

Radiopharmaceuticals, Drug Development and Pharmaceutical Regulations in Europe

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Abstract: Radiopharmaceuticals have a long tradition of clinical and research applications. Current legislation of developed Countries includes these compounds in the regulatory environment of medicinal products. Products used under a marketing authorisation license and investigational radiopharmaceuticals are then part of the clinical practice and scientific programs. Positron Emission Tomography has induced a strong increase in the number of potentially available radiopharmaceuticals and, beside being a breakthrough in diagnostic nuclear medicine, has demonstrated its value as research tool. Drug Development Research is searching new tools for reducing attrition and increasing efficiency in the identification and development of new medicines. Molecular Imaging, PET in particular seems to have important answers to this demand. The regulatory environment in Europe is hence revised in the perspective of utilisation of nuclear molecular imaging as a supporting tool for DDR. Relevant documents from European regulatory Agency (EMA) as well as their essential impact on radiopharmaceuticals have been summarised and discussed.

Keywords: Radiopharmaceuticals, drug legislation, positron emission tomography.

INTRODUCTION

The earliest process of drug discovery was strongly relying on physiology. Drugs were tested on the basis of their ability to reverse symptoms in disease models. The weakness of this approach was mostly related to the difficulties in adopting models fully representative of the disease and to limitation in their screening

This track unfortunately has not proved as efficient as expected while costs have become remarkably higher [2]; reintroduction of physiology has been felt as a possible strategy to reverse the situation and add to the system more efficiency and efficacy. However, how and when should this new issue be introduced into a well-settled track, Fig. (1) such as that developed in years with full agreement and

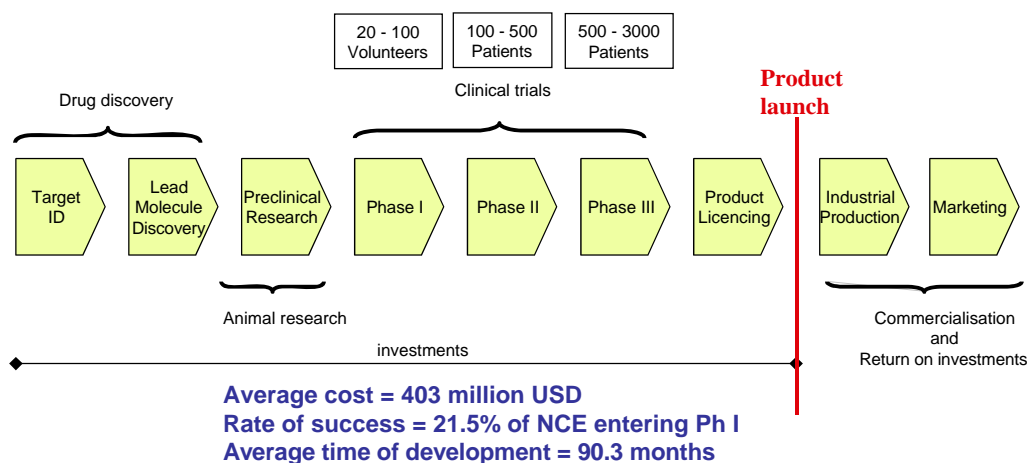


Fig. (1). Typical drug discovery and development pipeline. Statistical data were taken from Reference [2].

capacity. These sources of poor satisfaction have merged with the strong development of knowledge in biochemistry. This new wave of research and perspectives has led pharmaceutical research to move further into aspects of molecular mechanisms and switched attention of drug developers to target-based approach [1].

Target identification, rationale drug design, specific interaction and high-throughput approaches became common terms and an effort started to produce larger number of molecules and high-throughput screening tests. A wealth of research has been devoted to unravel Structure Activity Relationships (SARs) and to the adoption of computer simulation to make projective evaluations. In silico research and systems biology have sprouted from this area as new disciplines.

understanding between regulators and drug researchers, and which tool should be selected to reduce attrition (and costs) that are afflicting the Drug Development Research (DDR) process?

About 75% of costs result associated with early phase failures [3] and more than 35% killing rate of new medicines is linked to inappropriate pharmacokinetics detected during Phase I, i.e. moving from preclinical into humans.

The intimate link between some imaging modalities and the underlying biological-physiological-pathophysiological mechanisms suggested that this might be a suitable solution to make a robust step forward in getting higher efficiency from the conventional paradigm of drug discovery and development and be a new perspective that might interfere positively with the pipeline of drug development.

Although the first use of imaging in DDR was radiological monitoring of tumor masses (Response Evaluation Criteria In Solid Tumors, RECIST) to account for response to therapy, major

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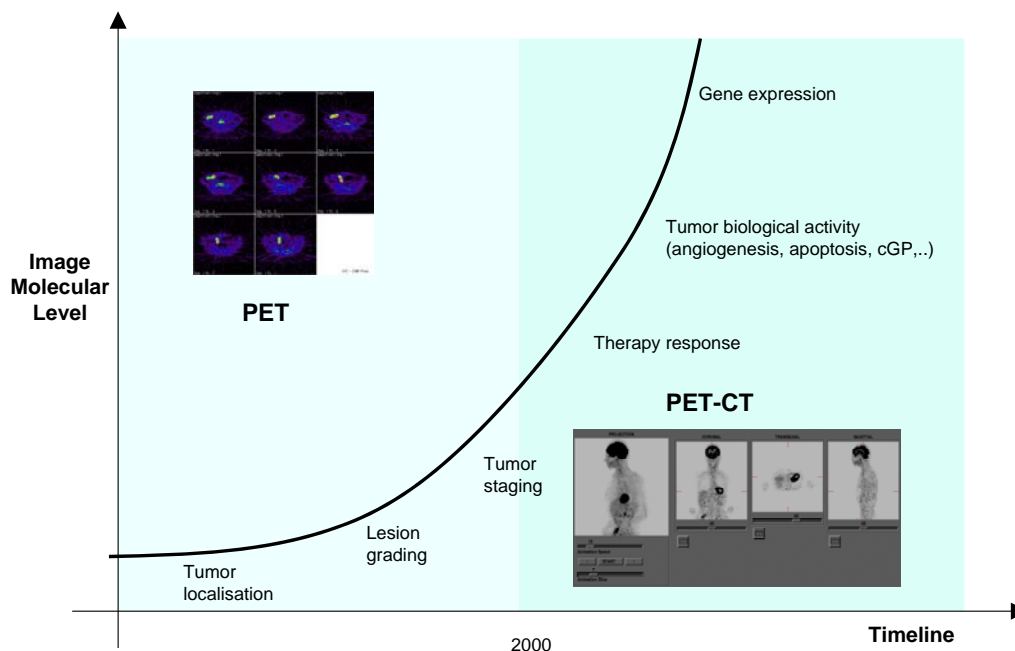


Fig. (2). Effect of technological/methodological improvements on capacity to explore molecular mechanisms expressed by PET imaging.

expectations are from Molecular Imaging (MI) [4]. This is strictly related to the ability demonstrated by molecular imaging modalities of providing *in vivo* measurements of a wide range of parameters such as biochemical processes further to anatomical variations and changes in physiology.

Positron Emission Tomography (PET) and associated radiotracer production have had a bright and intense technological and methodological development that has moved this imaging modality deeper and deeper into the molecular level, Fig. (2). Now, PET and Single Photon Emission Tomography (SPET) are considered at the leading edge of MI. In fact, the sound link between PET and SPET tracers and *in vivo* biochemistry has emerged from more than thirty years of scientific papers. During the last decade, a massive number of publications on the clinical use of PET as a diagnostic and therapy control tool in oncology has crossed the boundaries of Nuclear Medicine Departments.

A step forward has been the transition to PET/CT: this “hybrid” modality jointly produces anatomical, functional and molecular images. The advantage of getting all this information *in vivo* in intact subjects (non invasively) is well evident. Moreover, dynamic imaging studies can easily be performed. The addition of the time scale to imaging (4D images) moves up the complexity of the study, in particular with moving organs, and amount and size of data sets, but may be considered as the enabling factor towards *in vivo* pharmacokinetics. Due to these reasons, MI represents the latest promising tool in DDR.

It is far evident that radiopharmaceuticals are the bottleneck of the entire process and that their nature, quality and availability directly influence and regulate the ability to hit the target. Radiopharmaceuticals may have a twofold application in DDR: they can be used as reporter probes to monitor pharmacodynamic activity or pharmacologic profile of a candidate drug or, by direct labelling of the active principle, to determine its biodistribution and pharmacokinetics, Fig. (3).

Almost all of these applications can be performed in conditions of very high specific activity so that no macroscopic effect linked to product chemical toxicity or pharmacological effect is detected in the

subject. However some preparations, e.g. ^{99m}Tc -labelled macroaggregates or colloids, may not be considered void of any possible effect, and serious adverse reaction have occurred also among radiopharmaceuticals. As a matter of fact they are considered medicinal products and their production and use comply with specific laws.

RADIOPHARMACEUTICALS AS DRUGS

For quite a long time, radiopharmaceuticals have been exempted, together with other exclusive products -such as allergenes, vaccines and blood-derived products- from adopted pharmaceutical regulations. Applicable rules were on radiation protection and compliance to Pharmacopoeial monographs. As of 1992, European Pharmacopoeia had more than 30 monographs covering the majority of routinely used radiopharmaceuticals. Directive 89/343/EC extended the existing rules of medicinal products to radiopharmaceuticals compounds used as diagnostic or therapeutic agents (radiometabolic therapy). In particular, this Directive mentioned cold kits used to prepare Tc-labelled radiopharmaceuticals and Mo-Tc generators. This Directive was due for implementation by EU Member States in two years. The immediate consequence was the need to file a registration of radiopharmaceutical products, about 50, that have been on the market for more than twenty years. This posed no minor problems: on one side many industries involved did not have experience to manage the full registration dossier, on the other side running all expected protocols, including preclinical and clinical trials would require years. An abridged procedure was then accepted by regulators: a single file of pharmacological, toxicological and clinical support using available data or published literature was judged as appropriate. A Summary of product characteristics (SmPC) elaborated on the basis of a template issued by the top EC pharmaceutical committee (CPMP), was to be used by manufacturers as the basis of individual product pack leaflets. Data strictly linked to the production, such as part II: chemistry and pharmaceutical, containers and labelling were to be prepared by any single applicant.

Difficulties were immediately evident in applying standard regulations to radioactive compounds, many of them with remarkably

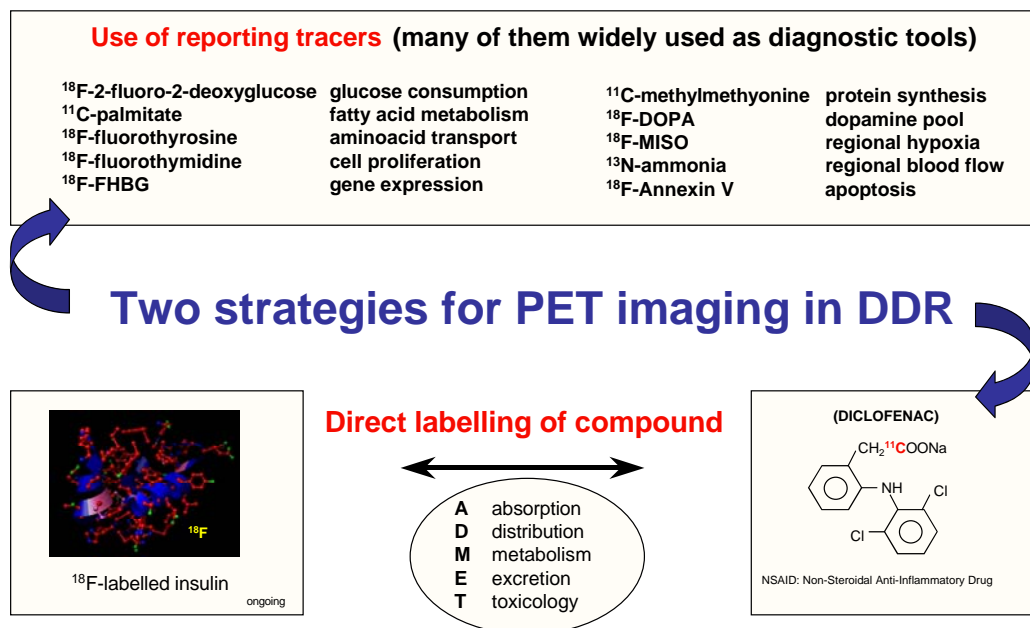


Fig. (3). Strategies for the use of PET imaging in Drug Development and Research.

short half-life. Similar difficulties were experienced by the various national reviewers in adopting common assessment standards, in particular dealing with what was for several a completely new subject area. On top of this, the peculiar nature of this kind of a medicinal product -e.g. limited number of items per batch, the need of multiple batches per week- made it very difficult to align what was due to what was possible. Not to mention the endless discussion between applicant and regulators concerning what to define as *strength* in a short-lived diagnostic agent. Some 15 years later the situation has not really changed, and many of the historical products have remained to be registered.

The dimension of nuclear medicine as compared to other diagnostics market, and the unpredictable direction of industrial strategies have led to the reduction of the number of radiopharmaceuticals and the clustering of manufacturers.

Positron Emission Tomography has appeared as a light-house in this landscape, bringing new impulse to research first, and gaining clinical value later on; most of the work has been done with one radiopharmaceutical, i.e. [¹⁸F]-2-fluoro-2-deoxyglucose (FDG), mentoring the clinicians community and the pharmaceutical researchers around the secrets of molecular medicine.

Since the 1989 Directive, nothing has been really done to clarify the situation of radiopharmaceuticals. From certain point of view, things have worsened because pharmaceutical regulations have been always kept as unique code, mostly focused on conventional medicinal products, and regulators have been reluctant to adopt separate regulations for special situations such as that of radiopharmaceuticals.

To make the issue even more complicated, the role of EMEA cannot be compared to that, for instance, of the equivalent Authority in US: FDA. European directives need to be adopted (implemented) by single Member States and this usually happens with the possibility of introducing changes and with different timeframes [5]. Although this fragmentation can be avoided for Marketing Authorisation (MA) applications, the situation is quite complex for clinical trials where researchers have to refer and apply to their national Competent

Authority. The evolution of the regulations has introduced tighter rules; latest Directives have extended GMP to R&D medicinal products and non-profit and academic research. Recently, AIPES has made a lobbying effort to draw attention of regulators on a simplification of registration procedures for radiopharmaceuticals or, even better, on adopting a separate regulation [6].

QUALITY IN RADIOPHARMACEUTICAL

The core legislation on the rules applying to studies on the development of new medicinal products (Investigational Medicinal Products, IMPs) and the conduct of clinical trials refers to:

- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (Official Journal L 121, 1/5/2001 p. 34 - 44);
- Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (Official Journal L 311, 28/11/2001 p. 67 - 128).

Directive 2001/83/EC has been amended by other Directives, such as 2002/98/EC for regulating medicines based on human blood and derivatives, and 2004/24/EC on special issues on Herbal Medicines. Directive 2003/63/EC directly dealt with radiopharmaceuticals and in particular introduced a revised version of the Annex I (Analytical, Pharmacotoxicological and Clinical and Protocols in respect of testing of Medicinal Products) aiming at giving more precise indications and instructions on the marketing applications. In particular, Part III on "Particular Medicinal Products" contains a chapter dedicated to "Radiopharmaceuticals and Precursors" [7].

The structure of the dossier to be presented for a MA is then well delineated even though some further detail on SmPC is added by Directive 2004/27/EC (SmPC of radiopharmaceuticals should include

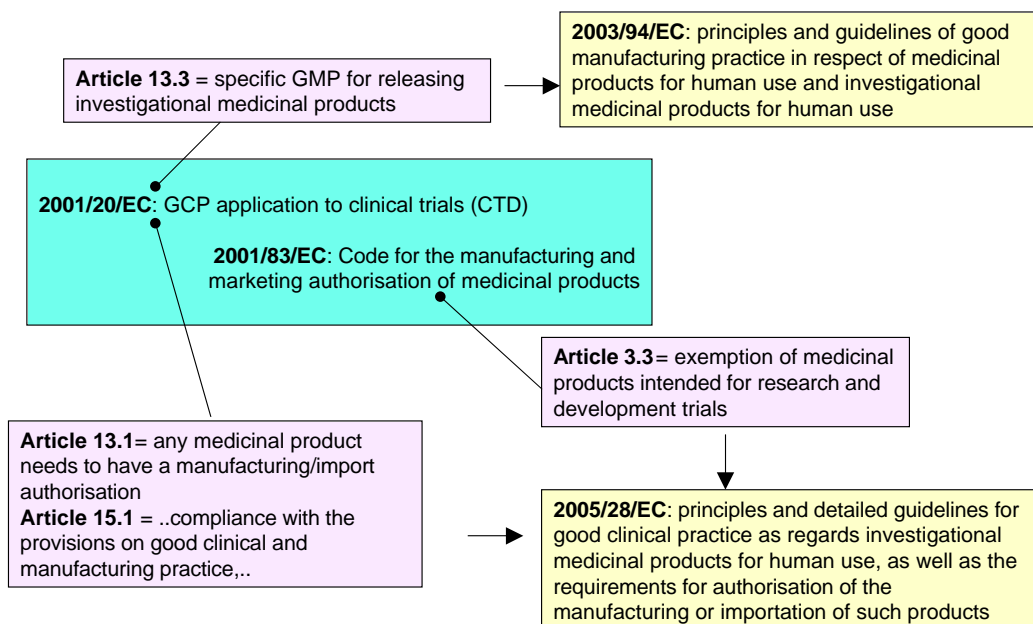


Fig. (4). Synoptic view of cross-references between issues on quality in Good Clinical Practice and specific regulations on medicinal products.

data on internal dosimetry and detailed instruction on extemporaneous preparation, quality control and shelf-life/expiration of ready for use products). This addition was meant to fully justify the exemption from MA for reconstitution of radiopharmaceutical cold kits and generator elution operation when both have received a MA. Although the 1992 abridged procedure of registration still has to be completed, the scenario for licensed radiopharmaceuticals is clear enough, and new radiopharmaceuticals have been licensed by both national and centralised procedures. FDG is one of the latest radiopharmaceutical products having received approval. However, the application of full GMP to manufacturing sites and authorisation application using official Dossier structure to such a short-lived product were not straightforward.

Quite a different situation is being faced by products lacking a MA. Directive 2001/20/EC defines in a strict way the necessity of applying GMP to the manufacturing of drugs used in clinical trials and IMPs. This last point has been addressed under practical principles and guidelines by Directive 2003/94/EC [8].

However, R&D products were still outside the obligations of GMP: they were exempted by full GMP application under provisions of article 3.3 of Directive 2001/83/EC. Therefore some conflict could be found between this last Directive and provisions of Clinical Trial Directive 2001/20/EC. Moreover, the revision of some annexes to the GMP EU Guide [9] included also radiopharmaceuticals, under Annex 3, and even though applying to MA track, the statement existed that, due to the increasingly application of short-lived radionuclides for PET in investigational and clinical use, production of radiopharmaceuticals in PET Centres, Nuclear Centres, Institutes or industrial manufacture should be covered by above-mentioned Annex 3.

Directive 2005/28/EC [10] has then covered this gap, by laying down the minimal requirements for and management of authorisations to manufacture or import investigational medicinal products, as well as for the granting and the content of the authorisations, in order to guarantee the quality of the investigational medicinal product used in the clinical trial. The situation in Europe is such that Member States have authority on clinical trial approval: therefore it will be extremely important how directive 2005/28/EC will be implemented and translated into national regulations with regards to homogeneity of requirements and obligations. Although

any clinical trial has to receive approval by the Ethical Committee and the National Competent Authority, they might operate with some different references.

This situation is going beyond radiopharmaceuticals and in general affects small-scale preparations used for research such as spontaneous, academic, no-profit programs that, at least in principle, should be run under full GCP. As a consequence of actual legislation, the investigational product(s) should be prepared under official EU GMP standards and this would have an extreme impact on premises and organisation. Serious concern on the future of this kind of research was expressed by many interested parties, mostly from Academia and Scientific Associations [5].

Applicable rules to radiopharmaceuticals are still quite vague and the response to the problem remains variable from Country to Country in Europe. Some Countries (e.g. Italy) have recently issued GMP guides for hospital pharmacies and, as a separate issue, on Good Practice for radiopharmaceutical preparation in Nuclear Medicine. Some others (e.g. UK) have adopted detailed guidance on radiopharmaceuticals and radiopharmacies since a long time; some other Countries have fair or unexisting specific regulation. In this situation, the possibility to conduct multicentric clinical trials with radiopharmaceuticals is of major concern.

A recent opening in the scenario is coming from the world of drug research: on both sides of the Atlantic a common understanding of the possible benefits introduced by MI into the DDR process has motivated the Regulatory Bodies of FDA and EMEA to issue documents providing official positions and guideline (FDA [11]) or announcing such a guideline (EMA [12]) on the use of microdosing concept in DDR. In this regard, it is interesting that, in the context of Positron Emission Tomography, if the study requires the measurement of both total and displaceable binding, the "single dose" may be divided into two separate infusions given within the estimated (chemical) half-life of the labelled ligand.

The impact of this guidelines in the field of DDR has still to be understood [13] nevertheless, some simplification effect might be expected on guidelines covering Radiopharmaceuticals [14] and Diagnostic Agents [15] and, possibly, on the regulation concerning high specific-activity short-lived radiopharmaceuticals. As a matter of fact the relevant EMEA document on Radiopharmaceuticals [16] and

Diagnostic Agents [17] (DAs) should be revised soon. It is worth of notice that EMEA considers DAs in direct conjunction with the equipment and procedures that are needed to assess the (clinical) test results, i.e. taking into consideration the technological development/improvement. A further reason for revision is the possibility that "radio-diagnostics" might be considered in a separate section from contrast media and other diagnostic agents (e.g. ^{13}C -urea for *helicobacter pylori* detection falls within DAs).

PERSPECTIVE

In the perspective of DDR, PET may extend its range of use from Phase 0 evaluation of pharmacokinetics and biodistribution/bioavailability, to the measurement of Proof-of-Concept, in particular wherever a direct connection between PoC and *in vivo* performance (e.g. receptor affinity/occupancy and target treatment endpoints) can be sought. This might also cover additional relevant issues, that have been addressed in EMEA documents concerning First-In-Man (FIM) trials as major points, such as the obtainment of supporting data to determine NOAEL (No Observed Adverse Effect Level) and MABEL (Minimal Anticipated Biological Effect Level).

On the side of this action of support to FIM, MI and PET in particular should be considered as validation tool for animal models. The number and complexity of animal models is increasing, as is the cost for their development. Humanised biotransformation seems highly promising to give more accurate and precise preclinical information: PET can then be used also to validate such models and to address the question on how close to human physiology is the humanised model.

In conclusion, all those obligations that are set by regulatory bodies but are not responding to a real risk-assessment approach, applying to radiopharmaceuticals and in particular to PET radiotracers, will be directly influencing the success of the application of MI modality in the context of DDR and, more in general, of clinical research on biochemistry, physiology and pathophysiology.

PET/CT has reached excellence in the management of the oncological patient and the PET/FDG protocol is being proposed as a

biomarker for oncology drugs [18]. This might be the beginning of a wider exploitation of the modality and a positive cross-link to other imaging modalities; however the effect of regulatory environment can be of formidable attrition to achieve this goal.

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