Translational approach to radiopharmaceutical development

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BIOMEDICAL IMAGING AND THERAPY FOR PERSONALIZED HEALTHCARE

RADIOPHARMACY: AN UPDATE

A TECHNOLOGIST'S GUIDE

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Foreword

Nuclear medicine, which encompasses the medical field of molecular imaging and radionuclide therapy, brings together many disciplines, and radiopharmacy requires that pharmacy, physics and medicine work together within a synergetic environment. It is undeniable that within nuclear medicine the baseline of any good procedure is the design and preparation of the radioactive pharmaceutical, referred to as the radiopharmaceutical.

After the introduction of a radiopharmaceutical into clinical practice, it is essential that the production and preparation of the radiopharmaceutical are done by highly qualified professionals, with a good theoretical background and highly developed practical skills. Within a multidisciplinary team, nuclear medicine technologists are professionals who are recognized for their competence in preparing radiopharmaceuticals and are also responsible for performing the control tests to determine the quality of the preparations.

The European Association of Nuclear Medicine (EANM) is a reference scientific body for the global nuclear medicine community. Taking this into account, in 2008 the EANM Technologist Committee (EANM-TC) made a joint effort to produce a book entitled The Radiopharmacy. This publication was intended to help professionals from different locations and professions to optimise their practice in radiopharmacy. Due to the rapid evolution of nuclear medicine and its associated procedures and practices in radiopharmacy, the EANM-TC reached the decision that it is time to revisit the topic of radiopharmacy and to produce an update to the previous edition of this guide.

Radiopharmacy: an Update is the outcome of the work of the EANM-TC in drawing together the expertise of many authors in order to produce a guide that addresses a variety of radiopharmacy-related topics, from the history and basic principles of radiopharmacy to the current generator- and cyclotron-produced radioisotopes, conventional nuclear medicine, PET and therapeutic radiopharmaceuticals. Additionally, good manufacturing practice (GMP), the translational approach to radiopharmaceutical production and radiation protection concerns in the design and workflow of a radiopharmacy are explored.

I would like to thank each of the authors of this book for lending their time to this project and for helping us to produce a guide that reflects their expertise. A special word of appreciation is due to the Translational Molecular Imaging and Therapy Committee for their contribution to this publication.

I would also like to express my gratitude to our colleagues from the Society of Nuclear Medicine and Molecular Imaging–Technologist Section (SNMMI-TS) for their contribution to the book.

In addition, I am very grateful for the work of the EANM-TC editorial group and to Rick Mills for his editing, reviewing and support throughout the entire process. Lastly, the EANM Board and the Executive Office deserve my words of appreciation for their support in ensuring the continuity of this project. Radiopharmacy: an Update would not have been possible without the contribution of all the above mentioned. Thank you very much!

Andrea Santos
Chair of the Technologist Committee

Introduction

In 2008, the EANM Technologist Committee published a Technologist's Guide entitled The Radiopharmacy. It is available online through the EANM website and covers topics relevant to daily radiopharmacy practice, such as design, preparation, dispensing and documentation. Since then, many radiopharmaceutical practices have changed, especially with the introduction of new radiotracers.

This year's Technologist's Guide includes the basics, starting from history of radiopharmaceuticals, and proceeds to the high-end radiopharmaceuticals used in translational medicine. Illustrations and tables have been included to facilitate the understanding of certain principles. The most widely used radiopharmaceuticals in SPECT and PET have been dealt with separately because of the breadth of development since the previous publication in 2008. This year's Technologist's Guide also covers radiopharmaceuticals used in therapy. Authors from different backgrounds have contributed to the Guide, ensuring that it will be an important addition to the knowledge base required to perform radiopharmacy. It is an unmissable collection of information that will prove an essential aid in the clinical setting and will keep the technologist up to date with the latest radiopharmacy principles and practices.

MarieClaire Attard
Main-Editor on behalf of the editors

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TRANSLATIONAL APPROACH TO RADIO-PHARMACEUTICAL DEVELOPMENT

by Latifa Rbah-Vidal, Pedro Fragoso Costa

INTRODUCTION

The translational process for radiopharmaceuticals (RPs), like that for conventional drugs, is a long and strenuous process. It starts with several steps of in vitro and in vivo preclinical testing research, which must be completed before clinical research can begin on an RP candidate. These evaluation and control steps aim to provide the necessary information for distribution and safety assessment permitting characterisation of potential adverse effects in humans.

Such preclinical experiments aim to demonstrate that the radiotracer:

- marks the targets and/or the mechanisms which it is designed to measure (specificity)
- shows a cell-killing effect in the case of a therapeutic RP
- shows suitable kinetics and metabolic stability
- does not display toxicity in healthy tissues and organs
- uptake is modulated by changes of target expression (sensitivity)

EVALUATION STEPS NEEDED FOR CLINICAL TRANSLATION

In vitro evaluation

Molecular targeting

One of the first aspects to take into account when developing a new imaging or therapeutic RP is the high uptake or tropism for the potential target site, and the need to prove that the RP specifically marks what it is designed to measure.

For radioligands (RPs which bind to receptors), the in vitro binding assay can be performed by incubating a fixed target concentration with increasing concentrations of the radiolabelled compounds. Bound radiolabelled tracer and free tracer are then separated by filtration and counted for radioactivity. Binding data can be analysed with curve-fitting software to calculate K_d (the ligand concentration that binds to half the receptor sites at equilibrium) and B_{max} (the maximum number of binding sites) to determine affinity.

Binding potential (BP) is the ratio of B_{max} (receptor density) to K_D (radioligand equilibrium dissociation constant), as defined by Mintun et al. [1]:

$$BP = \frac{B_{max}}{K_D} = \text{receptor density x affinity}$$

where B_{max} is the total density (concentration) of receptors in a sample of tissue, K_D is the (radioligand) equilibrium dissociation constant and the affinity of ligand binding is the inverse of K_D.

Targeting potential can also be assessed by cell uptake studies, performed by incubating the radiolabelled agent (e.g. antibody) with the cell expressing target (e.g. antigen).

Plasma protein binding

Like conventional drugs, RPs bind to plasma proteins to variable degrees. The estimation of plasma protein binding is one major determinant of the RP distribution in the body. This can be assessed by incubating the RP with fresh human plasma and performing measurements using several techniques such as dialysis, ultrafiltration and trichloroacetic acid (TCA) precipitation.

Metabolic stability

Another aspect to be considered in the preclinical development of an RP candidate is the metabolism. Metabolic stability can be assessed in vitro using human liver microsomes containing cytochrome P450 (CYP, a dominant group of metabolising enzymes) or other subcellular hepatic fractions which contain non-CYP enzymes (such as acetyl transferase or glucuronyl transferase) involved in drug metabolism. Hepatocytes and liver slices can also be used and are physiologically more relevant for measurement of the hepatic metabolism of RP.

Although in vitro and ex vivo experimental models can never accurately mimic the complexity of a whole organism, their simplicity allows procurement of initial information regarding the metabolism of the compound.

In vivo evaluation

Biodistribution studies

Although in vitro and cell uptake studies are extremely useful, in vivo animal studies are still required before RP candidates can progress from the stage of in vitro testing to the stage of toxicity assessment and, finally, first-in-human (FIH) studies.

In tissue biodistribution studies, the RP is injected into disease-bearing animals such as mice, rats or rabbits. All animal experiments have to be conducted in accordance with the European guidelines (2010/63/UE) [2] and have to be approved by the national or local animal use ethics committee.

This preclinical evaluation process often starts with imaging studies (PET or SPECT imaging) which can be coupled with autoradiography on tissue sections or ex vivo biodistribution studies, in which organs are harvested, weighed and counted for radioactivity following the injection of a radiotracer. All these methods are aimed at confirming that the RP interacts (in vivo or ex vivo) with the intended target (affinity) and shows minimal uptake in healthy tissues.

RP specificity for the target can also be

evaluated in vivo by imaging techniques using animal models expressing a modulation of target levels through under- or overexpression (such as tumour, overexpressed receptor). Note that, interestingly, RP uptake can be compared with that observed in "knock-out" mice which do not express the target of the RP.

Imaging is usually performed in the static or dynamic acquisition mode:

- **Static acquisition mode:** This is the basic acquisition mode, where the radiotracer distribution is assumed to be static throughout the acquisition. In this mode, a single image is generated representing the radiotracer distribution over the complete acquisition time. Acquired images are then processed by dedicated software for radioactive signal quantification. Usually, a semi-quantitative analysis is performed and the results are expressed in terms of the standardised uptake value (SUV), which is the ratio of the image-derived radioactivity concentration in a region of interest to the whole body concentration of the injected radioactivity and body weight, or the percentage of the injected radioactivity per gram of organ or tissue (%ID/g).
- **Dynamic acquisition mode:** In this acquisition mode, images are acquired according to a predefined temporal framing scheme (one acquisition interval). This mode is used when it is necessary to follow the uptake and clearance of an RP over an extended period. It provides more information on the kinetics of the RP by using absolute PET quantification and modelling. Indeed, pharmacokinetics (PK) parameters (clearance, volume of distribution, etc.) of the radiotracer can be evaluated from these biodistribution studies. The elimination half-life can be measured by collecting serial samples of blood at different time intervals after radiotracer administration and measuring the plasma radioactivity. Urinary and faecal excretion can also be determined quantitatively by collecting urine and faeces at defined intervals after RP administration and measuring radioactivity in the samples.

Even if PK evaluation in animals is still mandatory in the preclinical data package, estimation of PK in humans can also benefit from in vitro studies (e.g. regarding solubility, plasma stability) and bioanalytical methods and pharmacokinetic/pharmacodynamic (PK/PD) modelling.

Animal toxicity studies

Before an investigational RP can be administered to humans as part of an FIH trial, it must undergo safety testing in non-clinical studies [3]. RPs are a special class of drugs comprising two parts, one "cold" or non-radioactive (e.g. antibody, peptide) and one radioactive (e.g. fluorine-18, copper-64, gallium-68, iodine-131, actinium-225). Thus, the toxicity of RPs may be driven by the non-radioactive as well as the radioactive component. Considering the first version of the new guideline on non-clinical requirements for RPs [4], three schemes are possible:

- If the non-radioactive part of the RP is a known compound and if preclinical studies are available, then there is no need for additional toxicity studies if there is available information or data demonstrating that the radioactive atom does not change the pharmacology of the compound.
- If minimal modification of the structure of the non-radioactive compound has been performed (this is sometimes necessary for radiochemistry), then the possible risk related to that modification has to be considered.
- If the non-radioactive compound is unknown and no preclinical toxicity data are available, then full toxicity studies have to be performed and conducted under Good Laboratory Practice (GLP) regulations.

In general, it is recommended that toxicity tests are carried out in two different mammalian species (one rodent and one non-rodent) and that the risk of RP overdose is evaluated. This has in the past been achieved by injecting an acute dose of RP and monitoring animals for clinical signs and changes in parameters such as body weight and food intake, with subsequent post-mortem examination. Today, however, this approach has largely been replaced by so-called extended single-dose toxicity studies entailing assessment in only one mammalian species – usually a rodent with evaluation at day 1 and 14 days post dose administration to assess acute and delayed toxicity and/or recovery. Recently, a new approach (summarised in Table 1) has been proposed, based on the definition of three distinct toxicological limits [5]: toxicological limit 1 <1.5 µg, toxicological limit 2 <100 µg and toxicological limit 3 >100 µg.

Therapeutic RPs are regarded in every respect in the same way as any other medicinal product and therefore clinical

trials must comply with regulations regarding investigational medicinal products (IMPs). The mutagenic and carcinogenic potential of the non-radioactive component may be evaluated and studies should be designed to assess the radiation exposure of tissues due to the radioactive part, in order to predict the radioactive exposure in humans and to mitigate radiation-induced toxicity. Note that the radiation is a major contributor to cancer induction, so dosimetric considerations can cover the carcinogenic potential of the RP. Note also that radiation-induced clinical toxicity is covered by Directive 2013/59/Euratom [8].

Microdosing studies

The concept of microdosing assumes that key PK parameters of a new chemical entity (NCE) that is developed as a drug can be evaluated using very small doses (microdoses) of the investigational compound. Since such low doses are likely to be too small to have any pharmacodynamic effects or cause any major side effects after a single dose, it should be possible to undertake such studies in humans without having to perform the classical toxicology studies at therapeutically effective doses that are mandated prior to regular phase 1 trials.

This new approach, developed almost two decades ago [9], has been proposed as a powerful complementary tool to the existing approaches, and is often achievable with PET agents [10, 11]. The approach is known as human "microdosing studies" according to the European Medicines Agency (EMA) or as "exploratory clinical trials" according to the Food and Drug Administration (FDA). Both the EMA in 2004 [12] and the US FDA in 2006 [13] recognised the concept and its legitimacy with respect to the conduct of such studies. It is important to note that microdosing clinical studies are not meant to replace traditional phase 1 clinical trials.

The use of microdosing studies can be considered in the development process for RPs. In this case, very low single doses of the tested RP are administered to very few human subjects (healthy volunteers or patients) to investigate target receptor binding or tissue distribution in a PET study and/or to obtain basic PK parameters (such as volume of distribution, clearance and $t_{1/2}$) without the introduction of pharmacological effects.

According to the EMA, a microdose is defined as less than 1/100th of the dose calculated to yield a pharmacological effect of the test substance. This calculation is based on primary PD data obtained by in vitro and in vivo studies. Typically, the maximum dose must be less than 100 µg or 30 nMol [14]. The use of such a low amount of the RP means that human body exposure is limited, so no therapeutic, toxic or radiotoxic effects are expected.

To sum up, taking a RP from the bed to the bedside involves several steps in development, evaluation and control, entailing the participation of different disciplines, as illustrated in Figure 1.

GOOD MANUFACTURING PRACTICE (GMP) FOR RPS

Beside their efficacy for specific indications, RPs intended for use in humans should be sterile, pyrogen-free and safe. This implies that RP production should be transferred from the conventional laboratory to a GMP facility with a controlled environment, where manufacturing and quality control can be undertaken in a way compliant with the legal framework and regulatory procedures and in accordance with the principles of GMP for medicinal products [15].

GMP requires dedicated clean room facilities with the highest classification to ensure aseptic preparation of RPs. Preparation and quality control of RPs should be conducted only by competent and appropriately qualified personnel. The person responsible for preparation should be clearly identified and ideally should not be the same person as is responsible for quality control.

Production

In the clinic, RP synthesis requires much higher levels of radioactive materials, fast reaction times and reproducible results. Hence, it is mandatory to develop a straightforward GMP-compliant radiosynthesis using fully automated radiosynthesisers and including suitable procedures for quality control.

Quality control

All quality control procedures that are applied to non-radioactive drugs are applicable to RPs. Furthermore, since most RPs are short-lived products, the methods used for quality control should be fast and effective. Usually, tests must be completed before release of the drug product; however, some RPs with very short half-lives may have to be released and used after assessment of batch documentation even if all quality control tests have not been completed. The necessary steps in quality control are summarised in Table 2.

Additionally, GMP and the Clinical Trials Regulation impose the need for authorisation and require that a qualified person, according to Directive 2001/83, is responsible for the release of RPs.

Quality assurance

Furthermore, GMP implies the need for a highly sophisticated quality management framework where all the operations concerning production and manufacture

as well as quality control have to be documented and accurately recorded. Prior to clinical trials, standard operating procedures (SOP) for the preparation, quality control and quality assurance of RPs, as well as specifications for starting materials, should be in place. This ensures harmonisation of practice, traceability and maintenance of standards.

FIRST-IN-HUMAN IMAGING STUDIES

Before its use in FIH clinical trials, the RP has to be classified as an "investigational medicinal product" (IMP) and several mandatory documents, including an Investigator's Brochure (IB) and an Investigational Medicinal Product Dossier (IMPD), have to be prepared and submitted to the competent authorities and the ethics committee to obtain written approval. The IMPD should include all the useful information relating to the chemical and the RP quality of the compound, as well as non-clinical data relating to pharmacology, pharmacokinetics, toxicology and dosimetry [16].

Guidance on the preparation of IMPDs for RPs was published by the Radiopharmacy Committee of the EANM in 2014 [17]. Furthermore, a detailed study protocol has to be prepared in which every step of the protocol is documented. Acquisition of informed consent from the healthy volunteer or patient is also mandatory.

As RP imaging agents are usually employed at an extremely small mass dose (in the nanogram to microgram range) with no pharmacological effects, a very low incidence of adverse events and a short half-life, FIH studies aim to provide information on feasibility, target specificity, stability, safety biodistribution, pharmacokinetics and metabolism. Radiation dosimetry information regarding use of the RP in humans is also obtained to uncover any side effects.

The following are key aspects in the design of an FIH study:

- Study population: healthy volunteers and/or patients can be enrolled in one or multiple cohorts
- Demographic information from each subject (weight, body surface, age, gender etc.)
- Test RP and reference radiotracers (e.g. test compared with ^{18}F-FDG), or a standard of reference (histology or radiological imaging)
- Administered dose: usually, a single dose is administered via the intravenous route
- Choice of imaging parameters (scan duration, acquisition mode, number of scans per subject) for biodistribution and dosimetry
- Blood/urine sampling intervals for pharmacokinetic study
- Safety profile

FIH study design for diagnostic radiotracers is quite straightforward compared with interventional drug FIH clinical trials, where, for instance, healthy volunteers or patients receive a single dose of the investigational drug or a placebo, starting with a very low dose for the first cohort. Thereafter, the dose is escalated in the following cohorts (or stopped depending on the tolerability and safety). Single ascending dose studies are usually followed by multiple ascending dose studies in a very similar design, where the subjects receive multiple doses of the drug (or placebo).

FIH trials should be designed in a way that permits optimal results from the study, without exposing excessive numbers of subjects and while ensuring their safety. Thus, the EMA advises that it is usually appropriate to design the administration of the first dose so that a single subject receives a single dose of the active IMP, with justification of the period of observation before the next subject receives a dose. This is in order to mitigate the risks associated with exposing all subjects in the same cohort simultaneously [18].

In contrast to imaging studies, the FIH design of interventional drug studies takes into consideration the pharmacological effect of the drug, so the starting dose, maximum dose and exposure and maximum duration of treatment are carefully considered. Also, beside the route and frequency of administrations, the half-time and washout time of the IMP are determined, as are the sequence and interval between dosing of subjects within the same cohort. In the case of dose escalation increments, decisions on transition to the next dose increment cohort or next study part (if the FIH study includes several parts) must take into account tolerability and safety; moreover, stopping rules and the safety parameters that require monitoring have to be clearly established. Note that even if FIH clinical trials are primarily designed to assess the safety and tolerability of an interventional drug, the PK and, when appropriate and feasible, the PD are often included in order to facilitate the link with the non-clinical data and support dose escalation decisions. For both radiotracers and interventional drugs, the study design should take into consideration all the acquired preclinical knowledge, incorporating all available toxicology and pharmacology information on the compound candidate to ensure the safety of the subjects.

Compounds under <1.5 µg	Compounds under <100 µg		Compounds above 100 µg
One can consider that there is no risk (no genotoxic impurity related risk if <2 mg [5, 6]).	The microdosing approach can be considered [7]. In this case, two different approaches are possible:		Potential chemical toxicity studies have to be performed, including extended single dose toxicity studies [18] in rodent and non-rodent species in addition to genotoxicity assessment (Ames). Given that RPs are not usually administered to pregnant women, there is no need for teratogenicity studies. As RPs are given as low doses (exposure is limited to a single dose or a few doses), there is no need for either genotoxicity or carcinogenicity studies. Chronic toxicity studies are also usually not necessary.
	Approach 1: Would involve not more than a total dose of 100 µg, more than 1/100th of the non-observed adverse effect level (NOAEL) or more than 1/100th of the pharmacologically active dose. Toxicology studies consist in extended single-dose toxicity studies in one species, usually a rodent, with evaluation 14 days post dose to assess delayed toxicity and/or recovery. Genotoxicity studies are not recommended. For highly radioactive compounds such as PET probes, appropriate PK and dosimetry should be performed.	**Approach 2:** Consists in a maximum of 5 administrations with washout periods (>6 half-lives), with a total cumulative dose of <500 µg and with each administration <1/100th of the NOAEL and <1/100th of the pharmacologically active dose. Toxicology studies consist in a 7-day repeated dose toxicity study in one species, usually a rodent, and genotoxicity studies are not recommended. For highly radioactive compounds such as PET probes, appropriate PK and dosimetry should be performed.	

Table 1: *Possible approaches for toxicity evaluation depending on the mass of the compound*

Parameter	Evaluation methods/ objectives
Appearance	Evaluated by visual inspection: the solution must be clear and free from visible particles.
pH	pH is verified using paper strips. Initially, the pH paper should be validated against standard buffers and should be in the physiologically acceptable range (5.5–8).
Chemical purity	The purity of the precursor is determined by proton NMR and elemental analysis. This test is done once per batch of precursor.
Radiochemical purity/ yield	Radiochemical purity is assessed by HPLC and radio-TLC.
Radiochemical stability	Radiochemical stability is often tested in serum and saline using HPLC with a radioactivity detector or TLC and a radioactivity scanner (radio-TLC).
Radionuclide purity	Radionuclide purity can be determined by gamma spectrometry or by determination of the half-life.
Residual solvents (e.g. acetonitrile and dehydrated alcohol)	Presence of residual solvents is evaluated by gas chromatography.
Microbiology	Bacterial endotoxins: the limulus amoebocyte lysate test is the most popular.
Sterility	Sterility testing must be initiated after several hours of preparation. To assure sterility, each batch of product has to be tested using culture vials with aerobic and anaerobic materials and incubated with culture vials for at least 4 days at 37°C. Sterility is assayed by visualising the cloudiness of the solution.

Table 2: *The necessary steps in quality control for PRs used in the clinic*

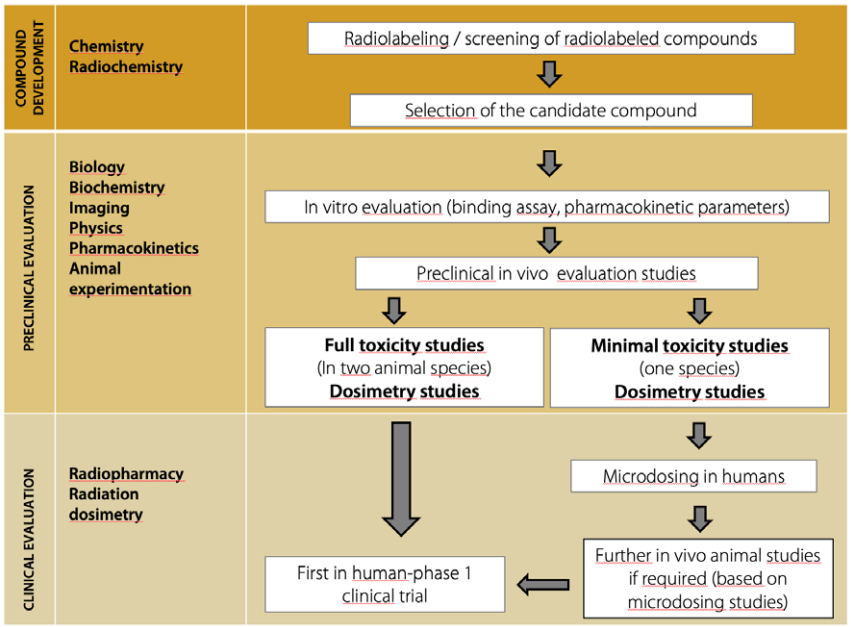

Figure 1: *Schematic of the RP evaluation steps needed for clinical translation*

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