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The search for consistency in the manufacture of PET radiopharmaceuticals

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Nuclear Medicine is the specialty of medical imaging, which utilizes a variety of radionuclides incorporated into specific compounds for diagnostic imaging and therapeutic applications. During recent years, research efforts in this discipline have concentrated on the decay characteristics of particular radionuclides and the design of unique radiolabeled tracers necessary to achieve time-dependent molecular images.

Various oncology applications have utilized specific PET and SPECT radiopharmaceuticals, which have allowed an extension from functional process imaging in tissue to pathologic processes and nuclide directed treatments. One of the most widely recognized advantages of positron emission tomography (PET) is its use of the attractive, positron-emitting biologic radiotracers that mimic natural substrates. However, a major disadvantage is that these substances are relatively short-lived and unable to be transported great distances. At this time, economic considerations and regulatory guidelines associated with the creation of a PET facility, as well as the operational costs of maintaining both the facility and the necessary procedural documentation, continue to create interesting strategic dilemmas.

This commentary will focus on the current approach and anticipated impact of pending regulations, which relate to the manufacture and formulation of a variety of PET radiopharmaceuticals used in clinical research and patient management at Memorial Hospital.

INTRODUCTION

COUPLED with the advancement in noninvasive cross-sectional imaging techniques for identifying structural alterations in diseased tissues, including computed tomography (CT) and magnetic resonance imaging (MRI), there have been significant advances in the development of *in vivo* methods for quantifying functional metabolism in both normal and diseased tissues. Positron emission tomography (PET) is an example of such a technique that has been shown to yield the physiologic information necessary for clinical oncology diagnoses based upon altered tissue metabolism. It has been proposed that correlative functional-anatomical imaging should permit the study of metabolic processes in the anatomic loci with the potential for the detection of changes indicative of tumor response to therapy prior to structural alterations.[1]

The ability to produce specific radiolabeled compounds combined with significant developments in radiation detector technology and information handling have changed the scope and increased the potential for the applications of radionuclide techniques in medicine. Today, the majority of clinical PET studies involving tumor metabolism are performed with radiolabeled glucose analogs and/or amino acids.

For various reasons, fluorine-18 labeled 2-fluoro-2-deoxy-D-glucose [^{18}FDG] has found widespread application in oncology and has assumed a role as the "gold standard" PET radiopharmaceutical for metabolic studies not only in the United States and Japan, but worldwide.[2] Other radiopharmaceuticals with specific applications to

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the evaluation of the pharmacodynamics and kinetics of cytostatic agents are being proposed. Since tumor heterogeneity is a well-known, accepted concept, imaging techniques designed to evaluate cancers will probably rely upon multiple radiotracers to adequately evaluate the lesions for diagnosis as well as for the monitoring of therapeutic responses. To date, although numerous drugs radiolabeled with PET nuclides have been proposed for potential utility, only a limited number of the radiolabeled compounds have found widespread clinical acceptance for PET studies.[3–7]

A review of historical developments allows us to appreciate how far, as a diagnostic imaging modality, PET technology has come in its transition from a research tool to a major component of medical imaging. Because of the growth of this technology, regulations specifically addressing the unique characteristics inherent in the manufacture of PET radiopharmaceuticals are currently being formalized. Such regulations are, in fact, shared goals of the radiopharmaceutical scientific staffs, to insure safe, efficient and effective products for patient management. Examples of salient points or deviations from current good manufacturing practices, which have been applicable to the more classical radiopharmaceutical drugs, are presented based upon our current practices within the Cyclotron/Radiochemistry Core Facility at Memorial Sloan-Kettering Cancer Center. Fluorine-18 labeled 2-fluoro-2-deoxy-D-glucose will serve appropriately as the example radiopharmaceutical, addressing concerns relative to its production and formulation. This article is intended not to be a prescription for PET radiopharmaceutical formulations, but rather to illustrate principles and problems currently being addressed to ensure production consistency during this time of evolution of a technology from a research tool to a clinical technique.

HISTORICAL PERSPECTIVE

The future application of PET, as proposed in 1982, was considered to be limited by lack of a "critical mass" of investigators to overcome both the intellectual nature and technical challenges of this emerging clinical tool. PET literature of that period was dominated by designs of scanners rather than clinical scientific reports. During this early development state, it was also recognized that in order to maintain a state-of-the-art scanner in a PET laboratory, there would be a need for large, ongoing financial investments.[8] The concerns and issues related to the manufacturing and distribution of PET tracers were neither major topics of discussion nor contemplation.

In a review published nearly a decade later,[9] the future of PET applications in oncology was limited due to the lack of a large number of whole-body PET systems. But the "critical mass" of investigators had entered the field and had demonstrated that PET would play a major role in the diagnosis and treatment of a variety of cancer patients. During this phase, it was recognized that PET could provide additional physiological information prior to anatomical changes.

With the passage of time, PET has become widely used in detecting tumors and metastases and in monitoring their response to treatment. The most widely used clinical PET radiotracer has been FDG, and its use for this purpose has been increasing rapidly.[7,10–12] The uptake of FDG in gliomas was recognized[13] to correlate with a tumor's histological grade and this finding remains a pivotal contribution to the application of PET in oncology. Numerous limited patient studies have been forthcoming detailing the sensitivity and specificity of PET to other imaging modalities. The influence of both chemotherapy and radiation therapy upon FDG accumulation in a variety of tumors is an active research area. Other tracers have been proposed to monitor additional properties of tumors, such as amino acid metabolism, cellular proliferation, multi-drug resistance, hypoxia, and receptor status to mention but a few areas,[2,14] all of which are valuable in monitoring patient treatment.

The ever-increasing amount of clinically relevant information being obtained primarily from [F-18]FDG studies has generated a demand for new synthetic routes for the widespread and cost-efficient use of positron emitting radiopharmaceuticals. Over the past decade the number of potential PET radiopharmaceuticals has grown significantly. Positron emission tomography applying non-conventional positron emitting radionuclides is an active area of research.[15] Moreover new dual-headed single photon emission tomograph cameras are being developed which offer coincidence detection. Instrumentation is being developed by several commercial manufacturers for fused images, combining anatomical imaging and PET imaging and software developments that allow fusion imaging using Picture Archiving and Communication Systems (PACS) for MRI, CT, and PET images.[16–19]

The financial costs associated with this technology continue to climb. In light of the increasing consumption of short-lived radiopharmaceuticals and the complexities associated with routine in-house radiopharmaceutical production, oversight efforts are being made to delineate and insure the safe and effective preparation of such drugs. One clear example within the United States, has been the realization of a clear distinction between research investigations involving animal modeling and the routine preparation of the final formulation for a patient study.[21]

MANUFACTURING PERSPECTIVES

Over the past few decades, PET studies with radiolabeled drugs have provided new information on drug uptake, distribution, and the kinetic relationships. An up-to-date critique on the design and development of PET radio-

pharmaceuticals has recently been published.[14] In addition, several articles involving the future of PET in drug research and development (14 and references therein) and applications of PET imaging involving oncological assessments, including gene transfer and expression, tumor hypoxia and multidrug resistance are appearing. The increasing amount of clinically relevant information being obtained with PET has generated a demand for new routes for the widespread and cost-effective use of positron emitting radiopharmaceuticals.

While radiopharmaceuticals in the United States are regulated under a number of agencies, because they are radioactive materials, and also are prescribed as "drugs" being administered to human beings, occasionally, an explicit need for the enactment of legislation arises. This may have been the case when, on November 21, 1997, President Clinton signed into law the Food and Drug Administration Modernization Act. Of importance to the nuclear medicine community, this legislation contained distinct provisions for PET diagnostic radiopharmaceuticals and required the Food and Drug Administration to develop appropriate approval procedures and current good manufacturing practice requirements for PET products within a two-year period.

There are also a number of independent agencies, which advise the federal agencies and affect the radiopharmaceutical industry. One such institution in the United States is the US Pharmacopoeia Convention (USP) which publishes the U.S. Pharmacopeia National Formulary, a compendium of production, quality control methods and standards. There are a number of monographs for PET radiopharmaceuticals that have appeared or are in the process of being prepared for the USP and these monographs, generally prepared with the assistance of scientists familiar with the radiopharmaceutical, become the definitive description of the product. For example, the monograph for [F-18]FDG, under the name of "fludeoxygucose," appeared initially in 1989.

During this period of transition, the FDA is conferring with patient advocacy groups, various associations and the emerging industry to develop production regulations. In addition, there are various other agencies, both state and federal, which have regulatory authority over medicine and pharmacy, and over the production, transportation, use and disposal of radioactive materials. These regulatory considerations combined with the economic considerations applied to the creation of a PET facility (both operational and procedural costs) are confronting the administrative and scientific staffs of existing facilities with interesting strategic dilemmas relative to the production and formulation of PET radiopharmaceuticals.

A few comments as examples of strategic policy planning considerations relative to the good manufacturing of the PET radiopharmaceuticals as compared to the more conventional drug products are appropriate. Most existing PET facilities are contained within university or medical centers with personnel configuration and space restricted. Often the space and equipment is a shared resource with other research activities. This is generally not the case with commercial endeavors in which the designated space is unique to manufacturing and processing aspects of the products. As for personnel, the PET facility generally has uniquely trained research investigators, who become responsible for the production of the specific formulation. Close supervision or management of the chemical procedure is not a primary issue for the particular investigator in this production role.[20]

The nature of a PET facility generally necessitates a cross over of responsibilities between manufacturing and quality assurances. Often the same personnel are performing the tasks of quality control and production making autonomy of efforts impossible. Moreover, completion of testing prior to distribution and/or release of the product is difficult; especially when one considers that the batch size for most PET protocol drugs may only be a single dose. This fact is particularly relevant when one considers oxygen-15 labeled blood flow agents, nitrogen-13 ammonia for myocardial function assessment and carbon-11 compounds such as C-11 methionine. Product strength is a concern for conventional drug manufacture but a difficult quantity to express for non-mass dependent PET drugs. Indeed, PET drugs are continually experiencing strength changes after production.

Considering that the bulk of the PET centers are established, radiation safety issues are a major concern and most centers take extreme care in maintaining radiation exposures to its personnel as low as reasonably achievable. But human intervention in the processing of a PET radiopharmaceutical for in-process sampling, a standard procedure in routine drug manufacture, is generally not considered prudent or wise.

CONCLUSION

Nuclear medicine remains a dynamic and evolving medical specialty because it is able to couple advances in basic science research with technological developments. The future role of PET in oncology is expected to provide detailed physiological information that can be correlated with morphological imaging. Already being reported is the concept of combining a PET scanner with a CT scanner to take advantage of the synergy between two complementary imaging modalities. The advantages of having coregistered images from complementary modalities has been widely recognized for years although most attempts have been limited to post realignment of images acquired on different instruments.[22] Application of Picture Archiving and Communication Systems (PACS) as an integral part of most modern medical imaging departments has now provided the foundation resource of image registration and fusion applications for medical imaging departments.

The advances in molecular biology and technology will create difficulties of designing non-endogenous radiotracers that reliably mimic natural substrates for the individuals involved in preparation and formulation of the radiopharmaceuticals. In addition, the transition from modeling experiments to clinical applications involving human subjects requires attention to numerous details to insure the delivery of safe and effective formulations. For years radiopharmaceuticals have been regulated under a number of headings since they are radioactive materials being administered to human subjects. Through years of research and development the more "classical" clinical radiopharmaceuticals have provided the nuclear medicine community with proven safe and effective drugs on demand. The evolution of PET radiopharmaceuticals has introduced a new class of "drugs" requiring production facilities and product formulations that must be closely aligned with the scheduled clinical utilization. Although existing regulations for the manufacturing of radiopharmaceuticals might be applied in principle, the unique decay characteristics of the current clinical PET radionuclides have necessitated a re-evaluation from a regulatory perspective. A concerted effort by the various regulatory agencies and members of existing and planned facilities to achieve a safe and effective methodology appropriate to the unique nature of PET formulations, is currently ongoing within the United States and other countries.

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