SURGE IN PET MONOGRAPHS

THE UNITED STATES PHARmacopeial Convention, Inc. (USP), a non-profit organization whose members are physicians, pharmacists, and scientists, issued its first chemical standard for a PET radiopharmaceutical in 1989, with the publication of a monograph on fluorine-18 (^{18}F) fluorodeoxyglucose (^{18}FDG) in the ninth supplement to the *United States Pharmacopeia XXI* (see *Newsline*, October 1989, p. 1587). In 1990, a standard was published for a second radiopharmaceutical used in PET, nitrogen-13 (^{13}N) ammonia ($^{13}NH_3$), in the third supplement to the *United States Pharmacopeia XXII*. The monograph for $^{13}NH_3$, written by S. John Gatley, PhD, a scientist at Brookhaven National Laboratory (BNL), Upton, New York, reviews the uses of $^{13}NH_3$ in nuclear medicine and analyzes the important quality assurance issues that must be considered for the clinical use of $^{13}NH_3$.

Carol S. Marcus, PhD, MD, associate professor of radiological sciences, University of California, Los Angeles (UCLA), director of nuclear medicine outpatient clinic at Harbor-UCLA Medical Center, and chairperson of the radiopharmaceutical advisory committee for USP's *Drug Information for the Health Care Professional*, notes that it is especially important to establish standards for the ^{18}F-labeled drugs because these radiopharmaceuticals are the "workhorses of PET." FDG, fluorodopa, and sodium fluoride labeled with ^{18}F provide physicians with a metabolic agent, a neurotransmitter, and a bone agent, respectively. Dr. Marcus says that the two-hour half-life of ^{18}F gives it a great advantage over other PET drugs with half-lives that are counted in minutes: oxygen-15 (^{15}O) has a half-life of two minutes, ^{13}N has a half-life of ten minutes, and carbon-11 (^{11}C) has a half-life of twenty minutes.

Dr. Marcus notes another advantage of ^{18}F-labeled drugs. "The energy of the particles gives slightly better resolution than some other elements." She adds that the ^{18}F attaches well, displaying good chemistry.

A number of other USP monographs and articles on PET radiopharmaceuticals are in various stages of completion. The new monograph proposals will be published in future issues of the *Pharmacopeial Forum*, a bimonthly USP publication, and after a period of public review and comment will be revised and published in the *United States Pharmacopeia*, which is published approximately every five years.

During the public comment period, the USP actively solicits international opinion by sending proposed monographs to the International Atomic Energy Agency and to selected international practitioners for their comments. It usually takes about two years for a monograph to complete the cycle of publication and revision before it reaches final approval and is published in the *United States Pharmacopeia*. Frank Barletta, a scientist in the USP's drugs standard division, says that the USP is a very conservative body and will address any adverse comment on proposed standards. Thus, the revised monographs are very conservative documents.

Once standards for a drug have been published in the USP, all hospitals and laboratories in the U.S. must abide by those standards when formulating the drug. This standardizes production of the drug, regardless of where it is manufactured, and researchers conducting clinical studies based on drugs formulated according to USP standards can be confident that results from different studies will not be skewed by the administration of different formulations of the drug in each study.

Mr. Barletta notes that the publication of standards for a drug in the *United States Pharmacopeia* brings other benefits as well. He points out that the standards provide legal protection to physicians, pharmacists, and technologists from potential lawsuits by patients with adverse reactions to a drug, as long as the hospital has followed the USP standards in formulating the drug.

The following are descriptions of monographs and articles that are in the production cycle and that the USP expects to publish in 1991 issues of *Pharmacopeial Forum*.

- A monograph on ^{18}F-fluorodopa by Jorge R. Barrio, PhD, professor of radiological sciences, UCLA School of Medicine, was published in the March/April 1990 *Pharmacopeial Forum* and is currently undergoing revision. It will be republished in an upcoming issue of the *Pharmacopeial Forum*.
- Dr. Gatley has written an article on ^{18}F-fluoromethane for the March/April 1991 *Pharmacopeial Forum*. The article briefly reviews the advantages of using ^{18}F- or ^{11}C-labeled fluoromethane as a radiopharmaceutical for measuring local rates of cerebral blood flow. The article also includes a compendium of published studies using fluoromethane.
- Ronald D. Finn, PhD, attending radiochemist at Memorial Sloan-Kettering Cancer Center, New York City, will write two monographs: one will discuss the use of ^{15}O-labeled water as a blood flow tracer. The other, coauthored by Steven M. Larson, MD, chief of nuclear medicine, Memorial Sloan-Kettering Cancer Center, will cover the standards for ^{18}F sodium fluoride. This compound was used in the past as a bone scanning agent with planar imaging. It will now have direct application to PET imaging using positron cameras that were not readily available in the past.
- Bonnie B. Dunn, PhD, head, quality assurance of cyclotron radiochemistry section, nuclear medicine department, National Institutes of Health (NIH), will develop a monograph on ^{11}C-labeled carbon monoxide. The monograph will describe the packaging, storage, and labeling of carbon monoxide, a gas that

is used in PET imaging studies to determine blood volume. It will also cover radionuclide identification and radionuclidic and chemical purity.

• A group from Squibb Diagnostics in Princeton, New Jersey will provide the monograph specifications for rubidium-82- (^{82}Rb)-labeled rubidium chloride obtained from the strontium-82/rubidium-82 generator.

• Jeffrey A. Clanton, MS, DPh, director of radiopharmacy services, Vanderbilt University Medical Center, and Ronald Manning, PhD, associate professor of radiology at Vanderbilt, have coauthored a description of an automated radiochemical synthesis module, known as the "black box" that was published in the September/October 1990 issue of *Pharmacopeial Forum*. The document outlines the basic designs, functions, and uses of automated synthesis modules used in PET to produce radiochemicals. The authors' discussion also encompasses robotic systems.

According to Mr. Barletta, the black box has not been definitively classified yet. If the black box is considered a medical device, the Food and Drug Administration (FDA) can regulate it, but if it is considered a piece of laboratory equipment, then it will not fall under the jurisdiction of the FDA. The black box is not a sterile environment. It produces a chemical that is then taken from the black box and formulated into a radiopharmaceutical. Classification will depend on whether the FDA decides to regulate the end-product, the radiopharmaceutical or the initial chemical component. Mr. Barletta notes that 90% of the ^{18}FDG produced in the United States is made through the use of a black box.

National Research Council

The USP is not the only organization that publishes PET monographs. The National Research Council, whose members are drawn from the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine, also publishes PET monographs through its Committee on Nuclear and Radiochemistry. The Committee's original mandate was to disseminate educational literature to scientists in the areas of nuclear chemistry and radiochemistry. According to Committee member Joanna S. Fowler, PhD, senior chemist at BNL, the Committee has broadened its focus and is now publishing a series of nuclear medicine monographs.

Monographs published by the Council are quite different in format than those published by the USP. While USP monographs are one or two pages long and are published as a group in one bound volume, Council monographs are usually 100-150 pages long, and each monograph is published separately. The following Council monographs are currently being written and, according to Dr. Fowler, the Committee expects most of these to be published within the next year.

• Stephen Moerlein, PhD, associate professor of radiation chemistry and biochemistry, Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Missouri, will develop a monograph on the production and applications of radiopharmaceuticals containing bromine (Br) radioisotopes. This monograph will deal with the production and synthetic incorporation of Br radioisotopes (^{75}Br, ^{76}Br, ^{77}Br, ^{80m}Br, and ^{82}Br) into organic molecules.

• James W. Brodack, PhD, senior research chemist, Mallinckrodt Medical, Inc., St. Louis, will develop a monograph on the automation of the production of positron-emitting radiopharmaceuticals. This monograph will cover a range of remote synthesis devices including operator-dependent and operator-independent devices and robotic systems. Dr. Brodack will discuss advantages and disadvantages of each mode and future perspectives on radiopharmaceutical production.

• Dr. Gatley will develop a monograph on PET and pharmacology that will review the radiotracers available for use in pharmacologic research and the published studies involving the effects of drugs on radiotracer behavior. Dr. Gatley will cover radiotracer design, development and validation of radiotracers, and the factors that must be considered before positron-labeled drugs are administered to human subjects.

• David Schyler, PhD, a chemist at BNL, will develop a monograph on cyclotron targetry that will cover the subject from a number of perspectives including the cyclotron itself, the nuclear physics involved, nuclear reactions and radionuclide yields, and the chemistry occurring in the target. Dr. Schyler will discuss targetry for the production of the short-lived "organic" positron emitters (^{11}C, ^{18}F, ^{15}O, and ^{13}N), iodine-123, thallium-201, gallium-67, indium-111, rubidium-81, and others. The monograph will explore engineering aspects including heat transfer and target materials and will include a section on computer modeling of the target and practical limitations and safety considerations.

Regulation and Reimbursement

The emergence of USP standards for PET radiopharmaceuticals is a sign that all regulation of these drugs may eventually reside with state boards of pharmacy. Physicians and state boards argue that the Food, Drug and Cosmetic Act gives states the power to regulate the practice of medicine and pharmacy and thus gives physicians the freedom to manufacture drugs for their patients in a hospital without the need for regulatory approval from the FDA. The FDA, however, has stated that all drugs must undergo the new drug application (NDA) process.

The struggle for regulatory control of PET drugs may affect how third-party payers establish their criteria for reimbursement. These payers look at what is clinically appropriate when they decide whether or not to reimburse a practitioner or hospital for PET procedures. Currently, the FDA considers all PET drugs experimental and, thus, the federal government will not reimburse hospitals for procedures that use PET drugs.

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