

## FDA and Devices for Unmet Medical Needs

The U.S. Food and Drug Administration (FDA) on April 23 announced a proposal for a new program to provide earlier access to high-risk medical devices that are intended to treat or diagnose patients with serious conditions with medical needs unmet by current technology. The proposed Expedited Access Premarket Approval Application for Unmet Medical Needs for Life-Threatening or Irreversibly Debilitating Diseases or Conditions (Expedited Access PMA or EAP) program features earlier and more interactive engagement with FDA staff—including involvement of senior management and a collaboratively developed plan for collecting scientific and clinical data to support approval. Taken together, the proposed features are designed to provide specific types of patients with earlier access to safe and effective medical devices.

In a press release, the FDA stressed that EAP is not a new pathway to market but, instead, a collaborative approach to facilitate product development under the agency's existing regulatory authorities. Other existing device programs have focused on reducing the time for premarket review, but EAP also seeks to reduce the time associated with product development. "We are excited to offer a proposed program for expedited access for certain high-risk medical devices," said Jeffrey Shuren, MD, director of the FDA's Center for Devices and Radiological Health. "The program allows manufacturers to engage early and often with the agency. We expect most devices that enter this program will be in the preclinical trial phase."

To be eligible for participation in the program, a medical device must: be intended to treat or diagnose a life-threatening or irreversibly debilitating disease or condition and be assignable to at least 1 of the following categories: (1) no approved alternative treatment/diagnostic exists; (2) a breakthrough

technology that provides a clinically meaningful advantage over existing technology; (3) offers a significant, clinically meaningful advantage over existing approved alternatives; (4) availability is in the patient's best interest; or (5) have an acceptable data development plan that has been approved by the FDA

In the EAP program, the FDA will continue to apply the current approval standard of demonstrating a reasonable assurance of safety and efficacy. The FDA published a separate draft guidance outlining the agency's current policy on data collection after product approval and what actions are available to the FDA if approval conditions (such as postmarket data collection) are not met. Included in the guidance is advice on the use of surrogate or independent markers to support approval, similar to data points used for accelerated approval of prescription drugs. Additional information is available at: [www.fda.gov/medicaldevices/default.htm](http://www.fda.gov/medicaldevices/default.htm).

*U.S. Food and Drug Administration*

## INDs for PET Imaging Probes

In an article e-published on April 15 ahead of print in *Molecular Imaging and Biology*, Mosessian et al. from the David Geffen School of Medicine at the University of California Los Angeles reported on the development of an "efficient, streamlined, cost-effective approach" to obtain Investigational New Drug approvals for PET imaging probes from the U.S. Food and Drug Administration (FDA). The authors described the collaborative pursuit of regulatory approval through coordinated efforts within an academic institution, involving a range of scientific disciplines and individuals with expertise in rigorously following and documenting requisite data and compliance. The success of this effort is detailed in the example of translation of 3 <sup>18</sup>F-fluoro-arabinofuranosylcytosine analog PET probes to phase 1 clinical trials. Through this and other efforts, the authors have established a mechanism that can be

replicated for fulfilling FDA regulatory requirements for translating promising PET imaging probes from preclinical research into human clinical trials within and using solely the resources of an academic institution in an efficient and cost-effective manner.

*Molecular Imaging and Biology*

## Nordion to Go Private

Nordion, Inc., based in Ottawa, Canada, and one of the world's leading producers of <sup>99</sup>Mo, announced on March 28 that it had entered into a "definitive agreement" to be acquired by Sterigenics, a Deerfield, IL-based sterilization services provider owned by the private equity firm GTCR LLC, for \$727 million. Earlier in the day and preceding this announcement, legislation was introduced through which the Canadian government would remove the current 25% foreign investment cap in cases deemed to be of "net benefit" to Canada.

According to an accompanying press and financial release, Nordion will operate as a standalone company within Sterigenics and will continue to operate under the Nordion name. The transaction marked the completion of a strategic review by Nordion and comes after more than a decade of supply challenges as a result of shutdowns and reactor inactivity at the aging Atomic Energy of Canada Ltd. facility in Chalk River, Ontario. Although these challenges have directly affected the nuclear community in sporadic shortages of <sup>99</sup>Mo for <sup>99m</sup>Tc applications, Sterigenics addressed only <sup>60</sup>Co as a product priority: "Nordion is a recognized global leader in the medical isotopes and sterilization sectors, sharing a similar mission to improve global public health," said Michael Mulhern, Chief Executive Officer, Sterigenics. "Through this acquisition, our focus is to ensure a stable long-term source of <sup>60</sup>Co that will maintain customer confidence in the future availability and growth of gamma sterilization as one of many sterilization options. In the short term, Nordion

customers should expect business as usual. Over the long run, we look forward to working with existing and new reactor partners to create a larger and more reliable supply of  $^{60}\text{Co}$  for the future.”

*Nordion, Inc.*

### **SNMMI Endorses Congress on SGR and Appropriate Use**

On April 3 SNMMI issued a statement endorsing actions by the U.S. Congress in “passing historic legislation linking physician payment to [appropriate use criteria], thus shifting focus to a more evidence-based health care system.” The Senate voted on April 2 to pass HR 4302, the Protecting Access to Medicare Act of 2014, which also passed the House of Representatives by voice vote on March 27. The changes cited by SNMMI were included as part of the most recent temporary patch to the Sustainable Growth Rate (SGR) system, which pushed the deadline for SGR repeal to April 1, 2015.

HR 4302 requires the Secretary of Health and Human Services to launch a program that encourages the use of AUC for advanced diagnostic imaging services no later than 2017. The Secretary, in consultation with stakeholders, must choose which AUC will be included in the program no later than November 15, 2015. SNMMI leadership and that of other professional imaging societies believe that with AUC, physicians will be able to better identify which nuclear medicine procedures are most appropriate for specific patients. In turn, this could lead to cost savings through better allocation of health care resources. AUC, which must be created or endorsed by national medical specialty societies or other provider-led entities, must also have stakeholder consensus, be scientifically valid and evidence based, and be based on studies that are published and reviewable by stakeholders.

In its statement, SNMMI expressed concerns about the “broadness” of the legislative language, which puts implementation of the new payment structure at the Secretary’s discretion, and noted that “SNMMI will continue to work with Congress and the Secretary

to ensure that smaller specialty societies have a voice in selecting the AUCs that will be applicable to the program.”

SNMMI also noted with approval Congressional passage of the 1-y patch to the SGR system, which delays an overall 24% cut to provider payments; delays implementation of ICD-10, which will replace existing coding for medical diagnoses and inpatient procedures, until October 2015; phases in cuts to medical services >20% over a 2-y period; and imposes new requirements for data from the Centers for Medicare and Medicaid Services on the 25% multiple procedure payment reduction, which affects certain multiple imaging procedures provided to a patient in a single session.

*SNMMI*

### **Interactive Research Conduct Site**

The U.S. Department of Health and Human Services Office of Research Integrity (ORI) and Office for Human Research Protections on March 31 launched The Research Clinic, a Web-based interactive training video aimed at teaching clinical and social researchers how to better protect research subjects and avoid research misconduct. The video allows the viewer to assume the role of 1 of 4 characters and determine the outcome of the storyline by selecting decision-making choices for each playable character. The characters include: (1) A principal investigator (PI), a busy oncologist who must balance doing what he thinks best for his patients and for his research; (2) a clinical research coordinator, an overworked nurse whose research PI pressures her to falsify data and violate study protocols; (3) a research assistant who has difficulties obtaining informed consent and following research protocols; and (4) an Institutional Review Board chair tasked with ensuring that research subjects and the integrity of the research enterprise are protected while dealing with a culture resistant to change. Viewers make choices in various scenarios, and those choices lead to divergent and sometimes adverse outcomes. The video highlights scenarios to help identify research

misconduct in the clinical setting and provides solutions to help researchers avoid such missteps. “We suspect research misconduct in clinical research may be underreported because review of clinical research data often focuses on issues other than falsification, fabrication, or plagiarism,” said Don Wright, MD, MPH, ORI acting director. The training video is available at <http://ori.hhs.gov/theresearchclinic>. A similar interactive site for biomedical research has been available since 2011 at <http://ori.hhs.gov/thelab>.

*U.S. Department of Health and Human Services*

### **Outpatient Diagnostic Errors in 5% of Adults**

According to a study published on April 17 ahead of print in *BMJ Quality & Safety*, diagnostic errors (defined as “missed opportunities to make a timely or correct diagnosis based on available evidence”) occur in >5% of adults in outpatient care in the United States each year. Singh and researchers from the Veterans Affairs Medical Center, Baylor College of Medicine, and University of Texas Medical School at Houston (all in Houston, TX) reported on “The frequency of diagnostic errors in outpatient care: estimations from 3 large observational studies involving U.S. adult populations,” as part of a study partially funded by the Agency for Healthcare Research and Quality (AHRQ). The 3 observational studies used to provide data for extrapolations about misdiagnoses focused on general primary care, colorectal cancer, and lung cancer. The authors looked for abnormal patterns in rates of return visits, and diagnostic errors were confirmed through detailed chart reviews. Singh et al. estimated that about half of the diagnostic errors could have severely harmed patients.

“Misdiagnosis is clearly a serious problem for the health care field,” said Singh. “This population-based estimate should provide a foundation for policy-makers, health care organizations, and researchers to strengthen efforts to measure and reduce diagnostic errors.” Singh noted that the findings, which are consistent with recent data from

general public resources, are robust and based on large-sample-size studies.

Ensuring that test results are not lost or misplaced, including through the use of health information technology, is a critical part of reducing diagnostic errors. AHRQ recently published a toolkit to help doctors, nurses, and medical office staff improve processes for tracking, reporting, and following up with patients after medical laboratory tests. The toolkit, *Improving Your Office Testing Process*, is available at: [www.ahrq.gov/professionals/quality-patient-safety/quality-resources/tools/office-testing-toolkit/](http://www.ahrq.gov/professionals/quality-patient-safety/quality-resources/tools/office-testing-toolkit/). The Office of the National Coordinator for Health Information Technology recently released the “SAFER Guides”—a set of interactive tools to help health care providers more safely use electronic health information technology products, including test results reporting and follow-up. These guides are available at [www.healthit.gov/safer/safer-guides](http://www.healthit.gov/safer/safer-guides).

BMJ Quality & Safety  
*Agency for Healthcare Research  
and Quality*

### Accreditation and Diagnostic Imaging Access

The Government Accountability Office (GAO) on April 21 issued its second Congressionally mandated re-

port on implementation of the Medicare Improvements for Patients and Providers Act (MIPPA) of 2008 accreditation requirement for Medicare suppliers who provide the technical component of advanced diagnostic imaging (ADI) services. This report, “Medicare Imaging Accreditation: Effect on Access to Advanced Diagnostic Imaging is Unclear Amid Other Policy Changes,” follows the 2013 report “Medicare Imaging Accreditation: Establishing Minimum National Standards and an Oversight Framework Would Help Ensure Quality and Safety of Advanced Diagnostic Imaging Services.” MIPPA required that beginning on January 1, 2012, suppliers who produce images for Medicare-covered ADI services in office settings be accredited by an organization approved by the Centers for Medicare & Medicaid Services.

In the current report, the GAO looked at the effect the accreditation requirement may have had on beneficiary access to ADI services provided in the office setting. GAO staff examined trends in the use of CT, MR, and nuclear medicine imaging (including PET) provided to Medicare beneficiaries from 2009 through 2012 and subject to the ADI accreditation requirement. GAO also interviewed CMS officials; representatives from the Intersocietal

Accreditation Commission and the American College of Radiology (the 2 CMS-approved accrediting organizations that accounted for 99% of all accredited suppliers as of January 2013); and 19 accredited ADI suppliers reflecting a range of geographic areas, imaging services provided, and accrediting organizations. GAO also reviewed relevant literature to understand the context of observed changes in ADI services during the period.

The researchers found that the number of ADI services provided to Medicare beneficiaries in the office setting began declining before and continued declining after the accreditation requirement went into effect in 2012. The rate of decline from 2009 to 2010 was similar to the rate from 2011 to 2012 for all ADI modalities studied. They concluded that these data “suggest that the overall decline was driven, at least in part, by factors other than accreditation.” Reduced Medicare payments for specific imaging studies, for example, may have contributed to the decline in numbers for those services. In addition to payment reductions, other potential factors cited were changes in prior authorization policies and physician and patient awareness of risks associated with radiation.

*Government Accountability Office*

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## FROM THE LITERATURE

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*Each month the editor of Newsline selects articles on diagnostic, therapeutic, research, and practice issues from a range of international publications. Most selections come from outside the standard canon of nuclear medicine and radiology journals. These briefs are offered as a monthly window on the broad arena of medical and scientific endeavor in which nuclear medicine now plays an essential role. The lines between diagnosis and therapy are sometimes blurred, as radiolabels are increasingly used as adjuncts to therapy and/or as active agents in therapeutic regimens, and these shifting lines are reflected in*

*the briefs presented here. We have also added a small section on noteworthy reviews of the literature.*

### PET and Disorders of Consciousness

In an article e-published on April 15 ahead of print in *Lancet* that received press coverage around the world, Stender, from the University of Copenhagen (Denmark), and researchers from Belgium and Canada reported on the “Diagnostic precision of PET imaging and functional MR imaging in disorders of consciousness.” The study included patients diagnosed with unresponsive wakeful-

ness ( $n = 41$ ), locked-in syndrome ( $n = 4$ ), or minimally conscious states ( $n = 81$ ). Patients underwent standardized clinical assessments (Coma Recovery Scale–Revised) as well as cerebral  $^{18}\text{F}$ -FDG PET and functional MR imaging during mental activation tasks and were followed up at 12 mo with the Glasgow Outcome Scale–Extended. The researchers found that PET had high sensitivity for identification of patients in minimally conscious states and high correlation with Coma Recovery Scale scores. MR imaging was less sensitive and had poorer correlations. PET accurately predicted outcomes in 74% of