

Industrial Constraints in the Selection of Radionuclides and the Development of New Radiopharmaceuticals

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Abstract

During the past twenty years, the number of new radiolabeled molecules that have been published weekly in specialized nuclear medicine journals is quite amazing. On the other hand, one can only be astonished when it is compared to the number of new radiopharmaceuticals that came on the market during the same period. A good science is not sufficient to transform a molecule in a marketed drug. The budget required to demonstrate with a larger number of patients the value of the molecule linked to a limited market potential discourages investors to enter in this area. In fact, there are a series of other limitations and constraints that have to be taken into account before deciding to start clinical trials. This paper tries to identify all the difficulties that are encountered by radiopharmaceutical industries. They include the choice of the best but not necessary ideal radionuclide, the analysis of the market viability in the frame of the overall competition, the increasing safety constraints when working with multi-doses, the investment in usually non existing manufacturing tools for a worldwide access to the new drug, as well as the limiting regulatory aspects with yearly increasing constraints. Unfortunately it must be noted that each of these criteria is mainly driven by financial parameters and an expectation of a certain return on investment. This analysis can help research centers to better control and orient their programs and to explain the reasons of the lack of interest by industry for some even a priori interesting molecules, targets, radionuclides or indications.

Key words: radiopharmaceutical drug development, budget, industrial constraints, radionuclide selection.

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Introduction

Following the recent evolution of the imaging equipment, nuclear medicine starts now to be perceived as a unique tool for the functional analysis of in vivo human biological processes. Both PET (Positron Emission Tomography) and SPECT (Single Photon Emission Computed Tomography) technologies have reached a high level of development in terms of image quality while becoming available at a much larger extend. At the same time new PET radiopharmaceuticals are used at different places although FDG (F-18 Fludeoxyglucose) remains the only PET drug with official marketing authorization. More and more convincing data show that diagnostic radiopharmaceuticals will become also the best tools for the detection, the follow up and the therapy outcome prognosis in oncology and neurology. In therapy, metabolic radiotherapeutics could become ideal substitutes to chemotherapy in late stage cancer treatment and the most recent results published with Y-90 labeled Rituximab (1) are the best examples to illustrate this potential new orientation for therapeutic applications. Eventually, combining prognosis evaluation with radiopharmaceutical imaging tools to select positive responders for chemotherapy or radiotherapy becomes the first example of personalized medicine applications. It is clear that selection of patients before therapy will become standard in a near future, not only for oncology, but also for neurodegenerative and cardiovascular diseases, leaving to Nuclear Medicine a very important role next to CT (X-ray Computed Tomography) and MRI (Magnetic Resonance Imaging) (2).

In terms of manufacturing capacities, the industry is now mature to provide almost all common SPECT and PET radionuclides, maybe with the exception of Iodine-123, at a worldwide level. The network of PET manufacturing centers is spreading in the US, Europe and Australia and new industrial centers start being built in some larger Asian countries, the rest of North America and some countries of South America, the Maghreb and South Africa. There is no doubt that within the next five years probably all of the major countries will have access to fluorine 18. The access to associated drugs is progressing as well, while the access to PET drugs is of course following the increase in distribution of new PET cameras, themselves linked to the creation of PET manufacturing centers.

There is also a new gain of interest in nuclear medicine among physicians following two major changes introduced at the beginning of this century, i.e. the invention of the PET/CT technology that brought more interest to radiologists but also surgeons and oncologists, and the marketing of the first labeled radioimmunotherapeutics based on monoclonal antibodies labeled with either Y-90 or I-131 and used in the treatment of non-Hodgkin lymphoma. No doubt that further interest will be triggered as soon as these drugs demonstrate their efficacy when used in first line, replacing chemotherapy, which is without doubt predictable within the next three years. The introduction of the PET/MRI technology will for sure bring another group of experts becoming interested in nuclear medicine.

On the other hand there are hundreds of laboratories worldwide who became interested in radiolabeling, first to support classical pharmaceutical industries, but later becoming fully aware that these first developed molecules as pharmacological tools could have a second life as real imaging drugs. Unfortunately the work done so far was published in high level scientific journals and these molecules have only little chance to come on the market one day, due to lack of intellectual property.

Ideal new drug entity profile

Everybody is aware that before bringing any new drug on the market, the molecule must grow through a sequence of different steps that goes from chemical development, pharmacological profiling and toxicology studies up to the three levels of clinical trials leading to the set of information that is required to fill the NDA (New Drug Application) necessary to obtain the marketing authorization. Experts of radiopharmaceuticals know that some steps of this process can sometime be considerably reduced, some of these steps even merged in one or simply omitted. Compared to classical drugs, development of radiopharmaceuticals is supposed to be faster and much less expensive than classical drugs.

In the real world it appears that only a very limited number of new radiopharmaceutical drugs were brought to the market in the past twenty years. This is mainly due to the increasing constraints put by regulations on drug development in general and the low limited interest of big pharmaceutical companies to this specialty as a consequence of the limited market potential. In the future one can predict that only average size companies will continue to be interested in these drugs, limiting also the chances of bringing new drugs on the market.

Development of nuclear medicine is fully depending on the development and marketing of new drugs. Thousands of radiolabeled molecules, some of them with real good profiles, have been described in the literature in the past twenty years and scientists or physicians wonder why none of them have been taken by industry for further development and eventually being marketed.

In fact the answer is purely economical. Industry follows other rules than scientists to select the drug supposed to be marketed, and on the contrary to researchers who are more concentrating on the scientific and technical aspect of the product, industry starts analyzing any drug or concept by the very end of the process, i.e. the marketing potential and the industrial feasibility next to the increasing regulatory constraints (3).

Market analysis

A defined drug corresponds to a defined market which itself is linked to a single or rarely two indications. The potential market is analyzed in terms of number of doses to be sold, i.e. number of patients per indication, acceptance of this new drug by the medical community, accessibility of these patients to this drug, potential reimbursement. This analysis is not so easy and it must be performed country per country as the access to our specific technology is limited by the equipment and the local investments. This analysis must take in account the competition with other drugs or modality at the time of launch. Obtaining this part of the information is rather difficult as it is quite impossible to know at the time of start of a project which competitors are working in the same area, which one does have the same clinical target in mind and which is the development stage that already was reached for that potential competitive drug. For diagnostic drugs the risk vs. benefit must be analyzed when compared to other potential imaging technologies including computed tomography, magnetic resonance imaging, ultrasound and even non marketed technologies such as near infrared imaging. Diagnostic drugs must also be evaluated in comparison with in vitro tests based on urine or blood surrogate marker analysis. These in vitro methods will always be less expensive than any imaging modality. For therapy, the evolution of competitive cold drugs, but also surgery, external radiotherapy or any other new technique must be taken in account, which means well known at the beginning of the project and continuously surveyed during the progression of the project.

Finally about 8 to 10 years before launch, a dose price must be estimated. This price multiplied by the number of potential patients in the area where the drug can be reasonably sold gives a potential market value per year that becomes the basis of the overall evaluation of the drug.

In the pharmaceutical industry, it is usually assumed that a project can become profitable when the total money spent for its development, corresponds roughly to one year of peak sales. Nunn (4) made an interesting analysis of the cost of development of an imaging drug, but this evaluation was based on the rare data available at that time as no good example of a good pipeline for radiopharmaceuticals could be given as example. To us it seems possible to develop a new diagnostic drug for less than 50M€ and a therapeutic drug for about less than twice that amount. With these

figures that will be explained below, everybody will easily be able to calculate either the minimum number of doses to be sold for a single indication if the dose price is fixed or the minimum price per dose if the number of patients is limited. For example if only 10,000 "realistic" patients per year have been identified for a diagnostic drug, the drug would have to be sold at a 5,000€ per dose, a high figure which is obviously sufficient to kill the whole project before starting. The present sale's prices of FDG or sestamibi will be used in the future as reference for respectively PET and SPECT. Obviously, a higher price will be allowed for proprietary new chemical entities (NCE), but more than doubling or tripling their respective sale's values would render competitive projects questionable, unless it corresponds to a unique need. On the other hand the marketing of a complex immuno-radiotherapy molecule such as a labeled antibody could be justified by a price above 5,000€ per dose and as a result the program would be launched if a minimum of 20,000 realistic patients per year could be identified.

It has been claimed for a long time that the orphan drug status could be a good solution for developing radiopharmaceuticals. In fact this is true only in very rare cases in which the number of patients is very low. This limits even more the interest of industries for these specific drugs as this status does not bring advantages in terms of reduction of development costs. As a consequence this drug would become available only for very high prices, limiting even more the acceptance. The orphan drug status has however an advantage in nuclear medicine, as it gives a ten year protection that could help bringing on the market non proprietary drugs.

However, as there are so many gaps to fill and unmet needs in this area, industry is not specifically targeting a disease or a specialty. Competition between radiopharmaceutical companies is presently limited to the indications with big potential such as neurodegenerative diseases or the development of some cardiology imaging agent. In oncology the number of possibilities is such high that for the time being companies will orient their own development efforts in area where there is only limited overlapping risk with others company programs.

Proprietary aspect

The limited intellectual property coverage of new compounds is probably the major reason why the ratio of new marketed drugs to described molecules is so low. A few thousands fluorinated drugs are described in the literature and even interesting clinical data have been published recently, but probably the number of molecules from this list that will reach the market at an industrial scale can be counted with the fingers of one single hand. Today FDG is the only drug with a market authorization, but not even available in all countries, and it must be considered as a generic, with in some cases a high competition at local

levels. Industry is not ready to repeat the FDG experience in a near future at the same scale and prefers concentrating on patent protected NCEs. Developing a patented drug is as expensive as developing a non-proprietary drug. The risk to have the non protected drug sold in parallel by a competitor is such high that no serious industry will invest in their development. Of course FLT, F-DOPA or F-Choline are produced at local levels. But these drugs do not have marketing authorizations and will remain available with some price and quantity constraints. These molecules are used on the basis of compassionate use, in the frame of a clinical trial or under the sole responsibility of the local physicians. FDG is an exception and will remain probably the only drug of its kind. We must however be glad that FDG exists and that some companies took the risk to file a dossier for this diagnostic agent. FDG helped to create the network of manufacturing cyclotrons with distribution authorization and demonstrated the economic interest of the PET business. This existing network will become the basis network for the future PET proprietary drugs. Without this initial move and investment, development of the PET technology would have been restricted to the configuration of one cyclotron associated to one camera, as a consequence of the difficulties for hospitals to fulfill regulatory requirements.

Future NCEs must definitely be patent protected and radiochemists who are inventing these molecules must clearly decide upfront if they want to have this drug to the market or if they want to provide this information immediately to the scientific community. By publishing first they condemn the labeled drug to remain a pharmacological tool. From now on, radiopharmaceuticals that have a chance to come to the market will all have to be patented first. As industry is always trying to be safe in terms of potential competition, it is highly recommended that the initial patent is as broad as possible, including a larger number of radionuclides and indications and covering the largest area as possible. Geographically limited patent applications do not have interest as well.

Competition

We already addressed this issue several times which shows the importance of this topic. Although the number of industries specialized in nuclear medicine is rather limited, it remains in fact well correlated with the size of the market. As the market is constantly growing and will grow probably much faster in the next 10 years than in the past 50 years, newcomers, start-ups, spin-offs, will definitely appear on the market. These very small companies will rely first on a single drug, but eventually develop in multi-drug companies if not acquired in the meantime by larger ones. In both cases one has to consider that they have succeeded for both scientific and economic reasons. These small companies are already existing but still hidden. Knowing their existence and the drugs they are developing is of

<i>Number of molecules</i>	Preclinical phase (Proof of Concept)	Toxicology	Clinical phase I/II	Clinical phase III
Estimated chances of success	10-15%	20-25%	15-20%	25-33%
Number of molecules (°)	400-1,300	60-130	15-26	3-4
<i>Required budget (K€)</i>				
Cost per step	250-350	600-800	2,500-3,500	40,000-60,000
Overall budget per step	100-325,000	36-104,000	38-91,000	120-240,000

Table 1. Estimation of the minimum number of molecules and the budget necessary stepwise to assure one drug on the market (classical "cold" drug development)

This table gives the average estimated percentage of success to reach the next step from which is deduced the minimum number of molecules required to have at least one reaching the market. A therapeutic for oncology was taken as example.

(°) These figures represent the number of molecules that have to go through this test to obtain the minimum number of molecules required in the following step

utmost importance in this competitive environment. It does not make sense to start a development program if one is aware that another company, even a small one, is already targeting this indication with a realistic concept. This is another good reason to refuse developing analog drugs. Today there is not yet space in the radiopharmaceutical industry to develop so called "me-too's", i.e. analog drugs that could compete in the same area, or even "me-too plus", analogs with a slight marketing advantage. This will come in 20 years when all areas of nuclear medicine will be covered by efficient molecules.

Eventually it is important to analyze the competition at time to market and not today, which is one of the most difficult information to extrapolate.

Scientific aspect

Surprisingly science has only little importance when deciding to develop a new drug. Of course it makes sense to identify the mechanism of action of the drug, to have some knowledge about the pharmacology, the metabolism, the excretion processes, but as we are dealing with an imaging agent, even in the case of therapeutics, most of the information about the distribution of the drug will be obtained in real time. Therefore the images created with a set of animals or better, the first human distribution images do have much more value than any in vitro or in vivo model data. In the worst (or best) case, one does not even need animal data. If the first human image is not good, the drug has no utility. For radiopharmaceuticals, animal data are required only to help selecting the best drug candidate, to improve the distribution profile and to determine the level of toxicity. But even by multiplying these tests, one will never have enough data that can certify that the drug behaves the same and is as little toxic in human. Preclinical programs can be very limited and a large amount of preclinical data will not give better chances to a drug to come on the market. In the worst case a simple veterinary imaging agent could be developed.

Chances of success for cold drugs

The start of the development of a drug is far from being a guarantee of success. One has to count with failure and drop outs at all stages of the development and these molecules will have to be replaced. For a same indication, several drugs will need to be developed in parallel to guarantee that one reaches the market. Is it possible to estimate the minimum number of molecules one has to develop in parallel to be sure that at least one reaches the market? Let us try to estimate this number.

Some hypotheses need to be introduced. If one limits the discussion to diagnostics, it is now well accepted to consider that the development of radiopharmaceuticals is highly accelerated, compared to classical drugs, due to the possibilities of imaging the target tissues (5). Also there is almost no difference in terms of development time and costs between PET and SPECT drugs. A slight complexity is introduced if using ligands instead of basing labeling on covalent chemistry.

For radiotherapeutics, their development can be highly facilitated if the same vector can be labeled with an imaging radionuclide based on the same chemistry, by using pairs of equivalent isotopes. As a consequence development of pairs of diagnostic/therapeutic labeled drug can result in up to ten fold the reduction of development costs when compared to classical drugs.

From the experience we have from classical drug development (Table 1), one estimates that only 10 to 15% of the molecules that have shown some interesting in vitro profile pass the in vivo preclinical phase demonstrating the proof of concept. Almost three quarters of these molecules are eliminated during the toxicology studies, while the first clinical trials of phase I and II leaves only 20% alive. Finally, only one out of 3 or 4 molecules succeed the large phase III trials. By doing the calculation in the reverse way one can easily calculate that one needs 15 to 25 molecules entering clinical trials to have the adequate 3 or 4 candidates for phase III, which in return requires 60 to 130 molecules

<i>Number of molecules</i>	Preclinical phase (Proof of Concept)	Toxicology	Clinical phase I/II	Clinical phase III
<i>Diagnosis (Neurology or oncology)</i>				
Estimated chances of success	40%	80%	33%	80%
Number of molecules (*)	12	5	4	1
<i>Therapy (oncology)</i>				
Estimated chances of success	33%	80%	33% (†)	50%(†)
Number of molecules (*)	24	8	6	2

Table 2: Estimation of the minimum number of molecules stepwise necessary to assure one diagnostic or one therapeutic radiopharmaceutical drug on the market

(*) These figures represent the number of molecules that have to go through this test to obtain the minimum number of molecules required in the following step

(†) If developed in parallel with a radiodiagnostic drug

before toxicology studies and 400 to 1,300 molecules coming out of the in vitro research. In other words, one needs between 400 and 1,300 molecules out of the first in vitro tests to have one drug succeeding on the market. It is possible with this figure to estimate the cost of development of this single final drug. The proof of concept step can be estimated at 250 to 350 K€, the toxicology studies at 600 to 800 K€, the first clinical phases at 2,500 to 3,500 K€ while the most expensive clinical phase III will cost around 40 to 60 M€ per molecule. These figures have to be multiplied by the number of candidates per step to obtain the overall cost per step. Some one-shot other costs such as regulatory affairs of 900 K€ (only for the first area, Europe or USA) have to be added as well. Regulatory affairs is considered as successful in all case, but in reality there are about one molecule out of 5 or 10 that does not pass this hurdle. A constant research baseline expense of one million per year during ten years is taken in consideration as well. By adding all these figures one comes to a total of M€ 306 to 772. This represents the overall cost of development of a single classical drug. This is very close to the figures provided by the industry and also provided by Nunn (Nunn reports extremes between \$150M and \$1,700M depending on the source). In fact industry is performing this calculation in another way: they invest in average 12 to 20% of their yearly income in Research and Development. If one divides this figure by the number of Marketing authorization they get in average (or the number of NCE's reaching the market), one will also find a figure in the range of 600 to 900 M€ per product for large companies and something like 300 to 500 M€ for smaller ones. The difference can be explained by the targeted markets and indications, but it is obvious that not all small companies are targeting niche indications and probably large companies are wasting some money. The overall costs of the structure are proportional to the size of the company and small spin-offs with little budget can be as successful as larger companies.

Of course in the meantime more than a thousand molecule candidates were lost as inadequate. A lucky company that

would bet on a single molecule out of these 1,300 and bring it successfully through all the steps until marketing, would need only 46M€ to reach its target (figure obtained by adding the costs of each step only once). One easily understands that this kind of development makes sense if the targeted market reaches the same level of magnitude.

Chances of success for radiopharmaceuticals

The situation is completely different for radiopharmaceuticals (Table 2). Proof of concept in animal is easily demonstrated by imaging procedures. Only half of the molecules will drop out. The radiopharmaceuticals are not toxic, or at least the molecules are used at such a low dose that the toxicity of the vector will never been reached while the real radio-toxicity is known from the beginning and for a given radionuclide provides the limitation in use for humans. So, it can be estimate that only as little as 20% of the selected molecules would be eliminated, following the toxicology studies. The first injection in human is crucial and gives the real value of the drug. If the molecule is not enough specific or sensitive, the drug must be rejected. The chances to pass this test are estimated at about one third. But once they have succeeded in phase I/II, the little experience we have so far shows that phase III is usually only a confirmation of the potential of the drug and has a very high level of success. Drop outs come from the discovery of side-effects when used at a larger scale, and remain seldom. Again, because of the advantage to read images and the absence of placebo effect, the number of patients to be screened can remain limited (depending on the indication, between 200 and 500).By doing the same calculation as above, one finds out that one needs about a dozen molecules at the proof of concept level to bring at least one diagnostic drug on the market.

For radiotherapeutics, efficacy of the treatment has to be demonstrated, which is not obvious when only relying on images. However as these images show that the drug is really concentrating on its target, the chances of success

<i>Number of molecules</i>	Preclinical phase (Proof of Concept)	Toxicology	Clinical phase I/II	Clinical phase III
<i>Diagnosis (Neurology or oncology)</i>				
Estimated cost per step	250-300	400-500	1,000-2,000	6,000-10,000
Overall budget per step (ĉ)	3,000-3,600	2,000-2,500	4,000-8,000	6,000-10,000
<i>Therapy (oncology - non MAb based)</i>				
Estimated cost per step	250-300	400-600	1,500-2,500	10,000-18,000
Overall budget per step (ĉ)	6,000-7,200	3,200-4,800	9,000-15,000	20,000-36,000

Table 3. Estimation of the budget stepwise necessary to assure a minimum of one diagnostic or therapeutic radiopharmaceutical drug on the market

(ĉ) Figure obtained by multiplying the cost per step by the minimum number of molecules to be developed in this stage

remain pretty high. It can be estimated that only half of the molecules may not be efficient, a figure slightly higher than for the classical drugs above. For one therapeutic drug on the market, approximately two dozen of molecules will be needed at the beginning of the development program. This seem quite easy, but one should never forget that the result of a project development is also highly depending on the skills of the experts in defining the most adequate indication for which the drug can be used, based on pre-clinical data, the skill also of physicians and statisticians to determine the profile and eventually the number of patients that have to be enrolled.

Lower budget for radiopharmaceuticals

Each step could also be considered as being less expensive, but in fact the highest savings can be done during the phase III trial that will need only a few hundred of patients, reducing considerably the overall costs of development. Estimated figures are provided in Table 3 in which one shows that for individual steps, costs for the preclinical step is not really different and toxicology study costs are only smaller because one expects to rely on existing data from the equivalent pharmaceutical vector (e.g. only the radionuclide substitutes the cold isotope). If one is developing a completely new entity (e.g. a known vector linked to a metal by a chelating group that had to be grafted to the original molecule), the whole toxicology program has to be repeated and costs the same as for a new cold pharmaceutical. The reduced number of patients needed in the clinical trials has a direct impact on their costs, even higher for phase III. The higher cost for a therapeutic drug is not linked to a higher number of patients but to the very long follow up and observation period, as data on morbidity and mortality are usually needed to prove efficacy.

As above let us take on top of the figures from Table 3 a baseline budget of 500K€ for formulation and manufacturing which does not include equipment as well as a same amount of 900K€ for Regulatory Affairs including fees for the first area. Regulatory affairs is considered as

successful in all case, however sometimes with a huge impact on delays and hence on overall budget. Research baseline prior to Proof of Concept can be counted on the basis of a permanent yearly budget of 0.500K€ over a period of 10 years, which represents 5 M€ in total. The total development costs for a radiodiagnostic agent would be in the best case, i.e. if 100% success is reached for each step about 8M€. Radiotherapeutics would give about 14M€. Of course this situation never happens. The real world corresponds to the sum of all figures from the bottom line of the table for each step resulting in an estimated development cost of 22 to 30 M€ for radiodiagnostics and 44-69M€ for radiotherapeutics. The difference with classical pharmaceuticals is quite significant.

Budget difference compared to cold drugs

Our figures still remain below the ones provided by Nunn. There are several major explanations.

The principal is that some overheads have been taken in account but in fact all these calculations are based on an existing identified vector. No mechanism of action has to be demonstrated, no fundamental biology work has to be performed, no pharmacological tools have to be developed, while all chemistry is based on existing one. While all this fundamental work is usually paid by industry for cold drugs, nuclear medicine industry is relying on prepaid research data. This preclinical work was and still is supported by government, NCI, European funds and some of them by private funds supporting spin-off. To remain in adequacy with real figures, one should include all the amounts of money lost by all the small companies that are failing in this area, like stated by Nunn as well.

In terms of overall budget, this amount will then be indirectly taken in account by the radiopharmaceutical industries in form of higher royalties paid to the inventor or inventing companies. As a result, it will not have a direct impact on the cost of development but reduce the expected profit of the industry. Royalties or any other non direct reimbursement of research budget deduced from profits

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one the drug is on the market are of course not taken in account in these calculation.

The huge figure given by classical drug developers includes also all investment in the manufacturing tool, as well as pre-marketing and pre-launch budgets.

Limitation in manufacturing tools

Unfortunately all our figures have also to be completed by the investment in the manufacturing tool. When a drug like aspirin can be produced at a single site for a worldwide market, the half life of the radionuclide will decide the number of manufacturing centers to be implemented. In this respect it is of course much easier to manufacture I-124 labeled drugs that will probably only need 3 or 4 centers worldwide than F-18 labeled drugs that can be distributed at only three to five hours transportation distance around centers.

Some believe that the existing network of cyclotrons will facilitate the introduction of new fluorinated drugs. They too quickly forget that the existing centers have been built with a unique target of producing FDG, some of them having also a research aim and that the demand is continuously growing. Most of these centers will be saturated with FDG request when the new drugs will come on the market. They will need to be upgraded, if this is possible, and in the worst case a second site will have to be built in the same area only for the new drugs. In both cases investments will be needed to cover an area equivalent to the one covered presently by FDG. As such a center costs between 3 and 5M€ (see recent publications of Bruno Krug)(6), depending on the quality of the equipment and the investment in the building that is needed, I let you do the calculation of the overall investment that will be required if one tries to adapt only one manufacturing center per state, just to get a full coverage of the United States. Of course if one thinks that the drug will just be used as an add-on to FDG with a couple of doses per day per center, then all this investment is not required. But does it make sense then to develop a new drug?

Therefore if one wants to use realistic figures for radiopharmaceuticals and compare to cold drugs, one must include the manufacturing tool investments and will probably have to multiply by two the figures given in tables 2 and 3. An exact figure can therefore not be provided as it is directly depending from the radionuclide involved in the NCE and the level of development of the existing manufacturing tool.

Radionuclide selection

The choice of the ideal radionuclide remains the most difficult part in selecting the best molecule for development of a new radiopharmaceutical. Vectors, even really complicated ones such as long peptides or antibodies, never play a big role. They usually derive from drugs that are

already in development and most of their properties, in particularly toxic effects, are known. However, labeling an efficient drug has never created a good radiopharmaceutical. Distribution constraints, in particular background noise levels, are completely different for radiopharmaceuticals. Radio-pharmacists must target specificity which is not so important in therapeutic drugs when details of the real distribution of the drug do not play a big role. Once labeled molecule behavior can be surprising. Fortunately the first image in animal gives enough information to help decision on the development of the drug. The importance of the proof of concept study, through the set of images that shows that the drug is specific for a certain cell, tissue or organ, remains the most crucial.

On the contrary, choosing the best radionuclide for a defined target is not so obvious. The type of radiation, the half life, the energy, but also the chemistry, are all important parameters. The choice is multiple and specific criteria must be defined. On top of this, industry puts a new constraint that is usually ignored, i.e. the availability at an industrial scale of the radionuclide.

Very recently J.F. Chatal (7) published a survey organized in the frame of the new 70MeV cyclotron project Arronax in Nantes, France. European scientists were asked to propose or select their best choice of radionuclides. This survey was supposed to set priorities among radionuclides Arronax could produce. The conclusion was reported in a graph that shows that the ten most interesting radionuclides ranked as first or second follow the priority sequence 124I, 68Ga, 86Y, 67Cu, 64Cu, 82Rb, 211At, 213Bi, 52Fe and 89Zr. It is understood that this list includes only the radionuclides not available at the time of the survey. Obviously 99mTc, 90Y or all the common iodine radioisotopes are not to be on this list, but are 166Ho or 177Lu already considered as common radionuclides? In the meantime 124I and 89Zr became commercially available at least in certain areas.

The relevance of these results is questionable, and it must first be considered as a nice wish list from pure scientists. It is a list of potential opportunities for the year 2020 and beyond. Unfortunately it cannot be used by manufacturers as a reference lists for today. Selection criteria cannot only be based on physico-chemical properties. Manufacturers do have a lot of other constraints.

Industry's radionuclide selection criteria

The ideal radionuclide for radiopharmaceuticals does not exist. Industry's radionuclide selection criteria must take in account all the physico-chemical properties of the radionuclides, but also their precursors and daughter products. The type of radiation does not play a big role. It will simply define the imaging tool that will have to be used. In therapy there will be a big need for explanation to push the first alpha-emitter labeled drug through the authority hurdles, but if all guarantees in terms of safety are given there is no reason why it should be more difficult to get

authorizations than for high energy gamma emitters. Half life brings the first complication, as it affects the manufacturing conditions, the transport and the waste control. Injected radionuclides are usually in the range of two hours to two weeks half life. This is not a limitation, but more to be considered as a practical range. Below two hours, it becomes much too difficult to synthesize larger amounts of labeled drugs and to distribute several doses. ^{11}C labeled drugs will remain local drugs without worldwide manufacturing authorization. Industries might become interested if the manufacturing of these molecules could be done in a close automatic system with high yields and short synthesis times. The marketing authorization would then describe a complete kit including the equipment. Only customers with access to a cyclotron would benefit from this technology, resulting in a very limited market. The higher limit of two weeks is more conditioned by the increase of storage limit, in particular at hospitals. So it becomes more a recommendation than a rule.

On the other hand there is an upper limitation in half life for parent radionuclides. In the manufacturing process, one cannot produce drugs based on radionuclide decay products from parents having a half life higher than 30 years. This is supposed to minimize the risk of contamination of the final product with longer half life radioactive substances. ^{90}Y is the perfect example of an interesting therapeutic radionuclide that is the decay product of ^{90}Sr , with 28.8 years half life.

It must also be demonstrated that the final injectable drug does not contain impurities, by-products or decay products with a half life higher than 100 days. This is also more to avoid hospital waste tanks to be contaminated by long half life impurities. Luckily the 211,000 years half life of ^{99}Tc , the decay product of $^{99\text{m}}\text{Tc}$, is not relevant for this general rule. So there are some accepted exceptions.

The energy is of course really important as it has serious impact on the manufacturing conditions. Of course the energy level has an impact on the shielding at the hospital, but this issue is multiplied by a factor 100 to 1,000 when handling these radionuclides at an industrial level. Some radionuclides have such a high energy that the limitation in handling capacity limits also the maximum doses to be produced in parallel and eventually has an impact on the large scale feasibility, the manufacturing price becoming much too high.

Finally each radionuclide has its own chemistry, and the labeling process results in yields and specific activities that directly affect manufacturing costs.

Manufacturing tools and equipment

The way of producing the radionuclide (separation, generator or irradiation) (8), the access to parent radionuclide and the purification process as well as the quality of the final product affect also the overall cost of the drug. Among all those criteria, the most important remains

the overall availability (9). Developing new fluorinated drugs did not make sense ten years ago, if expecting a large distribution potential. Now, as the density of cyclotrons is much higher and continues to grow, new fluorinated drugs become really attractive in terms of profitability. An analogue situation can be considered for ^{68}Ga . Although this radionuclide is easily obtained from a $^{68}\text{Ge}/^{68}\text{Ga}$ generator, this tool is offered today only by a couple of companies and only a limited number of non-GMP manufactured generators can be manufactured and sold presently. It is impossible to build a realistic business plan to show profitability of a ^{68}Ga labeled compound if the construction of a generator manufacturing unit is not integrated, which investment would kill the project. However, with about three gallium labeled drugs on the market, such a plant begins making sense. So ^{68}Ga labeled drugs will be developed if investment in a large scale gallium generator is done while industry will invest in such a plant if there is a guarantee that there will be a market, i.e. three gallium drugs with marketing authorization. In fact the gallium labeled products will come on the market at about the same speed fluorine made it through. However the existence of the PET cameras network will facilitate this implementation compared to the history of FDG.

^{64}Cu presents a similar situation. In fact introducing such a new metal in drugs must present an advantage otherwise either $^{99\text{m}}\text{Tc}$ or ^{111}In would be sufficient, if one considers only non covalent binding metals. Developing ^{64}Cu labeled drugs makes real sense if the analogue ^{67}Cu labeled drug can also be developed, forming with the same vector a pair of diagnostic/therapeutic drugs. As described above, pairs of radionuclides can transform an isolated diagnostic drug project in something more realistic in terms of profitability if associated with the equivalent therapeutic drug. Unfortunately, at the present time there is no real solution to produce large industrial amounts of ^{67}Cu . No good large scale manufacturing solution exists for ^{211}At or ^{213}Bi either.

In summary, the selection of radionuclides that can today be used in the development of new drugs to come on the market by 2015-2020 is limited to the ones that have an already existing or already under construction network of manufacturing tools. For SPECT drugs this limits the radionuclides to $^{99\text{m}}\text{Tc}$ and ^{123}I , for PET drugs to ^{18}F and ^{124}I and for therapy to ^{131}I and ^{90}Y . Within the next ten years there is a good chance that manufacturing issues will be solved for ^{68}Ga and ^{211}At and one hopes that a way to produce ^{67}Cu in large quantities will be discovered, opening the road to ^{64}Cu labeled drugs. There is also some realistic expectations for ^{188}Re , ^{166}Ho , ^{177}Lu and ^{86}Y might go through during this period, but all other radionuclides are definitely to be considered available at larger scale only beyond 2020.

This statement must not discourage researchers to continue working on radionuclides not listed above. This fundamental work is the only guarantee for the future development of nuclear medicine.

Beside economics and radionuclide selection, industry is

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also confronted with technical issues related to quality of the final product. Most of them can be solved by different levels of investments and it was demonstrated with the existing marketed products that even constraining situations in terms of sterility classes, radioprotection or capacities have always been solved. The radiopharmaceutical industry is now mature and fully compliant with the regulatory aspects through the application of the Good Manufacturing Processes, like any other pharmaceutical industry.

Finally, even knowing that the development of radiopharmaceuticals is rather difficult and that there will remain limitations, there are good reasons to hope for a bright future for nuclear medicine. In October 2007, a first agreement between a national health authority (Great Britain) and a pharmaceutical company (Johnson & Johnson) was signed. This agreement defines the level of reimbursement of a myeloma therapy cold drug (bortezomib). However this same agreement constrains the pharmaceutical company to reimburse the government for each patient in which the drug is not efficient. Efficiency is evaluated on the basis of the tumor size decrease two months following the start of the procedure. Apparently this type of agreement will become more common in the near future, leading first to the development of tools for the evaluation of the progression of the disease after beginning of the treatment. Very probably, pharmaceutical companies will very soon prefer to select their patients rather than reimbursing. Nuclear medicine is ideally placed, if not the only modality to both help selecting the future positive responders to a therapy and to check efficacy of the treatment using functional imaging procedure. This becomes the very beginning of personalized medicine in which nuclear medicine will have a major role to play.

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