SNM Surveys Nuclear Pharmacies on Radionuclide Shortage

On September 9 SNM released the results of a survey of nuclear pharmacies that was designed to elicit a sampling of reports on the effect of ^{99}Mo/^{99m}Tc shortages caused by a reactor shutdown in Canada and slowdowns/scheduled maintenance at other reactors. According to the survey results, 60% of radiopharmacies in the United States have been affected by the most recent shortage. Nuclear medicine practitioners and pharmacists are making changes to cope with the shortage while attempting to maintain routinely high-quality levels of patient care.

"This situation is untenable," said Robert W. Atcher, PhD, MBA, chair of the SNM Domestic Isotope Availability Task Force. He noted that the survey indicated that 75% of physicians are rescheduling patient tests by at least 1 d and that in more than 33% of these cases, tests have been delayed for more than 1 mo. In addition to delays, more than 80% of nuclear medicine physicians and specialists are decreasing dosages, a practice that can lead to "longer exposure and less effective imaging scans," said Atcher.

"In some cases, waiting even a day can severely impact care, especially if the condition is progressing rapidly," said Michael M. Graham, MD, PhD, president of SNM. "Getting information early on in the disease progression is critical and is one of the real benefits of molecular imaging."

Although the shortage began in May when the National Research Universal reactor (NRU; Chalk River, Canada) went off line, radiopharmacists report being under increasing pressure to find alternative agents to offset the ^{99}Mo shortage. This pressure has only increased since the announcement that the NRU reactor would not resume production.

"Radiopharmacists are doing the best they can with the limited resources at their disposal," said Jeffrey P. Norenberg, PharmD, executive director of the National Association of Nuclear Pharmacies and a member of the SNM Domestic Isotope Availability Task Force. "But clearly, patients deserve better because better agents like ^{99m}Tc exist. Governments should work together to prevent such shortages from ever happening again."

No commercial reactors in the United States produce ^{99}Mo, making the isotope shortage especially acute. One encouraging note is the impetus the shortage has given to efforts to begin domestic U.S. production. These efforts include university reactor projects, government-backed initiatives, and corporate plans, several of which could come to fruition within a few years. Until a supply is ensured, however, nuclear medicine experts will continue to try to keep up with demand while using less effective products. "It's a juggling act," Atcher said.

SNM

FDA Expands Zevalin Approval

Spectrum Pharmaceuticals (Irvine, CA) announced on September 4 that its CD20-directed radioimmunotherapy (RIT) antibody product, Zevalin (ibritumomab tiuxetan) had received approval from the U.S. Food and Drug Administration (FDA) for an expanded label for the treatment of patients with previously untreated follicular non-Hodgkin lymphoma (NHL) who achieve a partial or complete response to first-line chemotherapy. This new and expanded indication supplements the 2002 FDA approval of Zevalin as treatment for patients with relapsed or refractory, low-grade or follicular B-cell NHL.

"We believe the approval of Zevalin as an effective treatment option following a first-line regimen represents a notable advance in the treatment of NHL and significantly expands the addressable population for Zevalin," said Rajesh C. Shrotriya, MD, chair, CEO, and president of Spectrum Pharmaceuticals. "We are confident that the strategic and tactical initiatives we have implemented will overcome the clinical, logistical, and reimbursement challenges that have previously hindered physician and patient access to Zevalin."

The approval of the new indication was based on data from the First-Line Indolent Therapy (FIT) study. This multicenter, randomized, open-label phase 3 study evaluated the safety and efficacy of Zevalin in 414 patients with CD20-positive follicular NHL who had achieved a partial response or a complete response after receiving a first-line chemotherapy regimen. At 3.5 y of follow-up, the FIT trial demonstrated that when used as part of first-line chemotherapy for patients with follicular NHL, Zevalin significantly improved the median progression-free survival time from 18 mo (control group) to 38 mo (Zevalin group).

Updated results with an additional year of follow up were presented at the American Society of Hematology 2008 annual meeting. The safety profile of Zevalin was consistent with previous clinical studies, with hematologic toxicity as the most common adverse reaction in the FIT study.

The National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium currently lists chemotherapy followed by RIT, such as Zevalin, for patients with follicular NHL with a Category 1 recommendation. The Centers for Medicare & Medicaid Services announced in June 2008 that it would recognize the NCCN Drugs & Biologics Compendium as a source of information to determine which drugs may be covered under Medicare Part B.

On September 10 SNM released a statement applauding the FDA decision to expand approval of Zevalin. "This is welcome news for patients

with NHL," said Michael M. Graham, MD, PhD, president of SNM. "We've known for some time that RIT works extremely well for many NHL patients. With the FDA's approval, more patients can take advantage of this promising treatment sooner rather than later, giving them more hope for a brighter future."

Spectrum Pharmaceuticals, Inc.
SNM

NRC Seeks Comments on QA/QC Guidance

The U.S. Nuclear Regulatory Commission (NRC) on September 24 issued for public comment a draft guide titled "Establishing Quality Assurance Programs for the Manufacture and Distribution of Sealed Sources and Devices Containing Byproduct Material" (DG-6007), a proposed revision of Regulatory Guide 6.9, dated February 1995. This regulatory guide directs the reader to the type of quality assurance (QA) and quality control (QC) program acceptable to the staff of the NRC during the review of an application to manufacture or distribute sealed sources and devices containing byproduct materials.

Title 10 of the *Code of Federal Regulations* (10 CFR) Part 32, "Specific Domestic Licenses to Manufacture or Transfer Certain Items Containing Byproduct Material," regulates the manufacture and distribution of sealed sources or devices containing byproduct material. Regulations in 10 CFR 32.210(c) require the applicant or registrant to submit information about the QC program in sufficient detail to allow NRC reviewers to ensure that the product is manufactured and distributed in a manner that is adequate to protect health and minimize danger to life and property. This regulatory guide endorses the methods and procedures for a QA/QC program described in Section 10.7, "Quality Assurance and Quality Control" of NUREG−1556, Volume 3, "Consolidated Guidance About Materials Licenses: Applications for Sealed Source and Device Evaluation and Registration," issued in April 2004, as a process that the NRC finds acceptable. As described in Volume 3 of NUREG−1556, the applicant must provide details of the QA program that ensure that the product is manufactured and distributed in accordance with the representations made in the application and the statements contained in the registration certificate for the product.

This regulatory guide is being issued in draft form to involve the public in the early stages of the development of a regulatory position in this area. It has not received final staff review or approval and does not represent an official NRC final staff position. Public comments are being solicited on this draft guide (including any implementation schedule) and its associated regulatory analysis or value/impact statement. Comments should be submitted by November 21 and accompanied by appropriate supporting data. Written comments may be submitted to the Rulemaking and Directives Branch, Office of Administration, U.S. NRC, Washington, DC 20555-0001, or through the NRC interactive rulemaking Web page at www.nrc.gov. Electronic copies of this draft regulatory guide are available through the NRC Electronic Reading Room at www.nrc.gov/reading-rm/doc-collections.

U.S. Nuclear Regulatory Commission

CMS Reissues Billing Instructions for PET NCD Changes

On September 18, the Centers for Medicare & Medicaid Services (CMS) released to Medicare administrative contractors (MACs) the long-awaited and reissued guidance and billing instructions for the April 2009 changes to the national coverage determination (NCD) on PET (FDG). Providers will have 2 new modifiers (in addition to the list of current modifiers) to consider when submitting claims with a date of service (DOS) on or after April 6, 2009, for CPT codes 78608 and 78811–78816 for oncologic procedures. Providers submitting claims with a DOS on or after April 6, 2009, for these codes, available on or after the implementation date of October 19, are now required to identify the procedure as either for initial treatment strategy or for subsequent treatment strategy by appending the modifiers PI or PS, respectively. The PI modifier should be used for PET or PET/CT procedures "to inform the initial treatment strategy of tumors that are biopsy proven or strongly suspected of being cancerous based on other diagnostic testing" (short descriptor: PET tumor init tx strat). The PS modifier should be used for PET or PET/CT procedures "to inform the subsequent treatment strategy of cancerous tumors when the beneficiary's treating physician determines that the PET study is needed to inform subsequent antitumor strategy" (short descriptor: PET tumor subsq tx strategy).

In a statement released on September 21, SNM praised CMS for a greatly simplified new set of billing instructions for ^{18}F-FDG PET procedures. CMS removed the previously identified ICD-9 range of codes allowing discretion at the local level with the MACs. Providers participating in the National Oncologic PET Registry for those procedures which continue to be covered only under coverage with evidence development (CED) continue to use the Q0 (zero) modifier and/or V70.7 in the second diagnosis position with condition code 30 in addition to using 1 of the 2 new modifiers. CMS plans to post additional information as part of an MLN Matters Educational article at http://www.cms.hhs.gov/MLNMattersArticles/.

Centers for Medicare & Medicaid Services

NIH Opens hESC Line Web Site

National Institutes of Health (NIH) Director Francis S. Collins, MD, PhD, announced on September 21 that NIH is now accepting requests for human embryonic stem cell (hESC) lines to be approved for use in NIH-funded research. Information may be submitted through NIH Form 2890, which is

available at http://stemcells.nih.gov/ as part of an interactive Web form allowing the submission of information online.

The NIH director also announced the members of a new working group of the Advisory Committee to the Director (ACD): the Working Group for Human Embryonic Stem Cell Eligibility Review. In announcing the members of the Working Group, Dr. Collins said, "I appreciate the willingness of these individuals to assist NIH in supporting responsible, scientifically worthy human stem cell research, as encouraged by the President's Executive Order. Their expertise and sound judgment will help NIH move forward in this important effort." Jeffrey R. Botkin, MD, MPH, will serve as the working group's chair. He is a professor of pediatrics and adjunct professor of medicine at the University of Utah School of Medicine (Salt Lake City). The other members of the working group are: Dena S. Davis, JD, PhD, Cleveland–Marshall College of Law/Cleveland State University (OH); Pamela B. Davis, MD, PhD, University of Kansas School of Medicine–Wichita; Richard P. Lifton, MD, PhD, Yale School of Medicine (New Haven, CT); Bernard Lo, MD, University of California, San Francisco, School of Medicine; Terry Magnuson, PhD, University of North Carolina at Chapel Hill School of Medicine; Jeffrey C. Murray, MD, University of Iowa Children's Hospital (Iowa City); and Carlos Pavão, MPA, Education Development Center, Inc. (Atlanta, GA).

On March 9, 2009, President Obama issued Executive Order 13505: Removing Barriers to Responsible Scientific Research Involving Human Stem Cells. The order states that the secretary of Health and Human Services, through the director of NIH, may support and conduct responsible, scientifically worthy human stem cell research, including hESC research, to the extent permitted by law. The NIH Guidelines for Human Stem Cell Research were published on July 7 and are available at http://stemcells.nih.gov/policy/2009guidelines.htm. The guidelines implement the executive order as it pertains to extramural NIH-funded stem cell research, establish policy and procedures under which the NIH will fund such research, and help ensure that NIH-funded research in this area is ethically responsible, scientifically worthy, and conducted in accordance with applicable law. In addition, on July 30, the president directed all federal departments and agencies that support and conduct stem cell research to adopt the guidelines. For hESCs derived from embryos donated in the United States on or after the effective date of the guidelines (July 7), specific provisions regarding the embryo donation and informed consent process apply and are detailed in Section II (A) of the guidelines.

As described in the guidelines, the working group will consider 2 other categories of hESCs and make recommendations to the ACD regarding their eligibility for use in NIH-funded research. After considering the analysis done by the working group, the ACD will make recommendations to the NIH director regarding the eligibility of specific hESCs for use in NIH-funded research. The NIH director will make the final decisions regarding the eligibility of the hESCs and list those deemed eligible on the NIH Human Embryonic Stem Cell Registry. Once an hESC line is listed on the registry, there is no need for further submissions requesting review of that particular line.

National Institutes of Health

New NIH Research Data and Results Tool

Comprehensive funding information for NIH grants and contracts is now available on the NIH Research Portfolio Online Reporting Tool (RePORT) through a new, user-friendly system called the RePORT Expenditures and Results, or RePORTER. RePORTER combines NIH project databases and funding records, PubMed abstracts, full-text articles from PubMed Central, and information from the U.S. Patent and Trademark Office with a robust search engine, allowing users to locate descriptions and funding details on NIH-funded projects along with research results that cite the NIH support.

"With the addition of RePORTER, we have taken a big step toward providing NIH's broad community of stakeholders—including biomedical researchers, research administrators, science policy makers, and members of the general public—with richer information, accessible in a form designed to meet their diverse set of needs," said Sally Rockey, PhD, acting deputy director of extramural research. "In addition to a being a public service to our stakeholders, it's a good example of the transparency and openness in government that the public deserves and has come to expect."

User-defined searches allow the public to refine, export, and analyze results and provide insights into NIH spending as well as research results across NIH-funded projects, institutions, investigators, or scientific concepts. Searching for grants funded by the Recovery Act is made especially easy by a checkbox that limits searches to that area of interest. Plans for improvements in RePORTER include allowing users to personalize their experience. NIH's goal is to provide users the ability to save favorite searches; set alerts for new grants, publications, and patents; and even export the entire RePORTER database.

RePORTER is the newest tool on the RePORT Web site, NIH's comprehensive online repository of reports, data, and analyses of research-related funding. RePORT data on NIH research-related grant and contract funding include general reports and statistics; funding by research, condition, and disease categories; new data visualization tools; and more. Dynamic reports and geographic mapping tools offer unparalleled access to information on NIH's Recovery Act grant funding on an individual project, state, or national level. RePORT is available at RePORT.nih.gov. The project search tool, RePORTER, is available through the RePORT site or by

going directly to ProjectRePORTER.nih.gov.

National Institutes of Health

NIH High-Risk Research and Innovation Awards

The National Institutes of Health (NIH) announced on September 24 the award of $348 million to encourage investigators to "explore bold ideas that have the potential to catapult fields forward and speed the translation of research into improved health." These awards were granted under 3 innovative research programs supported by the NIH Common Fund's Roadmap for Medical Research: the NIH Director's Transformative R01 (T-R01) Awards, Pioneer Awards, and New Innovator Awards. The Common Fund, enacted into law by Congress through the 2006 NIH Reform Act, supports cross-cutting, trans-NIH programs with a specific emphasis on innovation and risk taking. A portion of these New Innovator Awards is also supported by funding from the American Recovery and Reinvestment Act.

"The appeal of the Pioneer, New Innovator, and now the T-R01 programs is that investigators are encouraged to challenge the status quo with innovative ideas, while being given the necessary resources to test them," said NIH Director Francis S. Collins, MD, PhD. "The fact that we continue to receive such strong proposals for funding through the programs reflects the wealth of creative ideas in science today." Accelerating the current pace of discovery through the support of highly innovative research is an ongoing effort at the NIH, but the NIH Director's T-R01 Program is new this year. Named for the R-01, the standard investigator-initiated research project that NIH supports, the T-R01s provide a new opportunity for scientists that is unmatched by any other NIH program. Because no budget cap is imposed and preliminary results are not required, scientists are free to propose new, bold ideas that may require significant resources. They are also given the flexibility to work in large, complex teams if the complexity of the research problem demands it.

This year, the NIH granted 115 NIH Director's High-Risk Research Awards: 42 T-R01 Awards, 18 Pioneer Awards, and 55 New Innovator Awards for early-stage investigators. The NIH expects to make competing awards of $30 million to T-R01 awardees, $13.5 million to Pioneer awardees, and approximately $131 million to New Innovators in fiscal year 2009. The total funding provided to this competing cohort over a 5-y period is estimated to be $348 million. The New Innovator total includes $23 million in funds through the Recovery Act.

More information on the T-R01 Award is at http://nihroadmap.nih.gov/T-R01. For descriptions of the 2009 recipients' research plans, see http://nihroadmap.nih.gov/T-R01/Recipients09.asp. Information on the Pioneer Award is at http://nihroadmap.nih.gov/pioneer, including information on this year's awardees at http://nihroadmap.nih.gov/pioneer/Recipients09.aspx. More information on the New Innovator Award is at http://nihroadmap.nih.gov/newinnovator. For descriptions of the 2009 recipients' research plans, see http://nihroadmap.nih.gov/newinnovator/Recipients09.asp.

National Institutes of Health

IOM to Study Premarket Device Clearance

The U.S. Food and Drug Administration (FDA) announced on September 23 that it has commissioned the Institute of Medicine (IOM) to study the premarket notification process used to review and clear certain medical devices marketed in the United States. The IOM study will examine the premarket notification program, also called the 510(k) process, for medical devices. While the IOM study is underway, the FDA's Center for Devices and Radiological Health (CDRH) will convene its own internal working group to evaluate and improve the consistency of FDA decision making in the 510(k) process.

"Good government conducts periodic reviews and evaluations of its programs," said Jeffrey Shuren, MD, acting director of CDRH. "Our working group and the IOM's independent evaluation will help us determine how the 510(k) process can be improved to better support FDA's mission to protect and promote the public health."

The 510(k) process was established under the Medical Device Amendments of 1976 with 2 goals: (1) make safe and effective devices available to consumers; and (2) promote innovation in the medical device industry. During the intervening 3 decades, technologies and the medical device industry have changed, making it an appropriate time for CDRH to review the adequacy of the premarket notification program in meeting these 2 goals.

The IOM provides independent, objective, evidence-based advice to policymakers, health professionals, the private sector, and the public. As part of the study, the IOM will convene a committee to answer 2 focus questions: (1) Does the current 510(k) process optimally protect patients and promote innovation in support of public health? (2) If not, what legislative, regulatory, or administrative changes are recommended to achieve the goals of the 510(k) process?

The $1.3 million IOM review is slated for completion in 2011 and is one of 6 priorities Shuren has outlined for CDRH. Others include creating an internal task force on the use of science in regulatory decision making, developing an effective compliance strategy, optimally integrating premarket and postmarket information, increasing transparency in decision making, and establishing clear procedures to resolve differences of opinion.

The IOM will hold 2 public workshops during the next 9 mo as part of its review and will publish a final report in March 2011 with conclusions and recommendations.

U.S. Food and Drug Administration

FDA AWARDS PEDIATRIC MEDICAL DEVICE GRANTS

The U.S. Food and Drug Administration (FDA) announced on September

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the target lesion. Mean ^{99m}Tc-MIBI activity also correlated negatively with change in the area of the largest transverse surface of the target lesion. The authors concluded that their series "demonstrated solid, negative correlations between prechemotherapy ^{99m}Tc-MIBI uptake and tumor size change measured by CT for advanced NSCLC," a finding that could have strong implications for new imaging protocols and treatment strategies in this patient group.

Molecular Imaging and Biology

MR and Sunitib in Renal Cell Carcinoma

In an article published in the September issue of *Neoplasia* (2009;11: 910–920), Hillman et al. from the Wayne State University School of Medicine (Detroit, MI) reported on dynamic contrast-enhanced MR imaging of antiangiogenic changes induced by sunitinib in papillary renal cell carcinoma xenografts. The study focused on an orthotopic KCI-18 model of human renal cell cancer xenografts in nude mice treated with various doses of sunitinib, followed by dynamic contrast-enhanced MR imaging and histologic studies. Sunitinib was found to induce dose-dependent vascular changes in kidney tumors and in normal kidneys. A dosage of 10 mg/kg/d caused mild changes in gadolinium uptake and clearance kinetics in kidney tumors. A dosage of 40 mg/kg/d induced increased vascular tumor permeability with gadolinium retention, which the authors attributed to destruction of tumor vasculature. This higher dosage also caused vascular alterations of normal vessels. Sunitinib at 20 mg/kg/d caused increased tumor perfusion and decreased the vascular permeability associated with thinning and regularization of tumor vessels while only mildly affecting normal vessels. Alterations in tumor vasculature were found to result in a significant inhibition of KCI-18 tumor growth at dosages of 20 and 40 mg/kg/d. In vitro studies showed that sunitinib also had direct cytotoxic effects in KCI-18 cells. The authors concluded that "these data suggest that a sunitinib dosage of 20 mg/kg per day, which inhibits renal cell carcinoma tumor growth and regularizes tumor vessels with milder effects on normal vessels, could be used to improve blood flow for combination with chemotherapy."

Neoplasia

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21 the award of 3 grants to stimulate the development and availability of medical devices for children. A panel of 6 experts with experience in medicine, business, and device development reviewed 16 applications for the grants, which will be administered by the FDA Office of Orphan Products Development. The recipients and grant amounts include: James Geiger, MD, and the Michigan Pediatric Device Consortium, $1 million; Pedro DelNido, MD, and the Pediatric Cardiovascular Device Consortium, $500,000; and Michael Harrison, MD, and the University of California at San Francisco Pediatric Device Consortium, $500,000.

The FDA noted that development of medical devices for children lags up to a decade behind similar devices intended for use in adults. Children differ among themselves and from adults in terms of size, growth, and body chemistry and present unique challenges to device designers. In addition, the activity level and ability to manage some implantable or long-term devices may vary greatly among children.

"Congress provided the FDA with this funding so that we could help connect innovators and their ideas with experienced professionals who assist them through development" said Timothy Cote, director of the FDA Office of Orphan Product Development. "These grants will strengthen public health by spurring the development of medical devices that safely and effectively meet the special and unique needs of our children."

Those receiving the grants will encourage innovation and connect qualified individuals with good pediatric device ideas to potential manufacturers; mentor and manage pediatric device projects through their development, including prototype design and marketing; connect innovators and physicians to existing federal and nonfederal resources; and assess the scientific and medical merit of proposed pediatric projects and provide assistance and advice on business development, training, prototype development, and postmarketing needs. Each of the grant recipients will coordinate among the FDA, device companies, and the National Institutes of Health Eunice Kennedy Shriver National Institute of Child Health and Human Development to facilitate research and any necessary applications for device approval or clearance.

U.S. Food and Drug Administration
Centers for Medicare & Medicaid Services