FDA Approves SNM Multicenter IND for ^{18}F-FLT

SNM announced on February 2 that the U.S. Food and Drug Administration (FDA) had approved the society's centralized multicenter investigational new drug (IND) application for ^{18}F-labeled 3′-deoxy-3′-fluorothymidine (FLT). The approval of multicenter Chemistry Manufacturing and Controls (CMC) in the IND represents a successful demonstration of an important FDA IND review process for PET imaging biomarkers. The FDA has agreed to allow multiple sources of FLT to be evaluated, reviewed, and accepted for use under a single IND and has also agreed to base the IND review process for acceptance of the various investigational FLT products on the end product specifications. Therapeutics developers who want to use FLT as a surrogate marker of effectiveness in the development of novel cancer therapies have sought access to a centralized, multicenter IND for FLT as a way of speeding and simplifying the drug development process.

SNM President Robert W. Atcher, PhD, MBA, said, "Until now, FLT has been evaluated for investigational use under an IND at a limited number of imaging centers that have FDA-approved INDs in place. With the SNM's centralized IND now approved, multicenter investigational imaging is achievable in large therapeutic clinical trials through a single cross reference letter." The IND application was made possible, in part, through a letter of cross-reference to a master FLT IND held by the Cancer Imaging Program at the National Cancer Institute (NCI). NCI's IND was the result of significant work and investment by NCI and other collaborators toward their goal of making investigational radiopharmaceuticals available for drug development.

"We're aware that we don't have the resources needed to conduct large Phase 3 trials," said Jim Tatum, MD, associate director of the Division of Cancer Treatment and Diagnosis at NCI. "Therefore, we strongly encourage imaging societies, academic institutions, cooperative groups, and commercial sectors to work together to effectively lower this last barrier." Over the past 4 y, NCI has allowed more than 20 entities to cross-reference this master IND. SNM combined the NCI information with information obtained from the University of Pennsylvania, Mayo Clinic, University of Iowa, University of Utah, and University of Washington. Most of these institutions hold a single-site–approved IND for FLT. However, each facility follows a different manufacturing process, so that individual INDs describe end-product FLT that is unique to each facility. FDA has not been asked previously to review these various production processes together or to base acceptance of the CMC on the end product formulation. Centralized, multicenter INDs are a key enabler for the recently formed SNM Clinical Trials Network, which has a mission to increase the use of imaging biomarkers in multicenter clinical trials.

"Since we received approval of SNM's centralized IND, several pharmaceutical developers have expressed interest in using FLT in near-term clinical trial multicenter work," said Atcher. "That's the real validation that this effort was worthwhile." Active clinical trials utilizing ^{18}F-FLT are expected to begin later this year.

SNM

Radiopharmaceuticals Market Remains Strong

In a press release issued on February 18, Global Industry Analysts, Inc. (San Jose, CA) described research indicating that the market for radiopharmaceuticals continues to gain momentum with heightened interest in therapeutic efficiency, acceptance and utilization of nuclear medicine equipment, and development of newer diagnostic and therapeutic agents. Higher disease incidence, development of newer diagnostic agents, widespread awareness among practitioners and patients, and continued breakthroughs in research and clinical applications areas are projected to send sales of radiopharmaceuticals in U.S. and European markets to $5.4 billion by 2015.

Advances in nuclear medicine technology are expected to represent a key strategic factor in opening up new clinical opportunities for radiopharmaceutical agents. In market analysis titled *Radiopharmaceuticals: A US & European Market Report,* Global Industry Analysts projected that growth in the radiopharmaceuticals market will be driven by the development of new products, a robust demand for cardiology procedures, and sales of oncology-related products, especially ^{18}F-FDG for PET.

The market for both diagnostic and therapeutic radiopharmaceuticals in the United States is expected to grow steadily through 2012. Sales of ^{18}F-FDG are projected to grow, along with increases in PET procedure volumes attributable to expanded oncology applications, novel PET radiopharmaceuticals in the research pipeline, and growth in cardiology applications. In addition, the report suggests that molecular imaging will increasingly be used in conjunction with therapy. Details about the report are available at: www.strategyr.com/Radiopharmaceuticals_Market_Report.asp.

Global Industry Analysts, Inc.

Ethical Issues and Globalization of Clinical Trials

In an article appearing in the February 19 issue of the *New England*

Journal of Medicine (2009;360:817–823), Glickman and colleagues from the Duke University Clinical Research Institute (Durham, NC) reported on the ethical and scientific implications of globalization of clinical research. As part of this phenomenon, pharmaceutical and device companies have made research on populations in developing countries a growing and integral part of their development and validation strategies. The authors addressed the growing number of ethical issues raised by the fact that many clinical trials of U.S.-based drugs and devices are now pursued outside the United States.

The authors reviewed a U.S. government clinical trials registry for reports on clinical trials. A study of 300 published reports in major medical journals showed that 157 of 509 Phase 3 drug trials by U.S. pharmaceutical companies were conducted entirely outside the United States. More than half of the study sites for these trials (13,521 of 24,206) were overseas, with many in Eastern Europe and Asia.

In addition, the number of U.S. Food and Drug Administration–regulated investigators running trials abroad has increased by 15% per year, with the corresponding figure for U.S.-based investigators declining by 5.5% per year.

Although advantages in lower cost and less regulatory complexity are obvious, the authors noted that this trend raises a number of complex ethical questions, including but not limited to: Who actually benefits from globalization of clinical trials? What is the potential for exploitation of individuals recruited to participate? Are trial results accurate and valid and can they be compared from one site to another and from one population to another? A chart identifying issues and potential solutions was provided as part of the article. Many of these solutions are to be found through cooperative efforts from international academic, industry, and regulatory partners. The authors called for a "comprehensive review including representatives from developed and developing countries, perhaps commissioned by the Institute of Medicine or the World Health Organization" to reach international consensus on these issues.

New England Journal of Medicine

Image Gently Campaign Releases Parent Education Tools

Continuing its efforts to raise awareness about opportunities to lower radiation dose in pediatric imaging exams, the Image Gently campaign announced in January new materials to educate parents about medical imaging and to help them track their children's past imaging exams. "Radiologists, radiologic technologists, and medical physicists are committed to working together to lower radiation dose used for CT scans in children. We also want to work with pediatricians and parents to help ensure that children get the most appropriate imaging for their medical situation," said Marilyn Goske, MD, chair of the Alliance for Radiation Safety in Pediatric Imaging.

The Image Gently campaign is led by the alliance, which was founded in 2008 by the Society for Pediatric Radiology, the American College of Radiology, the American Society of Radiologic Technologists, and the American Association of Physicists in Medicine (AAPM) and now includes 29 U.S. and international medical organizations. General recommendations by the group for those who perform pediatric CT imaging exams are to: "child-size" the amount of radiation used, refrain from overscanning (scan only when necessary and only in the indicated region and avoid multiphase scanning), and involve medical physicists to monitor imaging techniques and technologists to optimize scanning.

One of the latest alliance releases, *My Child's Medical Imaging Record*, allows parents to record where and when a study was performed as well as the type of radiologic exam. *What Parents Should Know About CT Scans for Children: Medical Radiation Safety* and *What Parents Should Know About Medical Radiation Safety* are downloadable patient education brochures that provide definitions and descriptions of various imaging exams and inform parents of potential risks. These brochures provide dose estimates in comparison to natural background radiation, discuss possible alternative examinations that do not utilize radiation, and equip parents with questions to ask imaging providers.

Physicians are encouraged to download the materials from the Image Gently Web site and make them available to parents in their waiting rooms and offices. A special section of the Image Gently Web site will also be dedicated to providing parents with the most up-to-date information about children's imaging and tools to help them understand the benefits and concerns associated with various procedures.

"Parents can make better health care decisions on behalf of their children if they are armed with the correct information. Although medical imaging is increasingly replacing more invasive techniques in all areas of medicine, its risks and rewards may not be entirely understood. These brochures can help allay parents' concerns and help them give better information to providers so that they can make the best possible diagnostic and treatment decisions for their child," said Gerald A. White Jr., MS, chair of the board of the AAPM.

The Image Gently Web site (www.imagegently.org) also contains the latest research and educational materials to aid imaging professionals in determining appropriate radiation techniques to be used in children. A key feature of the Web site is a library of acquisition protocols that can be used to lower doses in pediatric imaging.

American College of Radiology

GAO Urges Stringent Review of Medical Devices

In January the U.S. Government Accountability Office (GAO) issued a congressional watchdog report urging the adoption of a policy requiring that (in the words of the report's title) *FDA Should Take Steps to Ensure That High-Risk Device Types Are Approved Through the Most Stringent Process.*

Included in the report were data indicating that the U.S. Food and Drug Administration (FDA) had cleared more than 220 high-risk (Class III) devices to go through a less stringent review process originally intended for simpler products.

From 2003 through 2007 the FDA reviewed 13,199 submissions for class 1 and II devices through the 501(k) process, and cleared 11,935 (90%). In addition to the 228 (67%) of 342 submissions for Class III reviewed and cleared, an additional 217 original and 784 supplemental premarketing approval (PMA) submissions for Class II were cleared, and 78% and 85%, respectively, of these submissions were approved.

Congress had originally envisioned that Class III devices would be approved through a more stringent PMA process, and the Safe Medical Devices Act of 1990 required that FDA either reclassify or establish a schedule for requiring PMAs for Class III device types. Rep. Frank Pallone (D-NJ), chair of the Health Subcommittee of the House of Representatives Energy and Commerce Committee, told the press that he would hold hearings on the review process. "GAO's investigation confirms my concerns that the approval process for medical devices is woefully inadequate. For years, Congress has required high-risk medical devices to undergo stringent pre-market review, but GAO's findings show that is simply not happening in every case," said Pallone.

U.S. Government Accountability Office

Frequent Repairs at Chalk River

On February 23 the third heavy water leak since December was detected at the Atomic Energy Canada, Ltd. (AECL), National Research Universal (NRU) reactor in Chalk River, Ontario. The facility, which was off line for almost all of 2008, provides about half the global supply of isotopes used in medical imaging. Routine monitoring detected small amounts of heavy water containing tritium within the NRU reactor building's ventilation system. The source of the water loss was found to be a 2.5-in diameter pipe within 1 of the reactor's heavy water purification circuits. The production of isotopes was not interrupted by the leak or patching efforts.

The reactor was previously shut down from February 15 to 17 so that repairs could be made to the mechanism that extracts metal isotope rods. Although production of medical isotopes was maintained throughout the outage, yields were at a reduced level for 4 d, prompting warnings of potential shortages in supplies of medical radionuclides.

Other heavy water leaks were reported in January and December. Public outcry greeted delayed news of the December leak, despite assurances from the AECL and the Canadian Nuclear Safety Commission (CNSC) that no one had been at risk. Michael Binder, the new CSNC president, told a government committee that the age of the facility necessitated frequent repairs, likening the 47-kg leak in December to a home repair problem. "You know: drip, drip, drip. It's of the same order of magnitude," he said.

Atomic Energy Canada, Ltd.
Canadian news sources

Single Large FDA Campus Near Completion

The U.S. Food and Drug Administration (FDA) is consolidating its previously scattered offices and laboratories into a single campus on the 662-acre site of the now-closed Naval Surface Warfare Center in White Oak, MD, near Washington, DC. The consolidation will cost $1.15 billion and include 14 new buildings totaling 3.1 million sf of office and laboratory space. According to an article that appeared on February 25 in the *New York Times*, the move promises long-term cost efficiencies and advantages in proximity of research and administrative groups. For many years the FDA has rented private space in 27 separate buildings across Montgomery County, MD, operating under 49 different leases. The move to the federally owned land and facility will eliminate the complexities of the rental process and is projected to save the government more than $10 million each year.

The FDA will occupy about 130 acres of the site. Six of 11 planned new buildings have been completed, and 4,800 FDA employees are already on campus working in the life sciences, engineering, and physics laboratories. The total number of employees at the site is projected to grow to 8,800 by 2012.

The size of the campus and availability of land so close to the Capital Beltway have led to planned nongovernment biotech and medical developments that offer new possibilities for FDA professional and scientific staff. One example cited by the *New York Times* is the planned move of Washington Adventist Hospital, a 102-y-old institution in nearby Takoma Park, to land adjacent to the FDA site. In January, Adventist and FDA representatives signed an agreement to share doctors and resources. "Most FDA doctors today don't have private practices," said Jere D. Stocks, the president of Adventist. "But the model we're trying to develop would give them an opportunity to do clinical practice a couple days a month in the hospital, where they can see patients, keep their skills sharp, see how equipment and drugs work with patients, and become better scientists."

New York Times

Fowler Inducted into LI Technology Hall of Fame

In a ceremony and reception held on March 4, Joanna Fowler, PhD, director of Radiotracer Chemistry, Instrumentation and Biological Imaging Program, at the U.S. Department of Energy (DOE) Brookhaven National Laboratory (Upton, NY), was inducted into the Long Island Technology Hall of Fame. One of 4 new inductees, Fowler was recognized for major contributions to brain research and the use of PET to study diseases such as addiction. "I am delighted to receive this honor," Fowler said. "I'm gratified that my research has led to a better understanding of the mechanisms of addiction and other diseases and has also aided in the diagnosis of disease." The Long Island Technology Hall of Fame recognizes,

honors, and preserves the contributions, accomplishments, and dedication of historical figures or current leaders in science or technology who have an impact on society.

Fowler's current research centers on using PET to study brain circuits disrupted in addiction. She is also involved in PET studies designed to understand the action of therapeutic drugs and facilitate the introduction of new drugs into clinical use. Her recent work has focused on variations in monoamine oxidase genes and their effects on personality and vulnerability to psychiatric disorders.

Fowler's past honors include the SNM Paul Aebersold Award and the DOE E.O. Lawrence Award, both received in 1997; the American Chemical Society (ACS) Francis P. Garvin–John M. Olin Medal in 1998, and the ACS Glen T. Seaborg Award in 2002. She was elected to the National Academy of Sciences (NAS) in 2004 and has been selected to receive the NAS Award in Chemical Sciences in April. She has published more than 350 peer-reviewed articles and holds 8 patents for radiolabeling procedures.

Brookhaven National Laboratory

Chernobyl Public Health Research Coordinated By IARC

A February 24 press release from the International Agency for Research on Cancer (IARC) announced the launch of the Agenda for Research on Chernobyl Health (ARCH), a European Commission FP7 Project to develop a strategic research agenda for the health consequences of the 1986 reactor accident. The IARC is taking a coordinating role in a "scoping" study of all relevant research to determine where future research efforts are most needed and to advise on the potential value of proposed studies to public health decision making. Speaking at a meeting of the expert group and advisors of the ARCH project, Christopher Wild, MD, IARC director, said: "Twenty-two years after the accident, the health consequences of Chernobyl are still debated, and yet much of what we conclude about those health effects will be the measuring stick of our future guidelines in ionizing radiation protection: for this reason we need to know what we know and be sure of what we don't know."

The main output of ARCH will be a strategic research agenda (SRA) for short-, medium- and long-term studies on health consequences of the accident. These studies will require the coordinated efforts of experts throughout Europe, including the 3 most affected countries: Belarus, the Russian Federation, and Ukraine. ARCH will bring together experts in epidemiology, clinical practice, pathology, cancer, dosimetry, radiobiology, genetics, epigenetics, risk assessment, and public health to prepare a practical and cost-effective research strategy.

ARCH will also seek the active participation and input of the research community and members of the wider public while preparing the SRA. Scientists from outside Europe will also be included as advisors, to ensure harmonization with other existing or planned activities around the world. An ARCH Web site will serve as a forum for comment on the work of ARCH and through which individuals may submit their own proposals.

IARC noted that the Chernobyl accident provides a unique opportunity to test several scientific hypotheses regarding both the exact mechanisms underlying radiation action and biology/genetics in general. Results of the project will be communicated to the public health authorities of the 3 most affected countries to assist in planning long-term public health programs that aim to reduce the health impact of the Chernobyl accident. Results will also be shared with other affected countries in Europe. "Paving the way for a more engaged and informed society in relation to radiation protection and health risks associated with ionizing radiation is part of the IARC agenda. Transparency in terms of the Chernobyl accident's consequences is essential to research in general and radiation research in particular," said Wild.

International Agency for Research on Cancer