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Review article

Standardization of fluorine-18 manufacturing processes: New scientific challenges for PET

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ABSTRACT

In [^{18}F]fluoride chemistry, the minute amounts of radioactivity taking part in a radiolabeling reaction are easily outnumbered by other reactants. Surface areas become comparably larger and more influential than in standard fluorine chemistry, while leachables, extractables, and other components that normally are considered small impurities can have a considerable influence on the efficiency of the reaction. A number of techniques exist to give sufficient ^{18}F-tracer for a study in a pre-clinical or clinical system, but the chemical and pharmaceutical understanding has significant gaps when it comes to scaling up or making the reaction more efficient. Automation and standardization of [^{18}F]fluoride PET tracers is a prerequisite for reproducible manufacturing across multiple PET centers. So far, large-scale, multi-site manufacture has been established only for [^{18}F]FDG, but several new tracers are emerging. In general terms, this transition from small- to large-scale production has disclosed several scientific challenges that need to be addressed. There are still areas of limited knowledge in the fundamental [^{18}F]fluoride chemistry. The role of pharmaceutical factors that could influence the ^{18}F-radiosynthesis and the gaps in precise chemistry knowledge are discussed in this review based on a normal synthesis pattern.

1. Introduction

After nearly 30 years, the field of PET has moved from being a useful research tool in the understanding of biochemical processes *in vivo* to become a locomotive of molecular imaging [1,2]. The transition was largely due to the PET/CT breakthrough technology by merging the high anatomical resolution of CT with the high sensitivity for biochemical processes of PET with [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) [3]. New PET centers are coming into existence all over the world, and we are now approaching another watershed, where clinical PET will expand from the use of [^{18}F]FDG to a wider spectrum of ^{18}F-labeled radiopharmaceuticals.

A large number of these tracers have already been developed and tested in clinical investigations with promising results; examples include 3′-deoxy-3′-[^{18}F]fluorothymidine ([^{18}F]FLT) [4,5], ^{18}F-fluoromisonidazol ([^{18}F]F-MISO) [6,7], 1-(5-[^{18}F]fluoro-5-deoxy-α-D-arabinofuranosyl)-2-nitroimidazole ([18F]FAZA) [8–10], 2′-methoxyphenyl-(*N*-2′-pyridinyl)-p-[18F]fluoro-benzamidoethylpiperazine ([^{18}F]FMPPF) [11,12], [^{18}F]fluoroacetate [13,14], [^{18}F]-fallypride [15,16], and 16α-[^{18}F]fluoro-17β-estradiol ([18F]FES) [17,18].

Some of the basic problems associated with [^{18}F]fluoride chemistry from the late 70s and 80s are now considered as solved (unreactive fluoride, manual operation) [19–21]. Today, sufficient yields for a single dose can be obtained for most tracers allowing for pre-clinical and microdosing investigations. There is still, however, a considerable challenge regarding reproducibility. Production yields can vary substantially between sites, but also from day to day within one site. Even if the process is supervised by experts, large variations are seen. These discrepancies have perhaps not been a major concern for the isolated PET radiopharmaceutical manufacturing site but hamper the ability to perform multi-center trials required for regulatory approval of new agents and preclude setup of an effective pharmaceutical manufacturing network.

The production of [^{18}F]FDG is an exception in this regard. This process has been thoroughly optimized over the last 30 years. Its synthesis steps are well studied and pit-falls well known, although most of the knowledge come from empirical studies. This has culminated in a widespread automated process sufficiently robust to allow reproducible pharmaceutical production of [^{18}F]FDG despite variations in cyclotrons, automated platforms, personnel, and local environment.

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Currently, the production of [^{18}F]fluoride-labeled tracers other than [^{18}F]FDG is performed by self-contained units (PET centers) that are setting up manufacturing processes in their own specific way. A PET center adapts its production with certain fixed parameters; like cyclotron product, local environment, type of synthesis equipment, and even the choice of the starting material render the process unique for each individual site.

Much of the process development is also quite idiosyncratic. Over the years, PET chemists have adopted their own way of operating. For example, procedures of separating [^{18}F]fluoride from ^{18}O water, choice of reaction vessel material, phase-transfer catalyst, and fluoride drying parameters often vary from site to site.

Consistent production of a particular tracer across multiple sites needs a structured approach and is an important issue for regulatory approval of new PET radiopharmaceuticals. The standardization of PET tracer manufacturing equipment and processes can address many of these issues. Freshly made solutions of quality that can vary between sites can be replaced by well-characterized pre-filled vials and fixed components that can be stored on the shelf. Radiochemistry processes with variable yields need to be replaced by robust processes within a well-defined design space, as defined in regulatory guidelines [22], all the way from cyclotron targetry through the synthesis unit, purification, formulation, and dispensing. In this change of paradigm, it has become evident that there are major unsolved areas in basic [^{18}F]fluoride chemistry.

In this paper, we want to highlight the factors that we have found to be important in standardizing processes and equipment in order to facilitate rollout of uniform fluorine-18 tracer manufacturing processes across multiple sites, and we will point to key areas in [^{18}F]-chemistry that require academic attention.

2. A typical [^{18}F]-radiolabeling process

There are several routes available both for producing fluorine-18 and for the incorporation of [^{18}F]fluoride into a tracer [23,24]. This paper will only address nucleophilic substitution reactions with no-carrier-added (n.c.a.) [^{18}F]fluoride obtained from [^{18}O]H_2O targets via the ^{18}O(p,n)^{18}F reaction [25]. This method is by far the most common route to ^{18}F-labeled pharmaceuticals and the closest to being a part of pharmaceutical manufacturing in the PET field [26].

A complete manufacture of a ^{18}F PET radiopharmaceutical starts with [^{18}F]fluoride coming out of a cyclotron and ends with a product ready to be injected into a patient. The process between these outer points is a complex mixture of organic synthesis, radiochemistry, and pharmaceutical manufacturing.

A nucleophilic substitution reaction with [^{18}F]fluoride looks at first glance relatively straightforward. In principle, the reaction is very similar to [^{19}F]fluoride chemistry. There are, however, some major differences:

- The quantity of [^{18}F]fluoride is minute (nanomoles or less) compared to the scale at which a synthetic chemist might typically operate with elemental [^{19}F]fluoride. Consequently, reaction kinetics are very different and trace amounts of an impurity can interact with [^{18}F]fluoride and impact the radiosynthesis in an unpredictable manner resulting in low incorporation yields or shift in the product profile.
- The radioactive nature of fluorine-18, in particular at high activities (multi-GBq), has been shown to result in radiolysis of solvents, reagents, or contact surfaces forming highly reactive free radicals and consequent degradation of substrate and intermediates during synthesis or of the final drug product.
- Due to the preferred production method of n.c.a. [^{18}F]fluoride via the O^{18}(p,n)^{18}F reaction, [^{18}F]fluoride is always obtained as an aqueous solution. Water must be removed in order to achieve sufficient reactivity of [^{18}F]fluoride.
- The organic solvent in which labeling takes place is not suitable as vehicle for administration to patients and must be removed at the end of the tracer synthesis.

A review of the tracers described in the literature, as well as our own experiences, reveals that the production process for almost all ^{18}F-labeled tracers from [^{18}F]fluoride contains the elements shown in Fig. 1.

For convenience, we have used the process elements shown in Fig. 1 to list important factors that from our experience require careful considerations during the development of a standardized and efficient manufacturing process for [^{18}F]fluoride-labeled tracers. Moreover, some aspects of the constraints relating to pharmaceutical production are addressed in the context of regulatory compliance (GMP).

2.1. Step 1: [^{18}F]fluoride production

[^{18}F]fluoride for medicinal purposes is produced in a cyclotron by proton bombardment of [^{18}O]water. The cyclotron itself is a sophisticated piece of equipment housed in heavy shielded vaults as consequence of the high radiation produced during operation. While the details of cyclotron operation are not covered here, some of the important parameters that can influence the downstream chemistry are discussed below.

2.1.1. [^{18}O]Water

Suppliers of enriched [^{18}O]water are few, despite an increasing global demand as the current preferred production route for [^{18}F]fluoride is via the ^{18}O(p,n)^{18}F nuclear reaction [19]. Besides the requirement of being highly enriched, other quality aspects of the water are important for pharmaceutical production. Typically, a manufacturer delivers the [^{18}O]water product in a borosilicate glass container, together with a specification list covering different inorganic salts. These salts are within chosen specification limits [27] since trace metals and other impurities can potentially follow the [^{18}F]fluoride from the cyclotron to the reaction vessel and interfere with the radiolabeling process. These disruptive interactions have been suggested in many cases [19,20,28], although investigations have been rather scattered and not very systematic. Therefore, specification limits are mainly determined from assumptions rather than academic knowledge.

3. Cyclotron irradiation and targetry

The target chamber housing the [^{18}O]water during bombardment is composed of a metal that can withstand the high proton beam current and elevated temperatures during irradiation. There has been a continuous development of [^{18}O]water targets since the 1980s, and the choice of target material has shifted from nickel-plated copper to silver, and today, niobium and tantalum are the most common choices [29–33]. The target entrance foil has seen a similar evolution as the target development including materials like Ti, Ni, Ag, stainless steel, and Havar. Havar foil is today the most common material, although Havar sputtered with Niobium has recently been presented as an important improvement [34].

The area of [^{18}O]H_2O targetry still remains, however, a developing area despite all the major improvements. The proton beam irradiation is highly aggressive and causes erosion of the target surfaces, which therefore leak both radioactive and non-radioactive impurities into the target water [35–37]. Such impurities are known to have a deteriorating effect on the reactivity of the [^{18}F]fluoride [28,30]. As more knowledge is gained on the down-

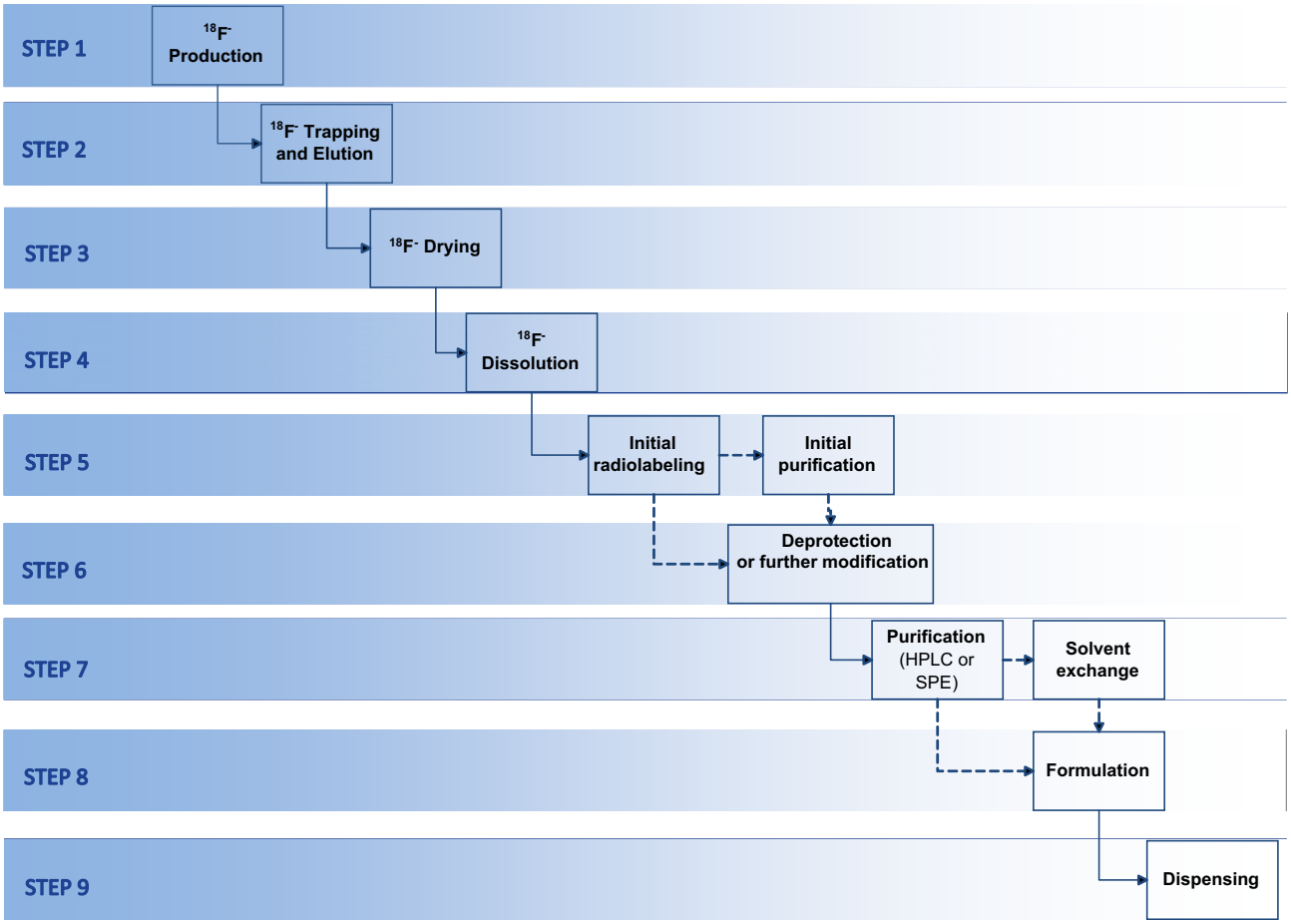

Fig. 1. Elements of [^{18}F]fluoride tracer production. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

stream impacts of targetry, foil materials, and age, it should be possible to narrow the specifications for these parameters resulting in more consistent radiochemical yields.

4. From cyclotron to synthesizer

After irradiation, the aqueous [^{18}F]fluoride solution is transferred from the cyclotron to the pharmaceutical production area. Typically, this is done by transfer through semi-permanent tubing kept under the floors of PET laboratory facilities. The aqueous solution of [^{18}F]fluoride is exposed to several meters of contact surfaces during this transfer. Type of tubing material, length, cleanliness, and age will vary for each PET center. The tubing is made of plastic materials like polyethylene or polypropylene or more chemically inert materials like PEEK and stainless steel. Teflon-based materials have been shown to be a source of carrier fluoride through radiolysis of the material and should be avoided especially where high specific activity of the [^{18}F]fluoride is a requisite [38].

Plastic materials can bleed components such as softeners commonly called leachables. These leachables can be detected by analytical methods and will only present a problem if they disturb the radiolabeling or end up in the final drug product in significant amounts.

Specifications for tubing material, replacement intervals, cleaning procedures, and flushing efficiency are routines that must be standardized across sites in the future. In our experience with radiolabeling of peptides in multiple PET facilities where presence of quantities of ^{19}F can give rise to non-radioactive impurities, we have seen that the presence of ^{19}F can be greatly reduced by the use of ethylenetetrafluoroethylene (ETFE, Tefzel) tubing and double-line washing with ^{16}O-water before use.

4.1. Step 2: [^{18}F]fluoride trapping and elution

After the transfer of irradiated water, it is ready to enter the synthesizer unit. Fluoride is highly hydrated in water and poorly reactive as a nucleophile; hence, careful removal of the ^{18}O-water and reconstitution of [^{18}F]fluoride in an organic solvent are required prior to the next reaction.

Customarily, the [^{18}F]fluoride is trapped on an anion exchange cartridge followed by elution with an inorganic anion dissolved in an organic–aqueous solution. While direct evaporation of the [^{18}O]water is also possible, the trap-elute step can potentially remove some target-derived impurities that otherwise would be carried through to the tracer synthesis. However, the solid phase used for the anion exchange can degrade over time, and although anion exchange capacity for the trace levels of [^{18}F]fluoride is not affected, other chemical impurities may be introduced [39]. While elution of the trapped [^{18}F]fluoride is readily achieved, the composition of the eluent containing the counterion must be prepared in such a manner that the subsequent steps have maximum efficiency.

The eluent volume should be high enough to recover the trapped radioactivity from the anion exchange cartridge but minimized to allow for as short a drying step as possible. Standardization of the process can be achieved by using a single or a few defined eluent compositions and a defined anion exchange cartridge of fixed dimensions. Where these are produced centrally to defined specifications and distributed to individual PET centers,

the shelf life of the eluent must be considered. The impact of degradation products and leachables from the eluent container has not been well studied. Typically, the eluent container is made of borosilicate glass in order to withstand organic solvents present. However, leachables from borosilicate glass like borates, silicates as well as aluminum can interfere with the reactivity of [^{18}F]fluoride [40]. Degradation of anion exchange material can also evolve during storage, and there is a potential for interactions between impurities generated in the eluent and from the anion exchange cartridge. While these impurities may be present at minute levels, even micromoles or lower levels of impurities will far exceed the [^{18}F]fluoride concentration. Radiolysis of these impurities at high levels of [^{18}F]fluoride may also be important, leading to differences in the labeling yields as the production scale is increased. Clearly, careful control of the eluent composition and understanding of the aging process are factors that may affect the robustness and effectiveness of the labeling step and highlight the importance of a well-defined and standardized process.

4.2. Step 3: [^{18}F]fluoride drying

The drying step intends to ensure water removal to a level where reproducible reactivity of [^{18}F]fluoride is obtained for the subsequent radiolabeling. Ideally, a drying step should be as swift as possible to minimize the decay of [^{18}F]fluoride. While vigorous heating may accelerate the drying process, too high temperatures can provoke uncontrolled splattering of the eluent. In our experience, splattered material may contain significant amounts of [^{18}F]fluoride which will be unavailable for radiolabeling. The design of the reaction vessel can be optimized to allow efficient and uniform heat transfer and reduce uncontrolled splattering during the evaporation step. Besides solvent volume, choice of phase-transfer catalyst and inorganic salt in the eluent also affects drying time.

A reproducible and robust drying step is a prerequisite for the success in the consecutive radiolabeling. Standardization of the drying chamber design, time, temperature, and pressure during the drying step are paramount for a consistent process.

Methods for omitting the drying step completely have also been investigated by Lemaire and co-workers. In their procedure, elution of the [^{18}F]fluoride was effected by using acetonitrile and an organic base containing trace amounts of water. The subsequent radiolabeling could then be performed directly in the presence of BTMG (2-tert-butyl-1,1,3,3-tetramethylguanidine) in high radiochemical yields [41].

4.3. Step 4: [^{18}F]fluoride dissolution

Typically, the [^{18}F]fluoride is dried in the presence of the anion and phase-transfer catalyst, commonly being carbonate with the associated counterion, tetrabutylammonium, or the potassium–kryptofix complex. As a consequence, the dried bulk of materials consist of minute amounts of [^{18}F]fluoride embedded in a paste of salt and organic material.

It is unlikely that the solid material in its dried state is homogenously distributed, and the rate at which each component dissolves in the organic solvent will vary. While the influence of the solvent in facilitating the radiolabeling reaction has been considered [42,43], the importance of the solvent in the physicochemical aspects of the process, such as phase equilibrium, solubility, mass transfers, and mixing, has not been well studied.

Material composition of the drying vessel may be important, as different contact surfaces will result in differing adsorption/adherence properties.

The reaction mixture is normally heated to secure an effective labeling reaction, but at the same time aids dissolution of solid materials. Magnetic stirring or turbulent gas flow may also aid dissolution.

4.4. Step 5: radiolabeling

The radiolabeling normally takes place under aprotic, but polar conditions. Solvents like acetonitrile and DMSO are commonly used. More recently, use of protic *tert*-alcohols as reaction medium has also been described by Kim et al. [43]. Choice of phase-transfer catalyst, inorganic salt, leaving group etc. are dependant on type of precursor and will therefore vary from reaction to reaction. There are, however, certain parameters that are more independent of the nature of the precursor. For instance, the influence of water during labeling has not been fully investigated. It is well known that high levels of water (due to inadequate drying) will render the [^{18}F]fluoride ion un-reactive due to the solvation shells. However, truly "naked" [^{18}F]fluoride is most likely never obtained. It has been speculated that for aromatic nucleophilic substitutions, high degree of dryness is needed, whereas for alkaline nucleophilic substitutions, less scrupulous dryness is tolerated [42].

It is likely that at a molecular level the water is not evenly distributed throughout the organic solvent but exists in the clusters of associated water molecules [44]. An understanding of the solvation shells and the association of the [^{18}F]fluoride with its counterion would contribute to a better understanding of the reaction picture.

The concentration of the precursor substrate is an important parameter for the reaction kinetics and overall yield. Sufficient amount of precursor should be used to ensure maximum incorporation of [^{18}F]fluoride in a short period of time. As the precursor is present in a larger excess compared with [^{18}F]fluoride, approximate pseudo-first order kinetics is expected, resulting in a more rapid incorporation of [^{18}F]fluoride than seen with normal stoichiometric one-to-one chemistry.

The precursor, obviously very reactive toward fluoride, will also be reactive to other nucleophiles generally present in much higher concentrations (carbonate, hydroxyl, leachables, and other anions) and can reduce the effective concentration available for reaction with [^{18}F]fluoride. Enough substrate should be used to account for this; however, the substrate itself is often expensive and removal of excess material and purification become increasingly challenging with a large excess of unmodified precursor or impurities. The pH of the radiolabeling reaction can have an impact on solubility and reactivity of the [^{18}F]fluoride as well as proton abstraction of the substrate. High local concentrations of water present in the reaction mixture can result in isolated pockets with large deviations in the pH.

Once the optimum reaction conditions are identified, parameters critical for reproducible results need to be worked on. Parameters where a small discrepancy can have a large impact on the reaction profile must be tightly controlled if the process is to run with consistent yields and purity from day to day and across multiple sites. A reproducible radiolabeling process is therefore more than just control of reaction time and temperature but is also very reliant on the processing of raw materials in the upstream processes, e.g., impurities, drying step, water content.

5. Initial purification

Proceeding directly to deprotection or purification may be feasible depending on the nature of the ^{18}F-labeled tracer. However, due to the complexities outlined above, a purification step is commonly adapted to remove major impurities. An intermediate purification step also gives the opportunity for a solvent exchange to remove the organic solvent and transition to a more pharmaceutically acceptable medium such as water or water–ethanol mixtures.

Impurities to be removed at this point can include phase-transfer catalyst, unreacted precursor, or related impurities. The rigor required for this step depends on the fate of any impurities in the downstream steps and whether they have any implications for the patient. A simple solid-phase extraction cartridge is often sufficient to remove major impurities at this stage. Successful purification and deprotection are reliant on the consistency in the upstream steps. A solid-phase extraction cartridge step is unlikely to give consistent results if significant changes in the mass of impurities or new impurities are introduced due to site-specific changes to the process.

5.1. Step 6: deprotection

Normally, a deprotection step is required before purification of the labeled tracer.

This step should be rapid and quantitative with respect to the [^{18}F]fluoride-containing material. Deprotection is typically a more straightforward and robust reaction than the radiolabeling step as the complications of multi-phase kinetics are no longer present and normally involve a base- or acid-catalyzed cleavage of the protective groups. However, many of the same constraints exist, e.g., potential for the degradation of reactants, need to optimize reaction conditions to maximize product yield and minimize related impurities.

5.2. Step 7: purification

Due to the complexity of the upstream process and the use of excess precursor relative to [^{18}F]fluoride, the ^{18}F-labeled tracer is present in a mixture of chemical species similar to the tracer itself.

For [^{18}F]FDG, these impurities are largely sugar related and acceptable in the final drug product; however, non-tracer-related impurities such as phase-transfer catalyst and residual solvent, in addition to any unreacted ^{18}F-fluoride, must be removed [45,46]. These impurities can be removed by solid-phase extraction (SPE) cartridge.

For other PET tracers, [^{18}F]FLT-related [47,48] substances are considered to present a safety concern and require removal. The related impurities are often structurally similar to the tracer itself and present in high chemical excess; thus, solid-phase extraction is not sufficient and a more tedious HPLC purification step is required. Especially for radiotracers targeting low mass receptors or saturable substrates, complete removal of related impurities is necessary to ensure effective specific activity and HPLC is so far the only solution. HPLC purification is a time-consuming process compared with SPE both in operation and in subsequent evaporation of organic solvents, resulting in reduced yields through radioactive decay. Significant volumes of radioactive waste are generated and skilled operators are needed to reliably isolate the desired product fraction eluted from the HPLC.

Moreover, each tracer requires specific HPLC conditions (column, solvents, flow). This means that a dedicated HPLC column may be needed for each tracer with consequent implications for the availability of multi-stream HPLC instruments.

In cases where two tracers can be purified using the same column type, it can be expected that use of a single column and associated fluid path for different products would be carefully scrutinized by pharmaceutical regulatory authorities. As a minimum, this must be subject to strict line clearance and validation to assure the absence of cross-contamination.

Clearly, single-use cartridges for SPE purification are desirable where possible for lower solvent volumes, simplicity in solvent exchange and avoiding sizable equipment. However, for both methods, a consistent and robust upstream process is critical for reliable purification.

5.3. Step 8: formulation

Once the ^{18}F-tracer is available in a medium suitable for intravenous administration, it must be formulated to its final composition. This can include

- A dilution step to adjust the radioactive concentration to the right level.
- pH adjustment and/or buffering.
- Addition of a radiostabilizer to prevent radiolysis.

The formulation should give a product that is suitable for clinical use and with a shelf life and a radioactive concentration allowing for distribution to off-site customers.

If several manufacturing sites will be included within a single regulatory authorization, it is critical that each site manufactures the product to the same final composition with regard to radioactive concentration at reference, pH, buffers, and radiostabilizers.

6. Factors influencing product stability: radiolysis

For radiopharmaceuticals in general, product shelf life is limited by the radioactive half life of the isotope used. For ^{18}F-labeled tracers, this is a matter of hours. However, radiolysis of the product can occur during the synthesis process even though the synthetic steps take only a few minutes. This is the time at which radioactive concentrations are at their highest. During purification, either by SPE cartridges or by HPLC, the product is concentrated in a narrow band on the solid phase making this a particularly vulnerable step for radiolysis. The degree of radiolysis of the labeled compound depends on the level of radioactivity, specific activity, the structure of the radiopharmaceutical, and the position of the radiolabel.

Radiolysis can be reduced to some extent by keeping the radioactive concentration (RAC) low. The bulk product delivered at the end of synthesis should be diluted as soon as possible to a higher volume. However, as the injection volume for a patient is a few ml, there is an upper limit to the dilution factor.

Dilution of the product may not be sufficient to control radiolysis. Therefore, addition of a radiostabilizer may be required. For radiopharmaceuticals, these usually take the form of radical scavengers. Examples include ascorbate, citrate, gentisic acid, and p-aminobenzoic acid and have all been reported as radiostabilizers in radiopharmaceuticals. For [^{18}F]FDG, ethanol has been shown to produce a radiostabilizing effect [49].

6.1. Step 9: dispensing

With few exceptions, ^{18}F-labeled radiopharmaceuticals are not terminally sterilized. Dispensing is therefore an aseptic operation and requires strict control of microbiological parameters.

The product from the end of the formulation step is transferred to the dispensing area, often an adjacent hot cell. Pharmaceutical regulations require a class A background for aseptic dispensing or a class C environment for dispensing through a 0.22-μm bacterial retentive filter in a closed system, which is the normal situation in most PET centers. A filter that is compatible with the specific product must be selected.

Also contact surfaces of the primary packaging, such as stoppers and glassware, should be selected to avoid leachables that may contaminate the product and absorbance of the product.

7. Regulatory compliance: GMP and ICH

Compliance with pharmaceutical guidelines for the production of [^{18}F]fluoride tracers is potentially more demanding than for

conventional pharmaceuticals due to the need to operate the multiple manufacturing sites required to give good geographical coverage. In USA, this problem has been recognized by the FDA, where GMP guidance specific for PET tracers is in place [50]. In Europe, radiopharmaceutical products are not exempt from the standard pharmaceutical regulations, but rather local agreements with national authorities may be made by the individual PET center.

Compliance with the regulations is facilitated by standardization of the production at each site as far as possible. In particular, standardization of equipment, reagents, consumables, and production parameters such as temperatures, times, and pressures is important. Where such standardization has been implemented, the operation can be compromised if any one of the standardized components is unavailable due to lack of availability from the selected supplier. This can be mitigated by active supplier management or maintaining high stock levels, but both strategies have a cost implication.

In addition to the GMP regulations, development of robust processes in line with the principles of ICH Q8, Pharmaceutical Development, facilitates rollout to multiple productions sites [22]. Specifications for a supply of consistent raw materials to sites can be linked to the known tolerances of standardized production equipment to establish a process that will always operate within a fixed design space.

Standardization of production equipment operating with predefined production parameters allows for elements of ICH Q9, Quality Risk Management, and ICH Q10, Pharmaceutical Quality System, to be addressed centrally and minimizes work that must be repeated at each site [51,52].

8. ^{18}F-tracer production: the future

As we have emphasized throughout this article, establishing consistency of manufacture across multiple production sites is a key requirement and success factor for new [^{18}F]-radiopharmaceuticals. This contributes significantly to patient safety as well as regulatory acceptance of the manufacturing strategy. This can be achieved by using pre-set process parameters that have been optimized during the development phase and standardized synthesizer equipment operating within a known design space.

However, it is our view that the process development of [^{18}F]-radiopharmaceuticals to date has been based on a largely empirical approach with insufficient understanding of the complex, multi-step, and multi-phase reactions. The [^{18}F]fluoride chemistry is not understood in sufficient depth to predict reactions and keep them consistent.

Further investigation into the fundamental [^{18}F]fluoride chemistry is necessary as there are several elements that are common to all ^{18}F-labeled tracers produced through nucleophilic substitution. Not least among these is the reactivity and dissolution of the [^{18}F]fluoride in the initial radiolabeling that is under strong influence of factors external to the fluoride ion itself. PET production involves large pieces of equipment like cyclotrons and handling routines that can contribute as a variable from site to site. As radiochemistry knowledge is built, standardization of ^{18}F irradiation processes would also benefit from a technology consensus. As shown in this review, side reactions and impurities generated by lack of understanding and control in the early steps in the synthesis of a [^{18}F]-radiopharmaceutical will carry through to the downstream steps and impact product quality and yield. Purification of the ^{18}F-labeled radiopharmaceutical after synthesis is often performed by HPLC, a time-consuming process that requires skilled operators, in addition to taking precious hot cell capacity. Solutions with solid-phase chemistry on small purification columns to replace HPLC have shown promise but have yet to be seen for routine production [53].

In summary, as processes become more standardized, we expect patient access to the benefits of PET to improve and molecular imaging to move toward its true potential. Improved understanding of [^{18}F]fluoride chemistry at its fundamental level will enhance the ability of those working in the field to develop robust and viable processes for new ^{18}F-radiopharmaceuticals that could lead to a revolutionary change in medical practice.

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