includes QC procedures for [N-13]Ammonia, [F-18]NaF and FDG.

These developments have led to large numbers of PET drug manufacturers relying on similar criteria and processes in release testing. This allows an automated solution developed for one user to be applicable across most of the industry.

14.2.2 Milestone 2 – The cGMP Compliance Challenge

Traditional QC testing involves multiple instruments, multiple manual test stations, multiple aliquots of the sample, and many data entries at every step of the way [30, 31]. Moreover, the operator needs to manage and track multiple expiry dates (e.g. for standards or equipment calibration). Until current Good Manufacturing Practice (**cGMP**) regulations took effect, such manual procedures were manageable, as they mostly focused on yielding the information needed for the product release [32].

That paradigm changed with the 21 Code of Federal Regulations (CFR) Part 212 regulations, cGMP for PET Drugs [33], which took effect in 2012. They specify the requirements for a high level of control while executing QC procedures (especially in Subpart G, "Laboratory Controls"). However, these regulations do not specify the details of the test procedures, which still follow the pharmacopeia. Thus, the definition of current QC procedures needs to address both USP and FDA requirements in an inter-related approach [34].

Manual methods have historically been subjective, variable, and dependent on the operator's experience, judgment, and consistency, with each operator having their own precision and accuracy. Thus, satisfying the increased level of control while running manual methods presented a challenge [35] and called for an increase in resources and operating costs. Analysis of statistics on 21 CRF Part 212 violations published by the FDA [36] leads to the conclusion that the vast majority of them result from poor control of manual processes. This is why cGMP regulation is such an important milestone leading to QC automation development.

Manual procedures are poorly traceable, making them either a high risk from a compliance perspective or costly if mechanisms are put in place to assure traceability of a manual process. Automation, by virtue of taking the person out of the process, eliminates the gaps in cGMP compliance. Every place where pen touches paper provides a data-integrity risk because it compromises compliance. Automation coupled with the data-integrity features of the corresponding software should eliminate all such opportunities. Furthermore, by eliminating the subjectivity and variability of operators, as well as the requirement for operator experience and judgment, automation will further reduce violations.

14.2.3 Milestone 3 – Emergence of New PET Tracers

Compounding the challenge to cGMP compliance has been the growth in PET procedures in the twenty-first century. Now millions of PET scans are performed annually with tracers that are released relying on error-prone, poorly traceable, manual QC processes. With multiple tracer production runs made daily, and two to five different tracers made in some facilities, the chance of error is high. Since QC is the least automated part of production, compliance assurance in this area has quickly become a bottleneck.

FDA approval of [F-18]Florbetapir (Amyvid) [37] as the first proprietary PET tracer in 2012 shows that new tracer development by commercial entities is relatively recent in the PET field. It also marks a critical milestone for the development of QC automation. A spur of new tracers has entered clinical development and received approval since 2012 [38]. PET tracer QC has grown in complexity and diversity as it no longer revolves around one product. It requires more equipment, larger facilities, and, most critically, more skilled staff – who are not readily available.

While manual QC procedures developed in the twentieth century were sustainable when FDG was the only major product, the paradigm shift to multi-tracer portfolios has multiplied the complexity of QC and now limits the number of new tracers a facility can support.

14.3 LABORATORY SETUP FOR QC IN PET TRACER PRODUCTION

The three milestones of standardization of PET QC procedures, cGMP regulations, and new tracer introductions have defined a typical laboratory that can be used to execute the modern QC process. Details of the most common laboratory setup required to execute the most current QC procedures are summarized in Table 14.1. The list of tests is based on the 2020 revision of USP General Chapter <823>. Tracers chosen as examples are FDG and 1-(2-hydroxy-3-[^{18}F]fluoropropyl)-2-nitroimidazole (FMISO). QC tests for FDG [27] are based on the latest USP monograph, while FMISO QC [39] examples were used to illustrate common tests that are required for non-FDG tracers. The Method and Detection Technology columns illustrate a diverse range of instruments and skills that are required to execute QC for PET tracers.

14.4 DRIVERS OF AUTOMATED QC

Now that the traditional QC procedures are defined, it is important to understand the drivers behind the need for automation as well as the barriers that challenge it. There is a critical difference between QC of short-lived radiopharmaceuticals and all other injectable drugs. The latter are made in large batches with low frequency and ample time for QC. The ratio of product doses per QC analysis is orders of magnitude higher than with PET drugs. In traditional drugs, QC is a minor contributor to the production cost of each

patient dose. In PET, it is a major contributor. Thus, improvements in QC efficiency and cost have an immediate and direct impact on product cost. It is especially important with the increasing number of PET procedures and PET drug diversity.

As will be seen in Section 14.6, independent QC automation efforts started at multiple organizations at about the same time, suggesting that the milestones defined earlier have created a stimulating environment for such innovation. While cGMP compliance and new tracer emergence stress the need for QC automation, process standardization via USP makes it possible to satisfy most users with a single solution. Furthermore, the need for QC automation has been driven incrementally by the following factors:

(1) *Safety/radiation exposure*: As with radiosynthesis automation, taking the person out of the process is an important factor for personnel safety in consideration of the "As Low as Reasonably Achievable" (ALARA) principle [40]. Radiosynthesis was performed behind shielding even before automation. Meanwhile, the effect of shielding is limited in QC, given the number of manual operations that cannot be performed remotely [41]. Thus, only complete automation of QC can eliminate the radiation exposure associated with these procedures. Although the total amount of starting radioactivity in QC is much lower than that in synthesis, absence of complete shielding in QC leads to higher exposure. Furthermore, the total personnel exposure continues to increase as the number of tracers produced per facility grows further.

(2) *Human error*: Any manual process is prone to human error. Given the number of FDG batches made every day, there is a high chance that at least one batch is affected by human error in QC. Some of these errors may stay undetected, while others require investigation (which in turn slows production and drives cost). A machine with validated performance and robustness is in a position to eliminate errors.

(3) *Operational efficiency and throughput*: As the number of PET scans grows every year, so do the volume of FDG production and number of new tracers. This means more production runs per facility per day. Many facilities have already run into their respective efficiency limits, which reduces their ability to take up new tracer production.

(4) *Skillset dependence*: Radiosynthesis has evolved to a point that any technician with minimal training can perform it. This leaves QC as the part of the PET tracer production process that requires the most operator experience, as well as judgment.

(5) *Footprint*: Current QC relies on multiple instruments and manual test stations, typically requiring substantial bench space. As labs take on more PET tracers, this space becomes increasingly scarce.

(6) *Operator variability*: It is inevitable that no two operators can execute QC the same way. In one company, the gold standard for precision and accuracy of gas chromatograph (**GC**) injections was a person. So, the goal of personnel training was to beat that person's performance, which was very difficult. As a result, each

operator had their own precision and accuracy, with the best ones getting results close to those of the reference person.

(7) *Complexity*: Currently, QC requires multiple devices, multiple manual test stations, multiple aliquots of the sample, and a large number of data entries, which are difficult to manage even before considering compliance requirements.

14.5 BARRIERS TO QC AUTOMATION

What has delayed QC automation? *Complexity of development* is one barrier. Automated solution developers need expertise in a broad range of analytical technologies involved in radiopharmaceutical QC. Also, unlike radiosynthesis [42, 43], QC automation cannot be based on predecessor automated devices, because there are none. Therefore, instead of incremental improvements, *ground-up development* has been needed. *Cost* is another factor. Adding automation on top of all the currently used QC instruments would increase the total solution cost. Therefore, either the number of components or the cost per component must be lowered for cost-effective automated solutions. Finally, *regulatory* aspects are a hurdle. Any departure from current QC procedures would require thorough validation. Most of the industry has the opinion that if a procedure does not follow pharmacopeial monographs, it cannot be used. Such a perception limits the motivation for innovation. And it is not far from reality, as the validation burden for new procedures is so great that in practice, it limits users' choices to those that follow monographs.

Despite the fact that both radiosynthesis and QC were required from the onset of PET imaging, automation in the former has preceded that in the latter by decades. The difference in the level of radiation exposure was the most likely reason for this priority. However, the complexity of the required automation efforts remained a major barrier for a long time. Traditional QC requires an assortment of complex instruments that are designed as general-purpose laboratory tools and have little in common among them. In addition, it relies on a set of manual tests (such as the Kryptofix 222 spot test) that have no instrumental analogs.

14.6 QC INNOVATION

14.6.1 Traditional Solutions

A laboratory for executing the procedures outlined in Table 14.1 can be outfitted by the user piece by piece or by purchasing a turn-key laboratory package. The former option involves procuring all the individual pieces of equipment from their respective manufacturers (e.g. GC, thin layer chromatography [**TLC**] scanner, endotoxin measurement device, dose calibrator), assembling test stations for the manual tests (e.g. pH, Kryptofix 222), developing analytical procedures, writing standard operating procedure (**SOP**) documents, and training staff. It also requires setting up a system of

batch records with an auditable approval path (either paper or electronic). Meanwhile, a turn-key laboratory option provides all these components as a package. The vendor delivers all equipment, installs and qualifies it, trains personnel, delivers SOPs, establishes a quality management system (QMS), and ties all instruments into a laboratory information management system (**LIMS**) that produces a batch record. Such solutions (Figure 14.1) that enable the tests presented in Table 14.1 are currently available from LabLogic LTD (Sheffield, UK) and Elysia-Raytest GmbH (Straubenhardt, Germany). It is important to note that besides the analytical equipment that is used to make measurements on a QC sample, additional equipment, such as an analytical balance, fume hood, and refrigerator, are required for an operational QC laboratory that executes traditional methods.

The innovation discussed in this section is presented as a stepwise progression along with a reduced correlation with current procedures. Automated methods may (i) match the structure of current procedures, (ii) match the function of current procedures, (iii) match the output of current procedures, or (iv) match only the product release decision. Each subsequent option relies on a greater departure from conventional methods than the previous one. The examples illustrate the progression from (i) to (iii), while approach (iv) is likely to emerge in the future and is discussed at the end of the chapter.

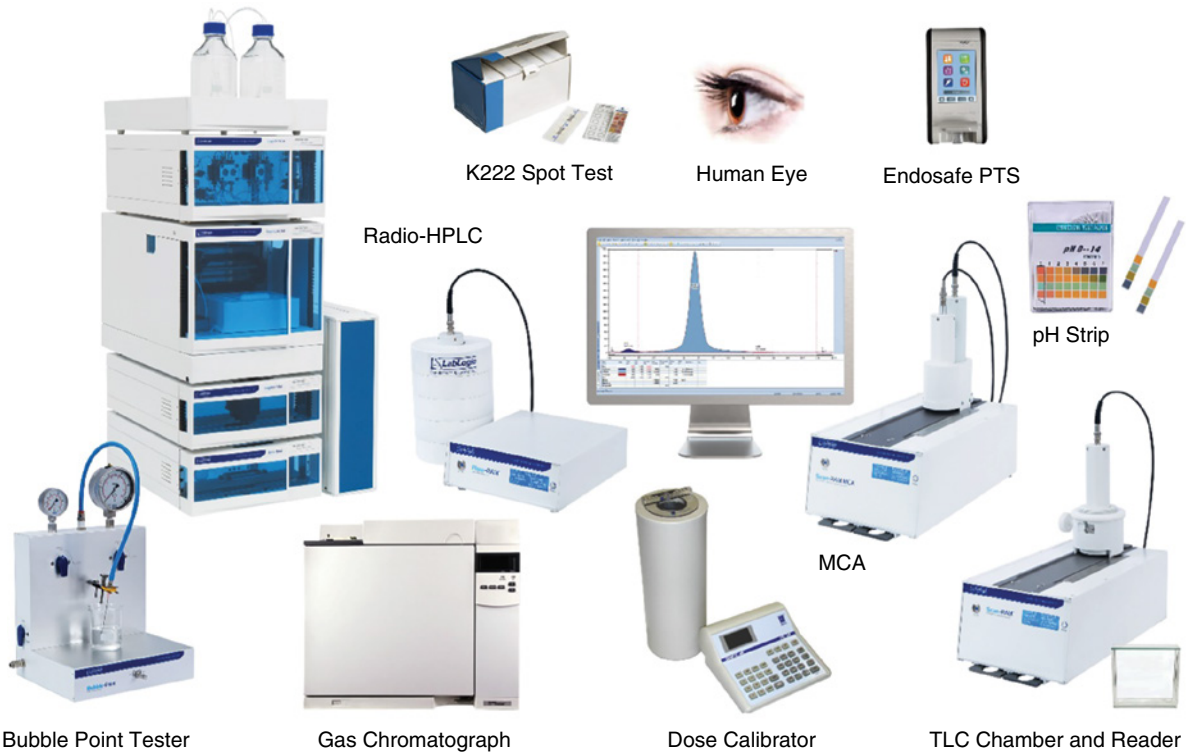


Figure 14.1 Traditional QC laboratory package. Source: Courtesy of LabLogic LTD.

14.6.2 Reducing the Footprint via a Cabinet

One of the issues with QC laboratories is their size. Large laboratory benches with an assortment of equipment and manual test stations on them are poorly scalable. Thus, the first and most logical innovative initiative that presents a measurable improvement over conventional QC is a spatial rearrangement of traditional equipment that reduces the overall floor space requirement while keeping all points of contact with the equipment easily accessible. Typically, laboratory cabinets below and above the equipment are used either to store supplies or not at all. This space is available to be repurposed to host more analytical equipment. Such an approach has been pursued by Elysia-Raytest, yielding a commercially available solution called the QC-Cubicle (Figure 14.2), where a customized cabinet requiring only 1 m^2 of floor space is configured to host all QC equipment and manual test stations required for the performance of FDG QC tests according to EP. Each instrument can be used in a standalone manner or support a full QC process. The cabinet also contains local shielding to reduce the user's radiation exposure. On-board QC equipment includes a GC with hydrogen generator, dose calibrator, high-performance liquid chromatography (**HPLC**), camera (for Kryptofix 222 and other visual tests), multichannel analyzer (**MCA**), osmometer, TLC scanner, endotoxin test device, and pH strip reader. The user still has to operate all the equipment and perform the individual tests manually, but with a much smaller laboratory.

Figure 14.2 QC-Cubicle by Elysia-Raytest. Source: Courtesy of Elysia-Raytest GmbH.

14.6.3 Adding Automation

The next level of innovation takes the previous concept and adds automation to it. In addition to conventional equipment arranged in a compact space, such solutions also include an automated system for distributing the QC sample between the various test stations. The added benefit of such solutions is that they reduce the dependence on operator variability and risk of human error. Such an approach has been pursued by multiple organizations, including Cardinal Health, Siemens, and Sumitomo.

The best-characterized example is a prototype system (Figure 14.3a) built by *Cardinal Health* (Dublin, OH, USA) [44]. This approach was geared to improve compliance with then-recent cGMP regulations by tying all of the QC processes together with software (Figure 14.3b). Most of the development was focused on the *communication flow,* which allowed an unprecedented degree of control and task coordination. Overall, this system focused on data integrity and eliminating the human in most error-prone aspects of QC. (Some manual operations were still required.)

QC tests enabled on this system included: color, clarity, pH, residual solvents, residual Kryptofix 222, bacterial endotoxin, radionuclidic identity, radionuclidic purity, radiochemical identity, and radiochemical purity. Components of the system included: HPLC (with UV, radiation, and conductivity detectors), GC, Endosafe PTS device (Charles River Laboratories, Inc., Wilmington, MA, USA), pH meter, and dose calibrator with real-time and time-stamped readings.

The expanded range of quality reports generated by this system included: (i) analytical tests performed on the PET tracer product, (ii) product yield, (iii) failure reports for the product, (iv) failure reports for systems or subsystems used to manufacture the product, and (v) operator error reports. The goal was to consider all aspects impacting the quality of the PET tracer in one central system – a powerful concept, built with a focus on cGMP compliance.

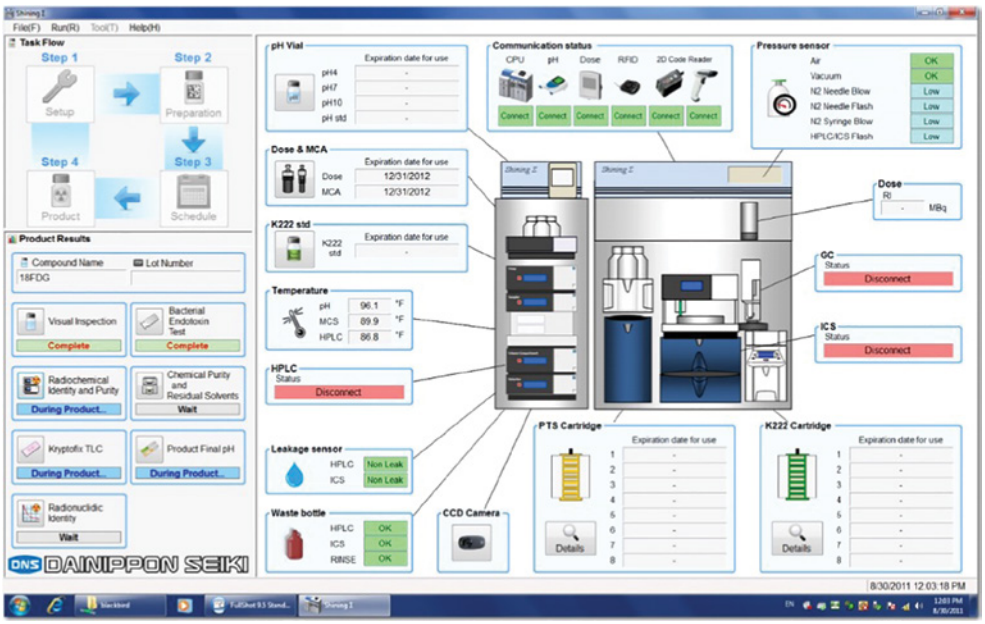
The graphical interface allowed the user to choose which tests to run and to set acceptance criteria based on the PET tracers being tested. Moreover, since some manual operations were still required, the system instructed the user what to do and when to do it, to minimize errors and omissions.

The scheduling component of the software allowed automated preparation of multiple QC instruments to be ready for the analysis scheduled on a given date and time. In that environment, it was conceivable that multiple products might be tested at the same time on multiple components of the system followed by the data being channeled to the correct batch records for each given product.

Another development in the "automated cabinet" group was that by *Siemens Molecular Imaging* (Knoxville, TN, USA) [45]. The principle of this system was based on a network of channels and valves that direct syringe-driven liquid. The system included an assembly of commercial instruments and novel test devices that were mounted to a frame. The system was configured to receive a single product sample via a sample delivery cartridge. Downstream of the cartridge was a rotary valve that could meter the sample into multiple aliquots and send them to different test stations via a network of channels and valves.

Figure 14.3
Automated QC prototype (a) and software (b) developed by Cardinal Health. Source: Courtesy of Cardinal Health Nuclear Pharmacy Services.

(a)



(b)

This network was designed such that a single sample injection via an onboard syringe would fill most of the test modules. The modules were: (i) HPLC module used for radiochemical and chemical purity and identity, specific activity, and radioactivity

concentration; (ii) radionuclidic module for radionuclidic purity determination; (iii) color and particulates module based on a flow cell coupled to a light source, detector, and laser for scattering; (iv) filter integrity test module that enabled conclusions by measuring the pressure drop across the used filter; (v) pH module with a pH meter in the flow path of the sample; (vi) Kryptofix 222 module with automated spotting of the sample within the iodine chamber; (vii) Endotoxin module that included an Endosafe PTS device with a disposable cartridge integrated into the sample delivery cartridge; and (viii) residual solvent module based on a compact commercially available GC instrument with sample delivery enabled via one of the channels within the system.

The unique value of the system was that all tests could be performed from one sample injection with no human actions between sample and report. However, after the completion of all tests, the system required cleaning and equilibration before the next run. A functional prototype of the system has been built and demonstrated to produce test results on all of the described parameters.

One more example in this group has been offered by *Sumitomo Heavy Industries* (Tokyo, Japan) [46]. Onboard components included at least an HPLC and a pH meter, and potentially other instruments. Over 40 functional systems rooted in the invention described in the cited patent application have been built and commissioned to date in Japan. The most interesting part of this development is that it yielded a commercial product in the 1990s – much earlier than any other examples and well before the last two of the milestones described at the beginning of this chapter (US cGMP regulations and proprietary tracers). An explanation is that the product was specifically developed for the Japanese market, where stricter regulations exerted pressure for such a solution much earlier than in the rest of the world. The unique value of the Sumitomo system is its integration into a complete solution that also included cyclotron, radiosynthesis, and dose dispensing.

Solutions presented in this group had two types of automation tasks: mechanical and analytical. The former is the delivery of samples and standards to the different instruments that perform the analysis (GC, HPLC, pH meter). Such solutions were based on existing liquid automation technologies and mostly consisted of pumps, channels, and valves. The analytical automation was more challenging as new test devices had to be designed to replace manual operation and assessments where the current detection technology is the human eye (Table 14.1). Innovative approaches amenable to automation had to be developed for Kryptofix 222 [47] and TLC [48] tests that require manual spotting and development.

14.6.4 Adding Miniaturization

Miniaturization of components enables the logical progression from an automated equipment cabinet to a bench-top instrument with similar functionality. Such an approach has been pursued by GE Healthcare (Chicago, IL, USA) and QC1 GmbH (Münster, Germany). A wide range of miniaturized components is required to make such instruments truly bench-top.

Figure 14.4 QC1 concept. Source: Courtesy of QC1 GmbH.

The *QC1* concept (Figure 14.4) was designed to receive PET tracer samples via either a sample vial or transfer tubing from either dispensing or production. Downstream of the injection port is a mechanism to distribute the sample between components of the system that perform different tests. The miniaturized components could include a GC, gamma counter and spectrometer, radio-HPLC with different chemical detectors (UV, RI, EC, CC), a column selector, and an isocratic or a gradient pump system. The "sample hub" is configured to perform pH, Kryptofix 222, and radio-TLC tests.

The unique feature of the system is that it was designed to be modular and offered multiple HPLC subsystems with different configurations required for different tracer types. This presented an opportunity for each laboratory to choose the components most relevant to their QC needs and later upgrade the system with added functionality as these needs changed. The main idea of the QC1 approach was to miniaturize and integrate the required components in order to fit all necessary equipment in a small footprint while complying with the appropriate pharmacopoeias (EP, USP). The methods were envisioned to be compendial to avoid validation.

The QC1 solution relied mostly on stationary subsystems that received sample via tubing and therefore needed cleaning with a reliable line-clearance procedure. Only the sample hub used disposable components, which kept consumables to a minimum. Daily system suitability tests and periodic calibration procedures were envisioned to be performed in an automated manner.

The emergence of QC1 as a company was an important milestone in the PET field. For the first time, PET tracer QC was not an exploration of added functionality by a cyclotron

or radiochemistry business. The fact that a standalone entity was formed solely for the purpose of QC automation was a signal that a solution is needed, and the demand for such solutions is confirmed and expected to grow. QC1 also envisioned that the "dose-on-demand" paradigm would become an important part of the industry. In view of that, the easier it became to perform synthesis, the more QC runs per day would be needed, aggravating the bottleneck formed by QC relying on an assortment of instruments and manual procedures.

Only the desired specifications presented earlier for the QC1 system are known. The performance yielded by various prototypes has not been published. The QC1 technology was transferred to Trasis SA (Ans, Belgium) in 2018 for further development.

GE Healthcare presented a concept that went further in its miniaturization innovation [49]. Although it never materialized, it demonstrated a vision where a compact system relying on miniaturized components had a disposable cartridge containing most of the test stations that came in contact with the sample. Meanwhile, the bulk of each miniaturized instrument that was not in any way touched by the sample remained within the stationary system. Such systems were envisioned to operate with minimal cleaning or delays.

In the spirit of the GE approach to radio-synthesis automation with its FASTlab and TRACERlab products, QC automation design revolved around the disposable cassette. Another key innovation was a departure from gas chromatography for the determination of organic solvent concentrations, which were proposed to be measured via head-space analysis mass spectrometer. Furthermore, the fluid path used for fractioning the QC sample and delivering it to the different analysis stations was completely disposable and contained within the cassette.

Separate subsystems were integrated for the following analyses: pH, chemical purity, radiochemical purity, radionuclidic purity, and appearance. The instruments within the system included an HPLC and capillary electrophoresis. Furthermore, innovative testing devices were to be designed within the cassette for endotoxin, pH, and Kryptofix 222 analyses.

Another unique feature of the GE concept was shielding. It was envisioned that the shield would be placed within the instrument to surround only the cassette where all analyses took place. Such arrangements would allow for a dramatic reduction in shielding weight compared to all other approaches, where the entire QC system is shielded on the outside.

Implementation of such a solution relies on the miniaturization of columns and detectors and making them part of a disposable cassette. Furthermore, it requires the development of multiple new miniaturized and highly innovative subsystems. It is feasible that one day a disposable HPLC column with detectors may become technically and commercially viable independently. Then, systems like the proposed concept may need to be revisited.

Representative embodiments show a cleanable path up to the cassette, including a coupling to a Mass Spectrometer (MS) or Gas Chromatograph (GC). The sample would enter the cassette after this coupling. The sample would go through a cleanable pump that would move it into the cassette.

Although the envisioned system has not been built or tested, it provided a conceptual vision radically different from all preceding work that defined subsequent developments in the field. Fluid channels (either permanent or disposable) allow a continuous path between the sample reservoir and every test station as well as eventually to the waste container. All locations are fluidically coupled. Liquids don't get from one location to another without following a fixed and completely enclosed fluid path.

While the two systems just discussed focused on the integration of miniaturized technologies into full-scope QC systems, substantial academic development has focused on the miniaturization of individual QC tests via *microfluidics* [50, 51] or replacement of HPLC by less complex and more compact chromatographic alternatives such as capillary electrophoresis [52]. Once these technologies mature, they are expected to reduce (i) the volume of the QC sample, (ii) the footprint of the instrument, and (iii) the time of analysis.

14.6.5 Exploiting Synergies to Remove Components

While all of the previously described innovation stages were enabled by either addition of components (e.g. cabinet, sample delivery system) or replacement of components (miniaturization), this group of developments aimed at *removing* components to make systems simpler. The premise here is using each component of the system for as many QC tests as possible in order to eliminate other components. Solutions in this group have been presented by ABT Molecular Imaging, Inc. (Louisville, TN, USA) and Trace-Ability, Inc. (Los Angeles, CA, USA).

ABT's ultimate goal was the Biomarker Generator [53], including a compact cyclotron, radiosynthesis module, and QC module integrated together. Such integration allowed opportunities to exploit synergies between the three typically distinct systems and processes.

The ABT team has focused on HPLC being the core of the QC system [54, 55], following a similar approach taken earlier in an academic setting [56]. Innovation in columns, detectors, temperature control, and the mobile phase allowed ABT to enable the following tests on the HPLC: residual solvents (ethanol and acetonitrile), radiochemical identity and purity, and Kryptofix 222. The only additional hardware was the microelectrode measurement device used for pH determination, coupled with a syringe driver for the sample delivery. Meanwhile, the filter integrity test was performed on the synthesis module that was part of the same integrated Biomarker Generator system. Another opportunity was to measure color and clarity inline as the sample was transferred to the final product vial.

The ABT Biomarker Generator system is unique in the way it integrates synthesis and QC. There have not been examples of systems where the QC (even partially) relied on the hardware used in synthesis. Meanwhile, automated sampling and HPLC injection have been enabled in the past on a one-off system at KFA Jülich [57].

The ABT approach was a hybrid between disposable and multi-use components. The synthesis cassette was single-use. Thus, QC functions performed in it (appearance and

filter integrity testing) also relied on the features of the disposable cassette. Meanwhile, chromatographic tests and pH relied on permanent hardware and a system of channels and valves for liquid transfers.

Although some tests, such as radionuclidic purity/identity, sterility, and endotoxin, were not enabled, it is important to recognize that this was not just a concept or a prototype. The solution was released as a product and installed in the field, providing significant simplification of QC compared to traditional methods. According to ABT records, the first complete Biomarker Generator system, including onboard automated QC, was installed and qualified at Sveta Marina Hospital in Varna, Bulgaria in 2013. In 2019, ABT joined the TeamBest group of companies, changing its name to Best ABT, Inc.

Trace-Ability, Inc. took the search for synergies that can reduce the number of components further, to the point where all tests (except filter integrity) required for FDG release in the US were performed on a single analytical instrument – a microplate reader [58, 59]. The Tracer-QC product (Figure 14.5) launched in 2017 is conceptually different from its predecessors as it resulted from a search for the optimal way to obtain the information needed for release testing without being limited by existing test methods. The philosophy followed by Trace-Ability was that what matters is *product quality*, which is manifested in the information yielded by the QC tests. The means of obtaining that information (as long as they are validated and reliable) did not matter. This focus on the goal, rather than means of achieving it, allowed Trace-Ability to expand the arsenal

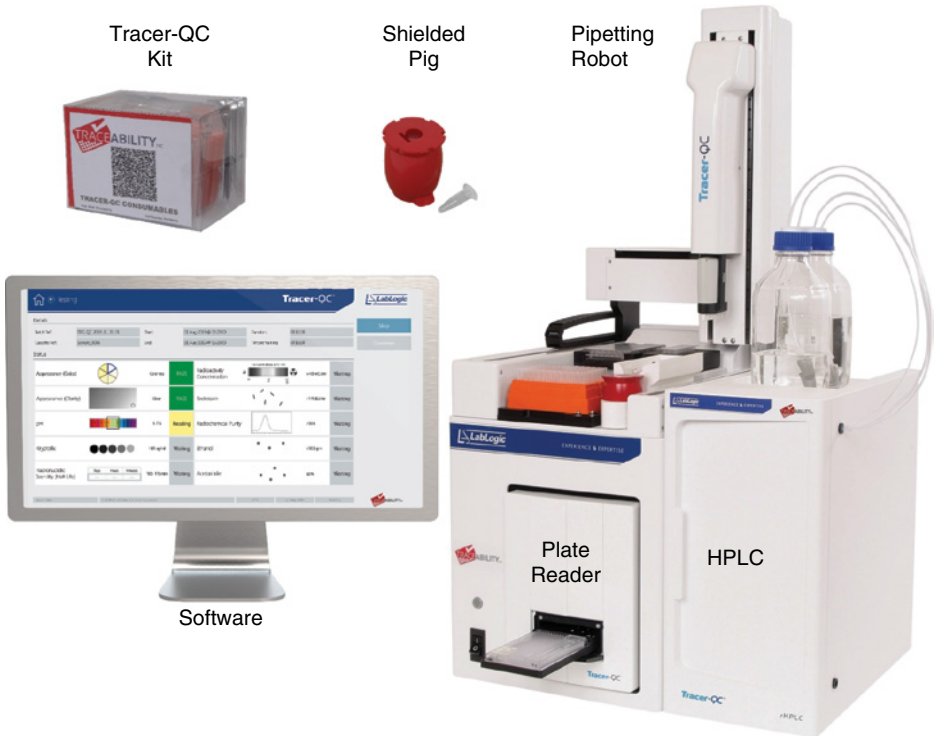


Figure 14.5 Tracer-QC rHPLC product by Trace-Ability. Source: Courtesy of Trace-Ability, Inc.

of applicable technologies and realize synergies that were absent between traditional QC methods.

Trace-Ability chose a plate reader as the core analytical instrument. Plate readers have been developed and perfected over decades for use in diagnostics (60) and other industries. Their performance in measuring absorbed and emitted light from microplates has been continuously improving as a result of competition between multiple manufacturers. A similar evolution has taken place in the microplates used for analysis in plate readers. Trace-Ability built on top of that development and focused the innovation on enabling new methods based on the capabilities offered by state-of-the-art plate readers. Answers for all QC tests are obtained via light measurements (absorbance and luminescence) inside a plate reader. This makes the analytical instrument very simple but requires the development of new tests. These tests and custom plates that enable them became the core innovation yielded by Trace-Ability. FDG QC tests are grouped in the following way:

- *Absorbance tests*, including color and clarity, which can be performed in a microplate on a pure sample by measuring light absorbed by the sample.
- *Indicator-based absorbance tests*, including pH, Kryptofix 222, endotoxin, and organic solvents. These tests require mixing the sample with an indicator that changes color in correlation with the concentration of one of the listed components. That color change is compared to the color change obtained in parallel from multiple standards, yielding a measurement of the concentration of the analyte.
- *Radiation tests*, including radionuclidic identity, radioactivity concentration, radiochemical purity, and radiochemical identity. These tests are enabled via interaction of the sample with scintillating materials within the custom microplate that emit light in response to radiation exposure. The light is measured by the plate reader in luminescence mode and translated into the value of each of the listed properties.

While all of these analyses are performed in a single custom microplate within a plate reader, sample manipulations (distribution and mixing with indicators) are performed by a compact automated pipettor located on top of the plate reader, yielding a completely automated, hands-free process from FDG sample to QC report in a compact footprint measuring under 14 inches in width. Such an approach, not limited by traditional methods, allowed a dramatic simplification of the hardware platform. Since there is no fixed architecture of channels and valves, processes can be easily changed, added, or removed. Microplates have an excessive number of wells, allowing a wide range of analyses to be performed. Thus, samples and standards are analyzed under the same conditions and at the same time, providing *in situ* system suitability confirmation with every run. Furthermore, this allows duplicate testing, which increases accuracy and precision while reducing the chances of invalid test results.

The sample never comes in contact with the instrument, while all contact components and reagents needed for one analysis run are packaged in a single-use kit. The kit is recognized by the system and installed prior to analysis. Then the sample is delivered in a shielded pig keyed to the instrument. Next, the analysis takes place automatically, with

the sample distributed by disposable pipette to the test locations directly from the pig. At the end of the analysis, most of the radioactive waste is aggregated in the same pig for easy removal without user exposure. The rest of the kit can be removed afterward, leaving the system completely free of any radioactive material and ready for the next analysis run.

Unique advantages for the user are presented by a completely disposable path requiring no cleaning and avoiding the risk of cross-contamination. System maintenance is also minimized since no liquids contact any of the permanent components and since the system has so few components. Inventory of consumables required for the analysis is reduced to one kit with a single expiry date. This solution successfully enables users to meet USP quality requirements for FDG while following non-USP methods that have been properly validated. By eliminating all manual operations and human judgments, Tracer-QC yields results that are completely objective and a completely traceable tamper-free data flow from measurement to batch record. These features enable unprecedented ease of compliance with cGMP regulations, further enhanced by software written to 21 CFR Part 11 standards by *LabLogic*. Finally, complete elimination of the person from the process leads to radiation exposure reduction, which is further assured by the compact shielding offered with Tracer-QC systems. Implementation of Tracer-QC in the field has confirmed these advantages along with equivalence to traditional QC methods [61].

To support the diversity of PET tracers beyond FDG, the first Tracer-QC system was closely followed by the second-generation product with integrated HPLC. Although it introduced some cleanable surfaces, the level of automation is such that HPLC cleaning and equilibration take place without user interaction. Moreover, coupling HPLC with a precise automated liquid handler allows the quantitative use of internal standards (supplied within the kit) in every sample injection. This reduces the number of injections required and produces more reliable quantification that has not been possible with standalone HPLCs – even those fitted with automated injectors (that cannot mix sample and standards in precise proportions).

This latest *Tracer-QC rHPLC* product supports a variety of PET tracers by performing all non-specific tests on the plate reader in parallel with running tracer-specific chromatographic tests on the HPLC component. This platform currently enables over 20 QC tests required for the most common PET tracers.

14.7 DISCUSSION OF AUTOMATED QC SOLUTIONS

The previous section presented the progression in PET tracer QC innovation in a sequence correlating with increasing departure from the traditional manual approach. The following discussion focuses on the advantages offered at each step in the context of cGMP production of a variety of PET tracers. At each step, there is a trade-off. Each user must determine the net value that these trade-offs leave them with.

When transitioning from a standard laboratory to a *cabinet*, there is a gain in floor space that is offset by the extra cost of the cabinet. If the user needs to expand their

tracer portfolio within the existing facility, then the extra space is well worth the investment.

When transitioning to an *automated cabinet* solution, there is an investment not only in the cabinet but also in the automation that is added on top of the cost of individual instruments. However, that investment should be balanced by the savings in labor that is eliminated via automation.

Transitioning to *miniaturization* may reduce the overall cost of the solution and offer further space savings compared to both previous solutions. The exact trade-off value will need to be calculated when such solutions are developed and available with known capital and running costs.

Transition to a *synergistic* system offers overall simplification of operation, ease of use, and compliance, all while offering a cost reduction. The trade-off is in the need to validate non-pharmacopeial methods. The latter is clearly a burden for users. However, if the equipment supplier performs such validation, it can dramatically reduce that burden for end users.

Overall, solution complexity goes up and then down as one progresses along this sequence. Adding automation on top of existing instruments increases complexity. Miniaturization may or may not reduce it. And then, only a synergistic approach allows a measurable reduction in solution complexity. A further comparison of the presented solutions is summarized in Table 14.2.

It is also important to recognize the drivers behind each of the presented developments. The GE, Sumitomo, and ABT solutions appear to have been driven by integration within the total tracer-production solution. Specifications were driven by the integration with cyclotron and specific chemistry modules and revolved around the capabilities and needs of the latter. The ABT design was further defined by the dose-on-demand concept. The Siemens and Cardinal systems' specifications were driven by the needs of the corresponding high-volume FDG production networks (PETNET Solutions and Cardinal Health NPS). QC1, and Trace-Ability developments driven by broad use cases.

14.8 CHOOSING AN AUTOMATED QC SYSTEM

As illustrated by the previous summary, there are currently three commercially available automated QC solutions offered by Sumitomo, Best ABT, and Trace-Ability. It is expected that this group will expand, with new solutions offering new features and benefits. Given how different the three systems are from one another, they are very difficult to compare. PET tracer manufacturers' use cases differ as well. Therefore, it is best to review the characteristics of the automated QC solutions that users should compare when choosing a solution for their specific needs. A good start is provided by the list of drivers of QC automation discussed earlier in section 14.4. It provides these reasons to switch to automated solutions: s*afety/radiation exposure, human error, operational efficiency and throughput, skillset dependence, footprint, operator variability, and complexity.* Thus, the user can compare the extent of the impacts provided by different automated solutions in

Table 14.2 Automated QC systems for radiopharmaceuticals: concepts, prototypes, and products.

Group	System	Key capabilities and benefits	Key innovative features	Challenges	Fluid path	Maturity
Cabinet	Elysia-Raytest	Compact footprint	Multi-level shielded cabinet	Procedures are still manual	Permanent	Product
Automated cabinet	Cardinal Health	Process controls; coordination of QC and production; data integrity	Software allowing an unprecedented degree of control and integration with synthesis; self-checks.	Some manual operations required; footprint; complexity; cost	Permanent	Prototype
	Siemens	Largest number of tests enabled on a working automated instrument	In-line test stations reached via tubing	Thorough cleaning between runs without feedback on cleanliness; complex maintenance; cost	Permanent	Prototype
	Sumitomo	Integrated with cyclotron, synthesis, and dispensing	Automated sample delivery from synthesis to QC modules	Lack of flexibility	Permanent	Product only in Japan
Miniaturization	GE	Compact instrument with capabilities of a laboratory	Miniaturization; MS for organic solvent analysis; capillary electrophoresis above 2D γ detector; disposable cassette	Requires technologies not currently available	Mostly disposable	Concept
	QC1 (Trasis)	Flexibility	Modular; configurable; single injected sample distributed to different components	Requires additional components to enable complete QC process	Mostly permanent	Prototype
Synergistic	ABT (Best ABT)	Biomarker Generator enablement; simplicity	Synergies enabled via integration of QC with cyclotron and radiosynthesis	Missing tests: appearance, radionuclidic purity/identity, sterility, endotoxin	Mostly permanent	Product
	Trace-Ability	Compact footprint; ease of use, maintenance and compliance	Integrated plate reader pipettor; tests performed within a disposable kit; flexible platform not limited by channels	New tests needed for new tracers	Disposable except for HPLC	Product

these categories. While they all offer an advantage in each category, the impact of that advantage differs in different facilities.

Furthermore, the following criteria that apply to automated solutions should be considered when making a selection: (i) reliability (and how it has been proven); (ii) net cost impact, including a balance of capital, operating, and compliance-driven cost changes yielded by the transition from the current solution to an automated one; (iii) ease of maintenance, driven by the complexity of instruments and skills required for maintenance; (iv) data integrity, which is mostly assured by the level of software compliance with 21 CFR Part 11 regulation; (v) cleaning requirements between runs, especially in systems with a permanent fluid path; (vi) suitability testing, including the complexity of such testing, level of feedback, and degree of automation offered for it; (vii) shielding (whether it is included and sufficient); and (viii) ease of implementation of regulatory transition (discussed next).

14.9 REGULATORY ASPECTS

14.9.1 Regulators' Benefits from Automated QC

While automated QC provides a tool for regulatory compliance that simplifies radiopharmaceutical production, regulators also benefit from its widespread adoption. Automated QC systems give regulators a tangible, verifiable record of manufacturing performance, without having to draw conclusions from secondary data or compare poorly traceable hand-written records.

For example, in the US, the FDA maintains statistics of violations recorded via Form 483 against specific regulatory requirements [36]. A search for 21 CFR Part 212 yields a list of relevant violations referencing the part of the regulation violated and the frequency of such violations. About one-third of all 21 CFR Part 212 violations are in *Laboratory Controls*. Analyzing the requirements and violations in detail, it becomes apparent that most of these violations are rooted in or impacted by manual procedures. The FDA recognizes this but cannot mandate much improvement in the absence of any alternatives to manual procedures. Consequently, the FDA becomes a major stakeholder in and beneficiary of QC automation. QC automation becomes not only a compliance tool for its users but also a QA and inspection tool for regulators. It allows them to have an unquestionable record of cGMP compliance that simplifies inspections and eliminates product quality concerns.

Thus, it is critically important for the developers of QC automation to start interacting with the FDA and regulators in other countries as early in the development process of their products as possible. They should understand the needs of the regulators, manage their expectations, know their concerns, and educate them about upcoming solutions well before the latter are released. Ideally, by the time a solution is on the market, regulatory agencies are aware of it, and the companies know exactly what proof of performance and regulatory submissions are expected by each agency for their products.

In the US, Trace-Ability set a precedent by starting to work with the FDA two years prior to product release, identifying the agency's needs, product performance characteristics, user specifications, and validation approach together with the Technical Committee at the Agency well in advance of these procedures being implemented. *Disclaimer: Funding for this development was made possible, in part, by the Food and Drug Administration through grant U01FD005517. Views expressed in this chapter do not necessarily reflect the official policies of the Department of Health and Human Services; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.*

14.9.2 Regulatory Approval Mechanism for Automated QC

The following definitions copied from USP General Chapter <823> should be helpful for the discussion of these procedures: "**Validation**: Establishment of documented evidence that a method, process, or system *meets its intended requirements*. **Verification**: Confirmation that an established method, process, or system meets predetermined acceptance criteria. **Performance Qualification** (**PQ**): PQ demonstrates that the equipment is capable of performing tasks required to make and test PET drugs in the operating environment and that the equipment provides the intended results. PQ should describe the required performance tasks for the equipment. If a USP compendial test procedure is employed, the procedure should be *verified* to demonstrate that the test works under the conditions of actual use. Non-compendial test procedures employed in the testing of a PET drug should be reliable and specific (which can be proven via *validation*).

A change in the process for producing an approved drug, such as the incorporation of automated QC, requires the filing of an NDA supplement with the FDA [62, 63] or similar regulatory submissions in other countries [64]. It is a burden, especially considering that such filings need to contain substantial support for the new method.

If the change uses a USP method, the burden of proof is a *verification,* and a CBE-30 supplement (changes being effected in 30 days in the absence of FDA objections) might suffice [65]. Therefore, USP methods have been the focus of several QC automation efforts. However, the internal complexity of automated systems with diverse instruments integrated via a network of channels and valves requires *validation* of robustness and the absence of cross-contamination. Therefore, most likely the more complex regulatory route of a prior approval supplement (**PAS**) would be required for these systems, despite using USP methods. The PAS mechanism is also appropriate for automated systems using non-USP methods, which require *validation* prior to use.

Radiopharmaceutical manufacturers wishing to adopt an automated QC system could *validate* such changes themselves by following the FDA guidance [66] on bioanalytical method validation. However, few have the resources to do so, which is an adoption barrier. To overcome this barrier, the makers of automated QC systems can validate their systems though collaborative studies with early adopters and present the validation data to the FDA via a drug master file (**DMF**). After the DMF examination is triggered by the

first cross-reference and found acceptable, subsequent adopters may then reference the DMF in their NDA supplements. This mechanism allows them to implement a new solution requiring only PQ without performing the validation study themselves, and may rely on a CBE30 mechanism.

Validation most commonly seeks to establish *equivalence* [67] with the method it is replacing. For automated QC systems that use pharmacopeial methods, this approach is best. However, additional validation is required to demonstrate that methods that are individually equivalent are not affected by other parts of the system. Method performance must be established in the context of the automated process. For example, validation of the robustness of the sample/aliquot management system is needed to ensure that it does not affect tests that may otherwise be equivalent.

The situation is more complicated when new methods are very different from old methods and cannot be considered compendial. Specifically, it can run into the following two types of issues:

(1) *Comparison is impossible*: The old method was incorporated historically without being properly validated. For example, the spot test for Kryptofix 222 that is in use today has no record on accuracy, precision, linearity, or limit of detection (**LOD**). Thus, it is difficult to come up with criteria for truly comparing the new method to the old one without having to validate the old method first.

(2) *The new method is inferior to the old one*: This statement may sound absurd. Why would anyone switch to an inferior method? Actually, as discussed earlier, some of the equipment used in QC of PET tracers is general-purpose laboratory equipment that is excessive in its capacity for the purpose of PET tracer QC. A good example is residual solvent analysis. A LOD on a GC is typically in **ppb** (parts per billion). Meanwhile, the release test only needs to answer the question of whether the concentration of acetonitrile in the sample is above or below 400 **ppm** (parts per million). For the purposes of answering this question, sub-ppm LOD is irrelevant. An instrument that has a 200 ppm LOD may answer this question adequately. The purpose for which GC is used in the QC of PET tracers does not require ppb sensitivity. Thus, methods should be compared based on how well they answer the QC question, rather than on their overall characteristics. In view of this, a method with 200 ppm LOD should suffice for acetonitrile test, as long as its accuracy and precision allow 95% confidence in answering the pass/fail question. Such methods should be validated via a mechanism different from overall equivalence or superiority.

Such validation approach is known as *fit for purpose* [68], which relates to the USP definition of *validation*, where the "intended requirements" for the method should be set based on the answer it needs to provide rather than overall analytical performance. Then, the validation study should be designed to determine whether the method meets these requirements. The absence of comparison to old methods eliminates the two issues presented earlier.

To date, the only automated QC solution that has undergone official validation in the US (with corresponding FDA submissions) is Tracer-QC. Both validation approaches

have been used. The *equivalence* approach was used for the TLC test for [N-13]Ammonia because the predicate USP test [69] was similar in principle. The latter method relies on a TLC spotted on the bench, developed vertically in a chamber, dried manually, and read on a TLC scanner, which generates a chromatogram for determining radiochemical identity (based on R_f) and radiochemical purity (peak integration). The Tracer-QC method relies on a horizontal TLC in a disposable kit with automatic spotting, development, and analysis. The study comparing the two methods was designed and executed at the Gordon Center for Medical Imaging at Massachusetts General Hospital (**MGH**). The results obtained on the same samples by both methods demonstrated equivalence. The data were submitted to the FDA via a CBE-30 supplement and resulted in a written approval letter.

The second validation approach used was *fit for purpose* because most of the Tracer-QC tests are different from the compendial ones. This approach was used to validate the entire system with a 10-test protocol for FDG at the Department of Radiology and Biomedical Imaging at the University of California, San Francisco (**UCSF**). Performance criteria were preset based on desired accuracy, precision, specificity, range, linearity in the pass/fail threshold range, and limits of detection and quantification. Additionally, a separate part of the study focused on robustness, with challenges to the system including various environmental conditions or operation near the limits of acceptable conditions (for example, after the kit has stayed open to the atmosphere for the longest allowed time). Multi-parametric validations can quickly become impractical – e.g. a full factorial validation study for a 10-test system can easily require thousands of experiments. Therefore, a more practical study had to be designed. Each experiment in this study assessed multiple tests in parallel, producing data that are parsed for easy review. This approach relied on the Tracer-QC's ability to measure multiple parameters at once. Additionally, this approach allowed for comprehensive testing of potential interferences, essentially placing very stringent requirements on the specificity of the individual tests.

Experimentally, this validation study consisted of repeated analyses of multiple FDG samples spiked with a mixture of specific impurities or water. Spiking solutions were carefully prepared to produce known concentrations of the impurities. For each run, an FDG sample was mixed with the spiking solution. FDG samples were produced according to the standard clinical production protocol. Due to radiation safety concerns, some experiments were performed with decayed FDG samples. This approach allowed measuring the analytical performance of the individual tests on the Tracer-QC platform. Complete validation was achieved over 28 individual runs that generated close to 400 individual data points.

These validation studies have drawn the most benefit from collaboration with the FDA. The development team had a chance to make the agency familiar with the system before designing validation studies. Then, when the studies were designed, they were reviewed with the FDA prior to execution. This approach allowed the Agency to challenge the methods and the validation approach before any of the laborious validation laboratory work. Thus, by the time the laboratory work was started, the developers and regulators had reached concurrence on the validation approach. During the study, interim validation reports were also reviewed with the Agency, resulting in the identification

of areas where additional data had to be gathered. Finally, the body of data was found sufficient by the FDA Technical Committee to conclude that the integrated multi-parametric QC method on Tracer-QC has been successfully validated. Trace-Ability now maintains a Type V DMF (#029891) with the FDA that includes system description and validation reports. Cross-referencing this DMF, enables new users to implement Tracer-QC without extensive validation.

This experience shows that validation of something radically different from compendial methods cannot have a clear prescription. It requires a proactive dialogue with regulators and the joint development of an approval path, which is much more productive than developing a validation strategy in a vacuum in hopes that it matches regulators' expectations after it has been executed. Such a risky approach has a strong chance of having the validation generate a data set that is insufficient or irrelevant for the regulators' decision regarding the new technology.

14.9.3 Pharmacopeia Incorporation

Ultimately, automated methods are expected to become the standard that is incorporated into pharmacopeial monographs. The USP standards-setting process enables anyone to bring a standards-setting issue to the attention of the USP, ranging from establishing a new standard to revising an existing one.

The USP-NF is a combination of two compendia: the USP and the National Formulary (**NF**). Monograph proposals for the USP-NF are submitted in writing to the USP along with explanations for the proposals and data to support them. Monograph submission guidelines [70] published by the USP provide detailed information, including recommendations for what data to submit with specific proposals. The monographs are routinely sponsored by the pharmaceutical companies that hold an approved NDA or abbreviated new drug application (ANDA) for the product of interest. The sponsor's proposal should provide supporting data from its approved application, including method-validation data for the analytical methods used for the drug product. Once an organization sponsors a monograph, a USP panel composed of USP scientific staff and expert volunteers reviews a draft to ensure that it has enough data to provide compelling evidence that the method is either equivalent to existing ones or fit for its intended purpose. Laboratory tests may also be conducted when needed. Once a new standard is developed for the USP-NF, it is proposed for a 90-day public review and comment period in the Pharmacopeial Forum (**PF**). After the public review and comment period, the Expert Committee considers the comments received and determines whether further changes to the standard should be made. To finalize the standard, the Expert Committee members vote independently on the proposal through an electronic balloting system. The standards that the USP deems official are set forth in its various compendia.

The USP allows multiple alternative analytical methods to be included in monographs at the same time for the same drug. As long as a monograph is being maintained by the sponsor, it can stay active, and users can choose the method that they find most appropriate. This process will be appropriate for the incorporation of automated QC solutions

into USP standards. Either the manufacturer of the automated solution or the manufacturer of the PET drug that relies on automated QC will sponsor a monograph (or a revision of one). The review process, including a thorough data analysis, will yield a decision regarding the new monograph.

14.10 FUTURE DEVELOPMENTS

This chapter has presented multiple automation approaches for PET tracer QC. Their relative strengths have been discussed in the context of satisfying today's needs. But what will the PET field look like in a number of years, and how will QC automation support it? To suggest answers to this question, there needs to be a vision for tracer production dynamics. Based on the observed trends, it can be assumed that no single tracer will surpass FDG in the number of doses and batches produced. But it is reasonable to believe that the total batch volume of other tracers will surpass FDG soon, and the total dose volume will do so as well in due time. This means QC laboratories will have to support more and more products each year; and relying on conventional methods if each tracer requires dedicated equipment (as is the case frequently today) will be impractical, as the laboratories will run out of space after the second or third tracer. Automated QC offers a footprint reduction. But if the IP owners of the different tracers demand dedicated equipment, the manufacturers will need an ever-growing number of automated QC machines.

One solution is the disposable path. If the opportunity for cross-contamination is eliminated, then different samples can be run on the same equipment. The disposable path is one measure against cross-contamination, as no surfaces come in contact with more than one sample. However, chromatography such as HPLC cannot yet be made in a disposable fashion (while being economical and practical). Thus, there has to be an automated cleaning procedure coupled with cleaning validation that confirms that any traces of any samples from the previous run are entirely removed before the next run. Also, it is possible that one day, a technology like that envisioned in the GE patent will become available, enabling a cost-effective disposable HPLC.

These trends may cover the immediate need. But if no further evolution takes place in QC automation, it will run into the next bottleneck in a few years when the number of tracers (with unique QC requirements) grows faster than the automated QC procedures available for their support. Even today, with over 100 new PET tracers in development, it is not possible to quickly design automated QC procedures for all tracers prior to Phase I clinical development. However, by the time a much smaller number of tracers enters Phase III, it will be difficult to switch methods, as doing so requires amendments when the sponsor cannot afford to lose any time and delay the NDA approval date. Thus, it is too early in Phase I and too late in Phase III.

To solve this issue, QC automation needs to be very flexible to accommodate methods that are not even conceived today. At the same time, new method development should be so easy that it does not delay tracer development. Thus, it is expected that the

next-generation technology that will replace QC automation summarized here will have these attributes: (i) a more universal platform that can accommodate new tests without hardware modifications, and (ii) a platform that enables method development so easily that it does not require additional resources or time in the tracer development process.

A trend toward merging QC into the total PET tracer production solution is likely to become stronger. Some of the approaches discussed in this chapter have explored this path already. However, within these solutions, synthesis and QC processes are still separate. In the future, it is logical to expect that merging synthesis and QC into one process may offer opportunities for in-process controls that provide early insight into product quality and possibly even enable corrective measures. By merging future innovation in synthesis and QC, the overall value will be greater than the sum of the benefits of the two components.

Yet another possible trend could be toward simplification or refocusing of QC based on the record of production. Automation (in any form) should enable more data that can be analyzed for trending. Such outputs can be used to predict failures before they happen or to prove the robustness of a process that may lead to reduced QC effort (making some per-batch tests periodic). Recent developments in big data analytics [71] should support the emergence of such solutions.

Finally, innovation in the tests themselves should lead to more reliable results. For example, the Kryptofix 222 spot test developed with iodine vapor is non-specific and can respond to a range of compounds besides Kryptofix 222. No such compounds have been observed in formulations of FDG over the years. But it is very possible to see them as intended or unintended constituents of new tracer formulations. Therefore, more specific tests will be needed as the range of PET tracers expands.

Automation approaches may correlate to manual QC in a number of gradually less dependent ways, as illustrated in this chapter. Each subsequent option relies on a greater departure from conventional methods than the previous one:

(1) Matching the structure of current procedures, such as in the automated cabinet approach

(2) Matching the function of current procedures, such as in the miniaturization approach

(3) Matching the output of current procedures, such as in the synergistic approach

(4) Matching only the product release decision

Currently, the last option remains unexplored. However, a well-supported product release decision is the ultimate purpose of release testing. Future developments are likely to focus on achieving this goal in more effective ways than the ones offered or conceived today. A more systematic approach is likely to take advantage of a combination of in-process controls, merging of synthesis and QC functions, trending analyses, more complex processing of large data sets from the same and different sites, and preventive alarms that trigger action before batches start drifting out of compliance.

The author hopes that there is healthy competition and collaboration between the major players in achieving this vision. It would be best if, yet again, multiple options

are offered by several companies, and possibly a hybrid between different approaches becomes the solution that can support the growth of PET radiotracer production for decades, enabling new diagnostics to reach patients rapidly and save lives.

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