EDITORIAL

"Clinical PET: Its Time Has Come?"

In April 1991, this journal published an issue proudly entitled "Clinical PET: Its Time Has Come." Now, more than two years later, it appears that this proclamation may have been premature. This is not because of any deficiencies in the science underlying positron emission tomography (PET), nor because PET has insufficient clinical potential; both the science and potential of PET were solidly documented in April 1991. Rather, the time for clinical PET has not yet arrived because of the practical issue of obtaining reimbursement for PET procedures, and this issue is in turn tightly coupled to the regulation of PET radiopharmaceuticals. Thus, progress towards achieving the potential of clinical PET has become mired in the alphabet soup HCFA, HIAA, OHTA, FDA, IND, NDA, ANDA and, potentially the worst, CGMP*.

Despite vociferous protests by the nuclear medicine community, the FDA maintains its position that it will regulate PET radiopharmaceuticals (*1,2*). Today, in April 1993, there is only one FDA approved PET radiopharmaceutical, and that is the chemically simple ^{82}Rb ion which is provided by the easily regulated, commercial ^{82}Sr/^{82}Rb generator. The chemically more complicated molecule ^{18}F-FDG is the workhorse of PET, and the PET community has been trying since 1990 to obtain FDA approval for it. The original NDA, filed on February 15, 1991, was deemed to have serious deficiencies and an improved, revised NDA was filed on January 15, 1993. Its fate is still unknown. The interactions which have taken place between the largely academic PET community and the FDA during development of this NDA have been, to say the least, sobering to the former. Steven Zigler, PhD, who organized the 1993 NDA submission, states "I believe the collective effort to assemble our NDA and see it through to conclusion . . . has literally strained the resources of the entire PET community" (*3*).

It is clear that the PET community, with its traditional focus on academic science and the concomitant use of complicated, biologically relevant molecules, is having, and will continue to have, great difficulty in satisfying governmental regulatory and manufacturing requirements. One approach to resolving this conundrum is to refocus PET radiopharmaceutical research towards agents that will more easily meet regulatory and manufacturing requirements. This is the approach taken by Green and his coworkers in their development of a ^{68}Ga radiopharmaceutical for monitoring myocardial perfusion (*4*).

The FDA has a long history with, and is presumably comfortable with, generator-produced radioisotopes and the processes of deriving radiopharmaceuticals from them. The ^{99}Mo/^{99m}Tc generator has long been the mainstay of nuclear medicine and the source of a large family of ^{99m}Tc radiopharmaceuticals derived from cold kits. Also, as noted above, the single PET radiopharmaceutical that currently enjoys FDA approval is derived from the ^{82}Sr/^{82}Rb generator. From the regulatory viewpoint, commercially manufactured generators and accompanying cold kits are much easier to regulate and control than short-lived radiopharmaceuticals produced onsite in a PET facility. It is much easier for the FDA to uniformly apply CGMPs under existing guidelines in a few commercial sites than it will be to apply "modified" CGMPs to a wide variety of local PET manufacturing centers. As noted by Ed Coleman, MD (past President of the ICP), the major limitations to utilizing regulated PET radiopharmaceuticals in clinical situations "relate to GMP standards; we are not manufacturers of drug products" (*2,3*).

In this context, the ^{68}Ge/^{68}Ga generator holds considerable promise for PET radiopharmaceutical development. The parent isotope has a sufficiently long physical half-life (271 days) to allow routine manufacture and shipment, while the chemical properties of germanium and gallium are sufficiently different to allow several different methods of efficient separation. Moreover, the physical half-life of the ^{68}Ga daughter (68 min) is compatible with the preparation of radiopharmaceuticals from cold kits and with many types of imaging studies. One could readily imagine a PET center which utilizes a combination of the ^{68}Ge/^{68}Ga generator with a range of cold kits to perform a variety of clinical PET studies, in much the same way that the ^{99}Mo/^{99m}Tc generator is used with a range of cold kits to perform a variety of SPECT studies.

To achieve this vision, much more detailed and fundamental knowledge about the chemistry, biodistributions and pharmacokinetics of ^{68}Ga radiopharmaceuticals will be required. Green and his co-workers have begun to construct these foundations for ^{68}Ga based myocardial perfusion imaging agents (*4*). Such agents might be able to replace cyclotron-produced ^{13}N-ammonia for monitoring myocardial flow alone (*5*) or in conjunction with ^{18}F-FDG as a marker for myocardial metabolism (*6*).

The salient result reported in the accompanying paper (*4*) is that cationic ^{68}Ga complexes are retained in the heart, whereas neutral ^{68}Ga complexes rapidly wash out of the heart. In light of what is now known about

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*Definitions of acronyms used in this editorial: ANDA = Amended New Drug Application; CGMP = Current Good Manufacturing Practices; FDA = Food and Drug Administration; FDG = fluoro-2-deoxyglucose; GMP = Good Manufacturing Practices; HCFA = Health Care Financing Administration; HIAA = Health Insurance Association of America; ICP = Institute for Clinical PET; IND = Investigational New Drug; NDA = New Drug Application; OHTA = Office of Health Technology Assessment.

the myocardial retention of neutral and cationic ^{99m}Tc agents, this is hardly a surprising result, but it does provide a comforting reinforcement of the basic biochemical principles that have recently been demonstrated to underlie the action of myocardial perfusion imaging radiopharmaceuticals. In general, neutral agents (whether based on ^{99m}Tc or ^{68}Ga) show higher initial myocardial uptake, but then exhibit myocardial washout; cationic agents (again, whether based on ^{99m}Tc or ^{68}Ga) generally exhibit lower initial uptake, but are retained in the myocardium and undergo little or no myocardial washout unless they suffer some in vivo reaction which destroys their positive charge (*7*).

The fundamental mechanisms underlying the phenomenon of myocardial uptake and retention of cationic agents remain unclear, although Piwinica-Worms and co-workers have demonstrated that the initial myocardial uptake of cationic agents is driven by relatively negative membrane potentials (*8*). These elegant studies provide a basis for understanding the initial accumulation of cationic agents in myocardial cells, and in the mitochondria contained within these cells, but have not yet elucidated the mechanism(s) by which cationic agents become trapped within the myocardium.

The ^{68}Ga agent reported in the accompanying paper (*4*) is clearly not an ideal myocardial perfusion imaging agent, especially with respect to the observed heart-to-liver ratio. However, it is equally clear that the chemical and biological properties of this protopical agent can be readily modified by eliminating aromatic rings, incorporating different functional groups to modify the balance between lipophilic and hydrophilic properties, etcetera. Moreover, just as ^{99m}Tc chemistry has been manipulated to provide a wide variety of cationic agents, a wide variety of chemical structures can be designed and developed to generate ^{68}Ga cations.

Thus, this work by Green and colleagues (*4*) represents the beginning of a new area of research that starts with the development of cationic ^{68}Ga radiopharmaceuticals for myocardial perfusion imaging and extends into the development of a family of ^{68}Ga radiopharmaceuticals that can be prepared from cold kits and a ^{68}Ge/^{68}Ga generator. If this research area should prove productive, and there is no fundamental reason why it should not, then many of the current problems concerning the regulation and manufacture of PET radiopharmaceuticals should be ameliorated or eliminated. Perhaps then the nuclear medicine community, and the FDA, can agree that the time for clinical PET has come.

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