Scientists Call for New Regulatory Approach to Radiopharmaceuticals

Nuclear medicine researchers, writing in the November/December issue of *Molecular Imaging and Biology* (2004;6:361–367), called for a new regulatory approach for PET molecular imaging probes, a model they also noted would be well applied to other diagnostic radiopharmaceuticals. Led by journal editor-in-chief Jorge Barrio, PhD, the writers outlined an approach in which PET imaging probes would be placed in a "no significant risk" category, much like the similarly designated category for devices in current Food and Drug Administration (FDA) regulations. The newly revitalized FDA-sanctioned Radioactive Drug Research Committee (RDRC) would then oversee all diagnostic research with these probes. The RDRC could approve "first in man" use applications and supervise a broader spectrum of diagnostic research protocols, including (among others) the use of molecular imaging probes as screening tools in drug discovery. This would eliminate the use of the current Investigational New Drug mechanism for diagnostic probes. Instead, after efficacy is proven, a newly constituted Radioactive Drug Advisory Committee would provide a binding assessment of safety and efficacy data. If such data led the committee to recommend the probe, the FDA would issue approval and the existing mechanism to seek reimbursement would be used. The FDA would retain its direct oversight function for traditional manufacturers engaged in commercial distribution of approved diagnostic molecular imaging probes (under a New Drug Approval). The authors noted that, "With abbreviated and more appropriate regulations, new PET molecular imaging probes for diagnostic use would be then rapidly incorporated into the mainstream diagnostic medicine. Equally importantly, this approach would facilitate the use of molecular imaging in drug discovery and development, which would substantially reduce the costs and time required to bring new therapeutic drugs to market."

Molecular Imaging and Biology

ICRP Issues Low-Dose Report, Supports LNT Model

On December 10, 2004, a task group of the International Commission on Radiological Protection (ICRP) released on its Web site (www.icrp.org) a draft report on *Low-Dose Extrapolation of Radiation-Related Cancer Risk*. The 214-page document considers "the evidence relating to cancer risk associated with exposure to low doses of low-LET [linear energy transfer] radiation, and particularly doses below current recommended limits for protection of radiation workers and the general public." The purpose of the report is to address "evidence regarding linearity of dose response for all cancers considered as a group, but not necessarily individually, at low doses (the so-called linear, no-threshold [LNT] hypothesis), and the possibility of a universal threshold dose below which there is no risk of radiation-related cancer."

To the disappointment of many in radiation research, the ICRP seems likely to join other groups, such as the United Nations Scientific Committee on the Effects of Atomic Radiation and the U.S. National Council on Radiation Protection and Measurements, in recommending that researchers, clinicians, and regulators continue to be guided by the LNT hypothesis.

The report is organized by scientific discipline, including epidemiologic studies of exposed human populations, the biology of low-dose risk, cellular consequences of radiation-induced damage, carcinogenic effects of ionizing radiation, and quantitative uncertainty analysis. The committee concludes that, "While existence of a low-dose threshold does not seem unlikely for radiation-related cancers of certain tissues and cannot be ruled out for all cancers as a group, the evidence as a whole does not favor the existence of a universal threshold, and there seems to be no particular reason to factor the possibility of a threshold into risk calculations for purposes of radiation protection. The LNT hypothesis, combined with an uncertain DDREF [dose and dose rate effectiveness factor] for extrapolation from high doses, remains a prudent basis for radiation protection at low doses and low dose rates." The authors add, "Moreover, the argument that radiation protection standards should be relaxed 'because it is possible that there may not be *any* risk at low doses' is unlikely to be persuasive to persons who are concerned about the possibility that risk associated with very low doses may be unacceptably high, and it may undermine the more realistic argument that the risk, which is understood rather well compared to that associated with other common carcinogens, is almost certainly less than some stated value which may be considered tolerable, for various reasons such as economic benefits or consideration of risks associated with alternative strategies involving less exposure."

Responding to the ICRP draft, Australian D.J. Higson wrote in the November issue of *Health Physics* (2004;87[suppl 5]:S47–S50) that the LNT model has been a "convenient

tool in the practice of radiation protection, but it is not supported by scientific data at doses less than about 100 millisieverts or at chronic dose rates up to at least 200 millisieverts per year." He added that "the assumption that such exposures are harmful may not even be conservative and has helped to foster an unwarranted fear of low-level radiation." He noted that "national societies for radiation protection may wish to consider the need to lobby the ICRP . . . to further relax adherence to the LNT assumption."

The ICRP will be accepting detailed responses to the draft report through March 18. The full report can be accessed and responses filed at www.icrp.org/draft_cancer.asp. The report is expected to be finalized later this year.

International Commission on Radiological Protection

Lauriston Sale Taylor 1902–2004

Lauriston S. Taylor, whose career in radiation science spanned most of the 20th century and was a pioneer in radiation protection and measurement, died on November 26, 2004, in Mitchellville, MD, at the age of 102. He was born in Brooklyn, NY, and grew up near South Orange, NJ, where on several occasions he visited Thomas Edison in his laboratory. Edison gave the boy a cold-cathode x-ray tube, beginning a lifelong interest in ionizing radiation. At the age of 26, Taylor founded the U.S. Advisory Committee on X-Ray and Radium Protection, which was chartered by Congress as the National Council on Radiation Protection and Measurements (NCRP) in 1964. He was also in the small group who founded the forerunner of the International Commission on Radiological Protection in 1929. He worked for almost 3 decades at the National Bureau of Standards (NBS) to develop the field of radiation dosimetry, including medical applications.

His service in scientific administration and education during World War II led to 2 Presidential Citations, the Medal of Freedom, and the Bronze Star (Presidential). In 1945 he was made Director of Operations of the Research Division of the U.S. Continental Air Command, but returned to the NBS in 1946. He retired as Associate Director in 1965.

From 1956 to 1971 he was Special Assistant to the President of the National Academy of Sciences and Executive Director of the Academy's Advisory Committee on Emergency Planning. From 1971 to 1977 he served as president of the newly reorganized NCRP. He received numerous honors over the course of his long career, including 2 honorary doctorates, the gold medal of the International Congress of Radiology, the gold medal of the Royal Swedish Academy of Sciences, the gold medal of the American Roentgen Ray Society, and the Distinguished Service Award from the Executive Office of the President.

A more complete tribute to Taylor and his remarkable life and accomplishments can be accessed at the NCRP Web site at www.ncrponline.org/LSTaylor%20obituary.pdf.

National Council on Radiation Protection and Measurements

NEMA Releases Revised DICOM Standard

The National Electrical Manufacturers Association (NEMA; Rosslyn, VA) released on December 20, 2004, a 16-part update of the Digital Imaging and Communications in Medicine (DICOM) standard. The DICOM Standard is a multipart set of rules that establishes a single language for exchanging digital images and related information, including patient name, reason for procedure, instrument used, and more. DICOM specifies protocols, commands, and standards that enable users to acquire, display, store, query, retrieve, move, or print medical images between instruments, computers, and hospitals and facilitates interoperability of medical imaging equipment. The DICOM Standard is the result of collaboration between software engineers from major imaging and computer companies, physicians (represented by professional societies, including SNM members), and government agencies and trade associations from around the world.

"About 25 new features have been added to the 2004 standard," said Dwight Simon, medical standards director at Merge eFilm and vendor chair of the DICOM committee, which oversees the publication. "These cover everything from Web access to new media, such as USB and flash memory devices, that can be used to transport DICOM information. We've added some functionality for some of the newer specialties that use DICOM, such as dentistry, ophthalmology, breast imaging, and ob/gyn. We keep adding features to help users capture the specific information they need to do reporting in such areas as cath lab, vascular and intravascular ultrasound, breast imaging, and echocardiography." He added that a newly enhanced DICOM conformance statement definition is designed to help users better understand a product's DICOM functionality and give a much better description of the product's ability to interoperate with another product that supports compatible DICOM features.

The 16 parts of the standard may be purchased separately, or the entire set may be purchased by visiting http://www.nema.org/stds/ps3set.cfm.

National Electrical Manufacturers Association

Insurer Adopts, Endorses ACS Criteria

UnitedHealthcare (Minneapolis, MN) announced in December 2004 that it plans to adopt as a guideline for its imaging providers the American College of Radiology (ACR) accreditation programs and imaging selection (appropriateness) criteria. An article in the January 1, 2005, issue of *Managed Care Outlook*

(Continued on page 30N)

(Continued from page 28N)
highlighted the significance of this move to accept a professional organization's practice and standards criteria. The company is the largest health insurer in the United States, providing coverage to more than 20 million individuals. Although UnitedHealthcare insists that it will not drop unaccredited facilities from its list, it does intend to "drive" more referrals to accredited facilities and to evaluate imaging practice on the basis of ACR criteria. "If a doctor does not follow the criteria, the insurer could refuse to allow an imaging examination to be performed or a physician could be directed to talk to a consultant to decide which exam is best," said James P. Borgstede, MD, chair of the ACR Board of Chancellors. "The goal is to educate the ordering physician on the most appropriate examination."

UnitedHealthcare plans to distribute the ACS Appropriateness Criteria to as many as 450,000 referring physicians, with an initial focus on oncology and musculoskeletal imaging. The SNM is working actively with the ACR on a number of nuclear medicine standards initiatives that could eventually be included, although these were not mentioned in initial announcements.

"Imaging utilization is going to be controlled in one fashion or another by the carriers, and we would like to be a player there," Borgstede stated. "That's the opportunity we've had with UnitedHealthcare, and why I'm so excited about it."

American College of Radiology

AMA Votes on Expert Testimony

After substantial debate, the American Medical Association (AMA) House of Delegates announced on December 6 at its meeting in Atlanta, GA, the intent to further efforts to ensure honest testimony from expert witnesses by creating model state legislation for physicians who testify in medical liability cases. The model legislation would be based on existing Federal Rules of Civil Procedure, which mandate full and timely disclosure of expert witness opinions, reports, qualifications, compensation, and prior testimonial experience. "Junk science has no place in the courtroom," said AMA Immediate Past President Donald J. Palmisano, MD. "We will continue to assist our state, county, and specialty medical societies to discipline physicians who provide false or misleading testimony."

The AMA emphasized that minimum statutory expert witness requirements should be established in medical liability cases, including requiring the witness to have comparable education, training, and occupational experience in the same field as the defendant. One of the most controversial issues in the debate was the question of whether board certification by a specialty organization should be required of an expert witness. Despite the historic unwillingness of the AMA to require board certification as a mark of expertise, the House voted that an expert witness should be certified by a board recognized by the American Board of Medical Specialties, the American Osteopathic Association, or by a board with equivalent standards. The expert also should be in active medical practice or teaching within 5 years of the occurrence giving rise to the claim. "We believe physicians who testify are practicing medicine," said Palmisano. "They should not accept contingency fees or do anything that might threaten the integrity of their judgment."

The AMA continues to look at the possibility of developing and maintaining an Internet-based registry of physicians who testify as expert witnesses in medical liability cases, although the AMA Board voted that previous proposals would be too costly and too difficult to administer.

American Medical Association

NIU and Fermilab Team Up for Neutron Therapy

Northern Illinois University (NIU; Napierville, IL) announced on December 6, 2004, plans to revive a unique and proven cancer treatment that blends advanced medical science with products from the proton linear accelerator at the Department of Energy (DOE) Fermi National Accelerator Laboratory (Batavia, IL). The newly formed NIU Institute for Neutron Therapy at Fermilab will deliver neutron therapy to patients and conduct extensive research on areas of therapy ncluding locally advanced prostate cancer, locally advanced head and neck tumors, inoperable sarcomas, and cancer of the salivary glands. The treatment is offered at only 2 other sites in the United States.

The institute will serve as many as 145 patients in its first year. Working in tandem with hospitals in the region, the previous neutron therapy center at Fermilab treated more than 3,100 patients over nearly 3 decades. The program was ended in 2003, when a local hospital curtailed its participation.

"The DOE Office of Science welcomes the NIU Institute for Neutron Therapy," said Dr. Raymond L. Orbach, Director of the DOE Office of Science. "From the earliest days of high-energy physics in the 1930s to the latest 21st-century initiatives, the innovative technologies of particle accelerators have created powerful new tools for medicine. The technology breakthroughs that allow physicists to unlock the deepest secrets of the universe also inspire advances in the understanding, diagnosis, and healing of disease. The NIU Institute for Neutron Therapy at Fermilab is a good example."

More information on the NIU Institute for Neutron Therapy at Fermilab is available online at www.neutrontherapy.niu.edu.

U.S. Department of Energy

(Continued on page 35N)

whether serum thyroglobulin (Tg) measured at the time of remnant ablation could be used to predict the persistence or recurrence of disease in low-risk patients with differentiated thyroid carcinoma. The study included 268 patients who had undergone total or near-total thyroidectomy and immediate ^{131}I remnant ablation. Serum Tg levels at the time of ablation were compared with those of the original diagnostic whole-body scan (WBS). Significant correlation was found between Tg levels at ablation and at whole-body scanning. Of 143 patients with ablation Tg >2 μg/L, 114 showed detectable (≥ 1 μg/L) Tg at whole-body scanning. Of 125 patients with ablation Tg ≤ 2 μg/L, 70 showed undetectable (<1 μg/L) Tg at whole-body scanning. After follow-up periods of 2.8–8.3 years, the positive predictive value for recurrence in patients with ablation Tg >2 μg/L was found to be 23.1%. The negative predictive value for recurrence in patients with ablation Tg ≤ 2 μg/L was 98.4%. The authors concluded that "these data indicate that serum Tg levels measured at the time of immediate postoperative ^{131}I remnant ablation correlated well with serum Tg levels at the time of the initial diagnostic WBS and had a complementary role for predicting persistence or recurrence of disease in the earliest postoperative period."

Journal of Clinical Endocrinology

PET Imaging of Suicide Gene Therapy

In an article e-published ahead of print in the December 10 issue of *Cancer Gene Therapy*, Yaghoubi et al. from the University of California at Los Angeles School of Medicine and the Stanford University School of Medicine (CA) described the use of a PET reporter probe (9-(4-^{18}F-fluoro-3-(hydroxymethyl)-butyl)guanine [^{18}F-FHBG]) to monitor the expression of a mutant herpes simplex virus 1 thymidine kinase (HSV1-sr39tk) in C6 glioma-implanted mice that received ganciclovir treatments. ^{18}F-FDG PET imaging was used to assess tumor cell uptake. Uptake of both radiolabeled tracers was high before initiation of ganciclovir treatment and declined significantly, as did tumor volumes, after 2 weeks of treatment. Three weeks after treatment was discontinued, the tumors began to grow. Imaging at that time revealed a significant increase in ^{18}F-FDG uptake, but concentrations of ^{18}F-FHBG in tumor remained at background levels, indicating that the effectiveness of ganciclovir therapy in eradicating HSV1-sr39tk-expressing cells can be monitored by ^{18}F-FHBG PET. This and similar molecular imaging of the process of suicide transgene expression promise to aid in the development of more precise targeting approaches and methods for assessing therapeutic efficacy.

Cancer Gene Therapy

(Continued from page 30N)

Focus on Molecular Imaging at BIROW III

The third annual Biomedical Imaging Research Opportunities Workshop (BIROW III) is scheduled for March 11 and 12 at the Hyatt Regency in Bethesda, MD. Organized by the Radiological Society of North America, the American Association of Physicists in Medicine, the Biomedical Engineering Society, the Academy of Radiology Research, and the American Institute for Medical and Biological Engineering, the goal of the workshop is to identify and explore new opportunities for basic science research and engineering development in biomedical imaging as well as related diagnosis and therapy.

The workshop is designed to provide information and ideas for new investigators to support accelerated development of biomedical imaging as a scientific discipline and to facilitate coordinated imaging research. It will include invited speakers on selected topics, focused breakout groups, and discussion with invited government representatives. The specific topics to be explored are:

- Cell trafficking;
- Informatics solutions in imaging;
- Image-guided treatment; and
- Technology development: from concept to clinic.

More information is available at www.birow.org.

Approximately 150 radiologic researchers, physicists, and engineers attended BIROW II in February 2004. The official report from that conference is scheduled for publication within the next few months. The official report from BIROW I includes an introduction and summaries from the breakout committees and can be viewed at www.birow.org.