



The University of New Mexico ♦ Health Sciences Center
COLLEGE OF PHARMACY



:::VOLUME 14, LESSON 1:::

***Meeting Critical Radioisotope Needs in a World
Concerned about Nuclear Terrorism***

Continuing Education for Nuclear Pharmacists
and
Nuclear Medicine Professionals

Darrell R. Fisher
Scientific Director, Office of National Isotope Programs
(Operated for the U.S. Department of Energy)
Pacific Northwest National Laboratory
902 Battelle Boulevard, P7-27
Richland, WA 99354



The University of New Mexico Health Sciences Center College of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmaceutical education. Program No. 039-000-08-001-H04-P and 039-000-08-001-H04-T. 1.0 Contact Hours or .1 CEUs.

-- Intentionally left blank --

Meeting Critical Radioisotope Needs in a World Concerned about Nuclear Terrorism

By
Darrell R. Fisher

Editor, CENP

Jeffrey Norenberg, MS, PharmD, BCNP, FASHP, FAPhA
UNM College of Pharmacy

Editorial Board

Sam Augustine, R.P, PharmD, FAPhA
Stephen Dragotakes, RPh, BCNP, FAPhA
Richard Kowalsky, PharmD, BCNP, FAPhA
Neil Petry, RPh, MS, BCNP, FAPhA
James Ponto, MS, RPh, BCNP, FAPhA
Tim Quinton, PharmD, BCNP, FAPhA
S. Duann Vanderslice, RPh, BCNP, FAPhA

Advisory Board

Mark Gurgone, BS, RPh.
Vivian Loveless, PharmD, BCNP, FAPhA
Lisa Marmon, RPh, BCNP
Michael Mosley, RPh, BCNP
Janet Robertson, BS, RPh, BCNP
Brantley Strickland, BCNP
John Yuen, PharmD, BCNP

Director, CENP

Kristina Wittstrom, RPh, BCNP
UNM College of Pharmacy

Administrator, CE & Web Publisher

Christina Muñoz, B.S.
UNM College of Pharmacy

While the advice and information in this publication are believed to be true and accurate at the time of press, the author(s), editors, or the publisher cannot accept any legal responsibility for any errors or omissions that may be made. The publisher makes no warranty, expressed or implied, with respect to the material contained herein.

Copyright 2008
University of New Mexico Health Sciences Center
Pharmacy Continuing Education
Albuquerque, New Mexico

MEETING CRITICAL RADIOISOTOPE NEEDS IN A WORLD CONCERNED ABOUT NUCLEAR TERRORISM

STATEMENT OF LEARNING OBJECTIVES:

Upon completion of this course, participants will be able to:

1. Recognize the risk of nuclear materials theft and misuse
2. Describe the roles of the federal agencies in nuclear material safeguards
3. Describe federal requirements for safeguarding nuclear materials. These requirements include new or proposed Nuclear Regulatory Commission requirements mandated by the Energy Policy Act of 2005.
4. Identify current problems in meeting U.S. needs for radioisotopes in nuclear medicine and other healthcare applications
5. Discuss the impact of federal policies and regulations on the ability of government and commercial isotope suppliers to supply radioisotopes for applications in medicine
6. State the actions needed to improve the availability of radioisotopes needed for new radiopharmaceutical research and development

COURSE OUTLINE

SUMMARY	7
THE ISOTOPE SUPPLY AND AVAILABILITY CHALLENGE	9
NUCLEAR AND RADIOLOGICAL TERRORISM	11
THE FEDERAL GOVERNMENT ROLE IN RADIOACTIVE MATERIAL SECURITY	13
NUCLEAR REGULATORY COMMISSION	13
<i>Security and Control of Radioactive Material</i>	14
<i>Accountability</i>	14
<i>Example</i>	14
<i>Case Study No. 1</i>	15
<i>Case Study No. 2</i>	15
DEPARTMENT OF HOMELAND SECURITY	16
NATIONAL NUCLEAR SECURITY ADMINISTRATION	16
DEPARTMENT OF TRANSPORTATION	17
ENVIRONMENTAL PROTECTION AGENCY	17
OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION	17
DEPARTMENT OF COMMERCE	18
FOOD AND DRUG ADMINISTRATION	18
ENERGY POLICY ACT OF 2005	18
<i>Fingerprinting and Background Checks</i>	20
<i>Radiation Source Tracking System</i>	20
<i>Source Security and Replacement Technology</i>	20
<i>Nuclear Infrastructure</i>	22
STATUS OF MEDICAL ISOTOPE PRODUCTION IN THE U.S.	22
CONCLUSIONS.....	24
ACKNOWLEDGEMENTS.....	24
REFERENCES.....	25
ASSESSMENT QUESTIONS	26

-- Intentionally left blank --

Presented at 2008 Annual APhA Meeting

MEETING CRITICAL RADIOISOTOPE NEEDS IN A WORLD CONCERNED ABOUT NUCLEAR TERRORISM

By

Darrell R. Fisher
Scientific Director, Office of National Isotope Programs
(Operated for the U.S. Department of Energy)
Pacific Northwest National Laboratory
902 Battelle Boulevard, P7-27
Richland, WA 99354

SUMMARY

Isotope availability is the single most critical issue in the practice of nuclear medicine and development of new radiopharmaceuticals. The United States relies on both imports and domestic production of radioisotopes to satisfy the everyday demand for radiopharmaceuticals used in nuclear medicine and for other applications in science and medicine. A substantial fraction of the commercial isotope demand is met by reliance on foreign suppliers. At the same time, availability of many research isotopes for new radiopharmaceutical development is poor.

An emerging challenge for isotope producers and users is the increasing threat of radiological terrorism, both in this country and internationally. One consequence of the increasing threat of nuclear and radiological terrorism is for government to place increasingly tighter controls on the production, transportation, and use of nuclear material for beneficial purposes, including the use of radioisotopes for medicine. Both the federal government and the states have increased security requirements to prevent malicious misuse of radioactive materials. For example, the Department of Homeland Security has increased border security against illegal import of nuclear and radiological materials by installing sensitive radiation detection instruments for screening vehicles and cargo entering the country. The Nuclear Regulatory Commission has improved tracking of radioactive materials shipments, and requires new physical security measures to prevent theft or diversion. The Energy Policy Act of 2005 stipulated several measures to increase nuclear material security, such as

- eliminating the use of highly enriched uranium in isotope-production reactors
- strengthening regulatory control over radioactive materials produced in accelerators, and discrete sources of radium-226
- restricting the amounts and types of radioactive materials that can be shipped domestically and internationally

- suggesting that electronic systems or non-radioactive material alternatives should replace common radiation source applications
- requiring the permanent disposal of legacy materials that are essential for producing medical isotopes needed for the next generation of cancer diagnostic and therapeutic agents

Nuclear pharmacists, nuclear medicine practitioners, researchers, and radiation safety officers need to be aware of current and proposed changes to nuclear materials security and accountability regulations. However, sometimes the heavy hand of regulation swings too far, thereby impeding legitimate production, commerce, and use of radioactive materials. Institutions that depend on radioisotopes for legitimate and beneficial purposes should recognize the trend of new regulations that could further restrict the availability of radioisotopes.

As professionals responsible for the safe use of radiation and radioactive materials, we must ensure that nuclear materials are used properly, handled safely, and protected against theft or diversion. The Energy Policy Act of 2005 strengthened safeguards but weakened domestic capability to produce medical isotopes. Congress will need to remedy this situation, recognizing that the modern practice of nuclear medicine relies on an affordable, continuous supply of medical isotopes.

This continuing education course reviews the issues of both radioisotope availability and radioactive material security. While both are necessary, the heavy response to terrorism concerns has had substantial impact on isotope production and transportation. We should also be active in supporting efforts to find an appropriate balance between necessary safeguards and radioisotope availability. In a world concerned about radiological terrorism, more action is needed to help the U.S. to better meet the needs for commercial and research isotopes.

Radioisotopes are essential components of all radiopharmaceuticals, and the ready availability of radioisotopes is the starting point for nuclear pharmacy. Reduced or hindered availability of radioisotopes is the single most challenging issue in nuclear medicine and in research toward new radiopharmaceutical development.

Competing with our concepts of legitimate commerce and trade, the use of modern medical technology for diagnosing and treating disease, and the development of advanced techniques in molecular nuclear medicine, is the increasing threat that nuclear materials, including common medical isotopes underpinning the legitimate practice of radiopharmacy and nuclear medicine, could possibly be diverted for use as terrorist weapons of mass disruption. Our world changed when terrorist documents were discovered in al-Qaeda caves indicating plans for radiological weapons containing nuclear

material. The extensive media coverage of potential for so-called “dirty bombs” resulted in a number of government efforts to improve materials safeguards to prevent theft and diversion for criminal purposes.

The purpose of this continuing education is to review current federal requirements for nuclear material safeguards in the medical setting. While recognizing the importance of preventing illicit use of these materials, we must also constantly be aware of the challenges that we face in maintaining and strengthening the availability of radioisotopes for the legitimate clinical practice of radiopharmacy and nuclear medicine.

The Isotope Supply and Availability Challenge

The U.S. need for isotopes is dynamic but ever-increasing. The spectrum of isotope products needed to support emerging applications in molecular nuclear medicine is broad; the technological requirements and exacting specifications for isotope production and safe delivery are complex and demanding.

As the need increases, a number of factors limit the ready availability of special-purpose radioisotopes. Many radioisotopes are difficult or expensive to produce. Some require production by nuclear reactors, and we have very few for this purpose in the United States; others require high-energy particle accelerators. For some radioisotopes, the target starting materials may be in short supply or unavailable.

Isotope availability is the single most challenging issue in the practice of nuclear medicine and new radiopharmaceutical development.

As a commodity, radioisotopes have a short shelf-life. Physical half-life determines whether a radioisotope must be produced locally or whether it can be imported from another region of the country--or from a foreign country. The relatively short physical half-lives of radioisotopes having the most desirable physical properties for specific applications in diagnostic or therapeutic nuclear medicine greatly increases the daily or weekly supply challenge.

For example, oxygen-15-water is useful for positron-emission tomography (PET) imaging of blood flow to different parts of the brain. However, oxygen-15 has only a two-minute half-life, and therefore it must be produced on-site and moved quickly from the production cyclotron to the PET imaging

systems for patient infusion. This short half-life requires that the cyclotron and PET imager be co-located. Another example is nitrogen-13 (10 minute half-life), which is used as N-13-ammonia for myocardial perfusion imaging. Both oxygen-15 and nitrogen-13 must be administered to the patient and imaged immediately after production in the cyclotron.

Fluorine-18, a versatile positron-emitter with a physical half-life of 110 minutes (just under 2 hours), is the most important new radioisotope for diagnostic imaging. F-18-fluorodeoxyglucose (^{18}F -FDG) is used to evaluate glucose metabolism in cancer detection, brain imaging, and heart imaging. Since few hospitals have dedicated medical cyclotrons, radioisotope suppliers have established extensive production and distribution networks for making and distributing fluorine-18. These networks use high-speed delivery (aircraft and cargo van) to move the product from cyclotron to radiopharmacy to PET imaging center over distances approaching 200 miles.

Most other radioisotopes for nuclear medicine can be shipped cross-country by next-day freight or overnight courier (such as FedEx) from production site to the radiopharmacy. Longer half-life examples include molybdenum-99/technetium-99m generators (2.75 days/6 hours) for multi-purpose gamma-camera imaging, thallium-201 (3 days) for myocardial assessment, and iodine-131 (8 days) for thyroid imaging and treatment. These delivery networks enable the current practice of nuclear medicine.

Substantial segments of the radioisotope production industry are based outside the United States. The National Research Universal (NRU) reactor at Chalk River near Ontario, Canada, operated by Atomic Energy of Canada, Limited, is the principal supplier of molybdenum-99 for technetium-99m generators, iodine-131, and xenon-133 for hospitals and clinics in the Western Hemisphere. The Canadian NRU reactor produces radioisotopes for 20 million medical procedures each year. Most of the yttrium-90 and iodine-125 used in the U.S. is also imported from Canada. We also import radioisotopes from Russia, Belgium, South Africa, Germany, France, and England. Disruptions in radioisotope supply may occur when production facilities are down for repair and maintenance, or when workers go on strike. One recent supply disruption occurred when the NRU Reactor was shut down to repair or maintain a critical safety system. Other supply disruptions have occurred to correct product sterility and other quality control problems.

The U.S. is highly dependent on foreign supplies of many radioisotopes for medical diagnostics and cancer treatment.

Nuclear and Radiological Terrorism

Security analysts believe that the most likely radioisotope candidates for radiological disperse weapons might involve both medical and industrial-application materials, such as phosphorus-32, cobalt-60, selenium-75, strontium-90, cesium-137, iridium-192, radium-226, americium-241, californium-252, or natural or depleted uranium--although any available radioactive material in the hands of terrorists could be used, including a molybdenum-99/technetium-99m generator.

The threat of nuclear terrorism did not begin with the discovery of al-Qaeda and Taliban plans in the caves of Afghanistan to use “radioactive medical waste” (understood to be cesium-137) mixed with common explosive, as a radiological disperse weapon.

The potential use of radioactive material as a weapon of war was contemplated during World War II by the German, Russian, and American war planners. The atomic bombs dropped on Hiroshima and Nagasaki in 1945 ended the war with Japan.

During the early 1980s, Iraqi dictator Saddam Hussein considered using spent nuclear fuel or irradiated zirconium fuel cladding mixed with explosive as a miniature nuclear device fixed to artillery shells.

In 1995, Chechen rebels reportedly planted a cesium-137 source in a Moscow park as a terrorist warning to the Russian government. A number of attempts to smuggle and sell radioactive materials are reported each year throughout the world. Most involved various amounts of uranium, but some involved medical isotopes.

In the U.S., several incidents, among others, involving misuse of radioactive material for criminal purposes have been investigated by the Federal Bureau of Investigation (FBI):

- In 1995, refrigerated food of a researcher and a water cooler used by staff were deliberately spiked with phosphorus-32 at the National Cancer Institute in Bethesda, Maryland.
- Also in 1995, food and clothing were intentionally contaminated with phosphorus-32 at the Massachusetts Institute of Technology in Cambridge, Massachusetts.
- In 1998, 19 cesium-137 brachytherapy sources were stolen from a hospital in Greensboro, North Carolina. The sources were never recovered.

- In 1999, deliberate phosphorus-32 contamination was found on the chair of a researcher at the University of California at Irvine. The person responsible was identified, and later resigned from the University.

In November 2006, the radiation poisoning of former Russian security agent Alexander Litvinyenko in London with polonium-210 further sensitized both the public and governments of many nations to the threat of radiological terrorism and criminal acts. While not a medical isotope from a radiopharmacy setting, this event nonetheless showed that: 1) the threat of radiological terrorism is real, 2) small amounts of common radioisotope materials can be harmful, particularly if ingested, 3) any radioactive material is a candidate for criminal act, and 4) efforts must be taken to ensure the security of radioactive materials that we use for legitimate purposes.

In the U.S., three types of radiation sources material are most potentially the target of thieves:

- 1) Radioactive material in hospitals and radiopharmacies, such as nuclear medicine generators and solutions, brachytherapy sources, and legacy sources such as radium-226 needles and calibration materials,
- 2) Research isotopes in university settings, such as biomedical and chemical tracers, and
- 3) Industrial radiography sources, including well-logging tools, density and moisture gauges, and radioisotope power sources and nuclear batteries.

Any unsecured radioactive material in the hands of a terrorist could be used as a radiological dispersive device, including a molybdenum-99/technetium-99m generator.

Hundreds of radioactive sources have been stolen from U.S. construction sites, perhaps inadvertently. These sources include mostly moisture density gauges containing americium-241 or cesium-137. Unshielded radiation sources have been found in public landfills, including one 40-curie iridium-192 source stolen from a pipe radiography system. In other countries, hundreds of people have been injured by discarded cesium-137 or cobalt-60 teletherapy sources.

Federal regulators have taken a number of steps to protect citizens against the threats of criminal theft of radioactive material and potential nuclear terrorism. Controls on foreign and domestic radioactive sources have increased. Some of these steps to secure and protect were designed to limit the overall availability of and commerce involving radioisotopes. Federal actions may also affect the future supply of radioisotopes needed for medical and industrial applications. In this paper, we consider the balance needed between radioactive material security and radioisotope availability. One consequence of the Energy Policy Act of 2005 is increased protection against the illegitimate use of radioactive

materials without the essential support needed to enhance production of isotopes needed for legitimate applications in healthcare.

The Federal Government Role in Radioactive Material Security

Several federal agencies share the responsibility, in various ways, for ensuring that radioactive materials are used appropriately and are not stolen or diverted for illicit use. The most important requirements that radiopharmacists know and understand are those established by the Nuclear Regulatory Commission requirements on security and accountability.

Nuclear Regulatory Commission

The U.S. Nuclear Regulatory Commission oversees and encourages the safe use of radioactive materials for beneficial civilian purposes, while ensuring that people and the environment are adequately protected. The Commission regulates the use of radioactive materials for medical use, issues radioactive materials licenses to users and custodians, inspects licensee facilities for compliance with the regulations, enforces compliance through administrative courts, and may levy fines against licensees for noncompliance.

The Commission and Agreement State agencies (states that have agreed to establish state agencies to regulate nuclear and radioactive materials within their borders) oversee the use of sealed sources, commercial manufacture and distribution of products containing radioactive materials, the medical and veterinary uses of radioactive materials for monitoring, imaging, and treating disease, and the use of radioactive materials by researchers at universities and other academic institutions. The regulations are found in Chapter I of Title 10, "Energy," of the *Code of Federal Regulations*. Part 35, "Medical Use of Byproduct Material", governs the use of radioactive materials in the medical setting, and Part 20, "Standards for Protection Against Radiation", provides radiation protection and safeguards requirements. Part 20 includes radiation dose limits for radiation workers and members of the public, requirements for monitoring and labeling radioactive materials, proper posting of radiation areas, and requirements for reporting the theft or loss of radioactive material.

Safeguards comprise a system of procedures, with appropriate equipment, to ensure that an institution can properly account for all relevant nuclear materials at all times. The Commission and Agreement States have established improved systems for tracking radioactive materials shipments, and have required strengthened physical security measures to prevent theft or diversion. Radioactive materials

must be secured in locked confines and storage areas when not in use. While in use, the licensee must maintain appropriate surveillance. Theft or loss of radioactive materials must be reported immediately. These requirements are described below:

Security and Control of Radioactive Material. Subpart I of 10CFR20 describes requirements for storing and maintaining control of licensed radioactive materials. Licensees must secure all radioactive sources from unauthorized removal or access to prevent theft and illicit use. This requirement applies to radioactive materials stored in both controlled areas and unrestricted areas. These requirements were strengthened and are more strictly enforced after the terrorist attacks of September 11, 2001. Radioactive materials in use at the hospital or radiopharmacy must not be left unattended at any time.

Accountability. Licensees must maintain records of radioactive materials in inventory. Loss or theft of radioactive material must be reported immediately to the regulatory authorities. Local law enforcement agencies must help find and retrieve lost or stolen sources.

In an effort to minimize the deliberate misuse of radiation sources, the Nuclear Regulatory Commission and the Agreement States have evaluated 20,000 licensees of sealed and unsealed radiation sources, initiated a registration program for tracking significant sources (including 66,000 devices used by about 16,000 licensees), developed a nuclear materials database, gathered and disposed of thousands of orphan sources (together with the Environmental Protection Agency and the Department of Energy), and enforced regulations on securing and safeguarding radioactive sources (resulting in about 300 to 400 citations per year). Infraction security levels include:

- Level I: An act of radiological sabotage in which a security system did not function as required.
- Level II: Entry of an unauthorized individual, who represents a threat, into a vital area.
- Level III: Failure to control access such that an unauthorized individual could easily gain undetected access.
- Level IV: Failure to secure or maintain surveillance over licensed radioactive material.

Example. One example of a criminal action cited recently by the Nuclear Regulatory Commission involved an incident where an unauthorized guest researcher copied the institution's NRC license to order 5 mCi of cadmium-109 and 5 mCi sodium-22 on behalf of the institution. He awaited

The new reality of radiological terrorism requires steps to secure radioactive material for legitimate uses in modern society. We need to ensure, however, that these actions do not further limit the availability of radioisotopes needed for the legitimate practice of nuclear medicine.

delivery, intercepted the first package, and mailed it to a foreign country. When the second package arrived, a staff member noticed the radioactive label and told the person that he must take the package to the radiation safety officer for processing. The radiation safety officer recognized the unauthorized purchase, and thwarted its shipment to the foreign country. The guest researcher had a prior criminal history, and was subsequently arrested and prosecuted.

Two case studies, given below, demonstrate the importance of securing and safeguarding radioactive materials in the healthcare setting:

Case Study No. 1. In 2003, a Nuclear Regulatory Commission inspector visited a nuclear medicine clinic and entered the radioactive materials area without being challenged. Radioactive materials were unsecured and unattended. Members of the hospital staff were engaged in activities outside the laboratory and did not provide the required constant surveillance. The hospital was cited and the Commission issued a Level III enforcement action (\$3,000).

Case Study No. 2. In 2001, a Nuclear Regulatory Commission inspector visited a hospital and observed that the door to the nuclear medicine hot laboratory was not locked or secured by technologists. The laboratory contained two check sources (240 uCi cesium-137 and 115 uCi barium-133), a 165 mCi molybdenum-99/technetium-99m generator, a vial with 20 mCi technetium-99m-Neotec, and 35 mCi technetium-99m-Cardiolite. The Commission issued a Level III enforcement action (notice of violation) against the hospital.

To prevent theft, all radioactive materials must be secured or controlled, and materials in use may not be left unattended at any time.

To prevent incidents of theft or misuse, the following checklist should be reviewed:

- Review security procedures
- Check the backgrounds of all persons with authorized access
- Perform frequent material inventories
- Reduce the number of storage areas
- Dispose of sources that will not have future need
- Report immediately any lost or missing sources
- Use locked storage areas, freezers, and cabinets
- Be alert to the presence of unauthorized persons

Unsecured radioactive sources must always be attended by an authorized staff member.

By policy, the Commission has chosen to not dictate the specific use of radioactive material or intrude on the practice of medicine by medical professionals, except as necessary to provide radiation safety for workers and the general public.

Department of Homeland Security

The Department of Homeland Security ascertains the threats, assesses vulnerabilities, and develops methods and technologies for detecting, deterring, and mitigating threats to our population and critical infrastructure. The Domestic Nuclear Detection Office develops capability to detect and report unauthorized attempts to import, possess, store, develop, or transport nuclear or radiological material for use against the Nation. Homeland Security deploys radiation detection systems at border crossings, seaports, airports, express package handling facilities, and rail crossings in partnership with U.S. Customs and Border Protection. Together, these agencies have deployed several thousand highly sensitive instruments for screening vehicles and cargo at U.S. ports of entry for illicit nuclear materials.

National Nuclear Security Administration

The National Nuclear Security Administration is a semi-autonomous agency within the Department of Energy responsible for enhancing national security through the military application of nuclear science. The agency maintains the safety, security, reliability and performance of the U.S. nuclear weapons stockpile, works to reduce global danger from weapons of mass destruction, provides the U.S. Navy with nuclear propulsion, and responds to nuclear and radiological emergencies in the United States. Nuclear nonproliferation activities, together with the governments of 60 other countries, seek to prevent the spread of weapons of mass destruction, including illicit use of radioactive material. The agency monitors nuclear weapons production, proliferation, and testing worldwide, helps to secure and eliminate vulnerable nuclear weapons and weapons-usable material, installs radiation detection equipment at border crossings and seaports to prevent illegal transport of nuclear material, and secures high-risk nuclear and radiological materials that pose a radiological threat. Another focus is the elimination of surplus highly enriched uranium. In 2004, the Department launched its Global Threat Reduction Initiative in partnership with the International Atomic Energy Agency and the Russian federation. Among its goals, this initiative seeks to minimize and eventually eliminate use of highly enriched uranium for civilian fuel-cycle purposes, and to convert research and test reactors worldwide from the use of highly enriched uranium to low-enriched uranium fuel and targets. The impacts of this initiative on medical isotope production and availability are further discussed below.

Department of Transportation

The Department of Transportation regulates interstate transport of radioactive materials and other dangerous goods. In cooperation with the Nuclear Regulatory Commission (10CFR Part71), the Department of Transportation approves the types of packages that may be used for transporting radioactive material. Regulations on transport of radioactive materials by land and air are given under Title 49 (Transportation) and Title 14 (Aeronautics and Space).

The Department has adopted international guidance for regulation and safe transport of radioactive material (as given by the International Atomic Energy Agency in its Safety Guide No. TS-G-1.1 (ST-2, June 2002). This guide provides uniform safety standards for materials transportation commensurate with the inherent hazards of the materials transported. The standards focus primarily on packaging design and integrity. The guide provides limits on the radioactivity of Type A packages for a long list of isotopes. These values have been adopted by the Department of Transportation (49CFR173.435). The activity limits given in the June 2002 guide are substantially reduced from values published previously by the International Atomic Energy Agency (ST-1, 1996). While limits on the amounts of radioactive material that may be shipped per package have not reduced the availability of isotopes for medicine, the reduced limits have increase the costs associated with radioactive materials shipping and transportation.

The International Atomic Energy Agency and the Department of Commerce have substantially reduced the amount of radioactive material that may be shipped in a single package.

Environmental Protection Agency

The Environmental Protection Agency (EPA) controls the release of radioactive material into the environment (air and water) through provisions of the Clean Air Act, the Safe Drinking Water Act, the Toxic Substances Control Act, the Resource Conservation and Recovery Act, and the Comprehensive Environmental Response, Compensation, and Liability Act.

Occupational Safety and Health Administration

The Occupational Safety and Health Administration of the Department of Labor oversees and regulates worker health and safety for radiation protection. The agency governs radiation protection in the workplace, including provisions addressing the exposure of minors to radioactive material in the workplace.

Department of Commerce

The Department of Commerce controls the export of radioactive material. Before the enactment of the Energy Policy Act of 2005, the Department of Commerce regulated the export of all radium-226. With the enactment of the Act, responsibility for the export of discrete sources of radium-226 shifted to the Nuclear Regulatory Commission. Commerce retained jurisdiction over export of non-discrete sources of radium-226. The Consumer Product Safety Commission regulations address hazardous substances other than byproduct, source, and special nuclear materials currently regulated by the Nuclear Regulatory Commission, such as the limited radioactive materials in common household products.

Food and Drug Administration

The Food and Drug Administration of the Department of Health and Human Services regulates all drugs (including radiopharmaceuticals) by requiring good manufacturing practices to assure the purity, potency, and consistency of finished drugs with their labeling in establishing the safety and effectiveness of these drugs. Though mainly concerned with bioterrorism, the Food and Drug Administration has focused substantial resources on preventing radiological and nuclear threats, developing medical countermeasures, and ensuring the nation's ability to respond quickly to any terrorist attack.

Energy Policy Act of 2005

Title VI (Nuclear Matters) of the Energy Policy Act of 2005 (Public Law 109-58, August 8, 2005) addressed both isotope production and nuclear materials security. The Act restricted use of U.S.-supplied highly enriched (greater than 20 percent uranium-235) uranium as reactor fuel to medical isotope-producing reactors in Canada, Belgium, France, Germany, and the Netherlands that agree to convert to an alternative fuel (low-enriched uranium). The Act required review of nuclear fuel physical protection, security, storage, and transportation. The Act also commissioned the National Academy of Sciences to review the feasibility of producing medical isotopes without using highly enriched uranium in reactor fuel and targets. Rather than focus on optimization of medical isotope production, improvement of technical capabilities, improving the isotope-production independence of the U.S., expansion of medical isotope

The Energy Policy Act tightened controls on isotope production and the legitimate use of radiation sources, but did little to enhance the availability of medical isotopes or to reduce U.S. dependence on foreign supplies.

availability, or production of critically needed research isotopes, the Act focused specifically on eliminating the use of highly enriched uranium as fuel or target material. Lastly, in this list, the Act required the National Academy of Sciences to investigate ways to eliminate or replace the use of certain high risk (category 1 and 2) radioactive sources with non-radioactive devices. The main radioisotope of concern was cesium-137 (blood irradiators, brachytherapy sources).

Security analysts fear that a terrorist organization could fabricate un-irradiated uranium reactor fuels (enriched to greater than 20 percent uranium-235) into a crude nuclear weapon. They postulate that highly enriched uranium at civilian facilities is vulnerable to theft, since such facilities are inadequately secured. Therefore, eliminating the use of highly enriched uranium for peaceful applications would reduce the opportunity for theft or diversion. However, a nuclear reactor specifically designed for use of highly enriched uranium for research or to produce medical isotopes cannot easily or inexpensively be converted to perform the same task using low-enriched uranium fuels or targets. Once fuel is irradiated in a reactor, it becomes so highly radioactive with gamma-emitting fission products that it cannot be handled as fresh uranium.

Research reactors worldwide are converting from use of high-enriched uranium fuel to low-enriched uranium fuel. However, isotope-production reactors cannot operate as efficiently or cost-effectively using low-enriched target material. Another concern is the increased radioactive waste generated by low-enriched fuel and targets and increase costs of disposal.

Highly enriched uranium is used in non-military applications to fuel research reactors and ships (ice-breakers). Highly enriched uranium also fuels our Navy's nuclear submarines and aircraft carriers.

Reactors in Canada, Belgium, France, the Netherlands, and South Africa that produce uranium-fission-product molybdenum-99 for technetium-99m generators, iodine-131, and xenon-133 for nuclear medicine use highly enriched uranium targets. The conversion to low-enriched targets cannot be accomplished without substantial reductions in isotope production efficiency and significant increases in cost of production. During conversion, the reactors would be shut down for extended periods of time (years), and medical isotopes could not be produced. Proposed replacement reactors in Canada (Maple 1 and Maple 2) are completed but are not operational due to safety concerns. The increased nuclear waste that would be produced by the low-enriched uranium targets presents additional technical and financial challenges to conversion. The U.S. remains highly dependent on the very old NRU reactor to sustain nuclear medicine practice.

Fingerprinting and Background Checks. Section 652 of the Act requires the Nuclear Regulatory Commission to mandate fingerprinting and criminal history record checks for any individual who is permitted unescorted access to facility safeguards information and high-risk (Category 1 and Category 2) radioactive materials. Category 1 sources include radioisotope thermoelectric generators, gamma and neutron irradiators, teletherapy sources, fixed or multi-beam teletherapy (gamma knife) sources. Category 2 sources include industrial gamma radiography sources and high or medium dose-rate brachytherapy sources (IAEA 2000; 2005). Costs of fingerprinting are to be borne by the licensee. In Section 656, background checks are also required for parties that transfer or receive certain radioactive materials covered by an import or export license, although these requirements are already part of 10 CFR Part 71. The fingerprinting and background checks do not apply to health care personnel only involved in the preparation, handling, and delivery of radiopharmaceuticals.

Radiation Source Tracking System. Section 651 of the Act on Nuclear Facility and Materials Security requires the Nuclear Regulatory Commission to establish a mandatory tracking system for Category 1 and Category 2 “high-risk” radioactive sources.

Source Security and Replacement Technology. Sections 651 and 957 of the Act requires the National Academy of Sciences to conduct a study of the industrial, research, and commercial uses for radiation sources to identify whether the same function could be achieved with an equivalent, non-radioactive source technology, or with a radiation source that would pose a lesser risk to public health and safety in the event of a terrorist attack involving such a source. A task force consisting of key federal agency administrators will evaluate radiation sources that should be further secured, based on activity levels, half-life, dispersibility, and chemical and material form. For radioactive materials with a medical use, the task force shall consider “the availability of the sources to physicians and patients for medical treatment,” apparently in the context that such sources are vulnerable to theft or diversion for terrorist actions. The Act also requires a national system for the proper disposal of such sources. This requirement continues a general federal policy requiring the permanent disposal of legacy radioactive materials. In many cases, however, these same materials are essential for producing medical isotopes needed for the next generation of cancer diagnostic and therapeutic agents. Examples include strontium-90 as the parent of yttrium-90, uranium-233 as the parent of thorium-229 (which is the parent of actinium-225 and bismuth-213), uranium-232 as the parent of bismuth-212, and actinium-227 as the parent of radium-223. Most of the

The Energy Policy Act was designed to eliminate or reduce the use of discrete radiation sources for medical and industrial applications.

U.S. supplies of radium-226 were disposed of before scientists realized the need for radium-226 targets to produce other short-lived medical isotopes. In Section 957, the Act encourages disposal options for currently deployed or future radioactive sources, and recommends legislative options so that Congress may consider further disposal remedies.

The secure sources section emphasizes the need to identify “alternative technologies” to radioactive source use in the U.S., and establishment of appropriate regulations and incentives for alternative technologies to replace devices and processes that use radiation source material (to reduce the number of such sources available in the U.S. for potential terrorist activities). Further, the Act requires creation of additional measures for improving the security of use, transportation, and storage of radiation sources, including audits of source security, evaluation of security measures, increased fines for violations of source security, criminal and background checks for transporters of radioactive sources, assurances of temporary storage facilities, and screening of shipments to ensure that they do not also contain explosive materials.

Byproduct Materials. The term “byproduct material” refers to the products of nuclear fission in a reactor or the uranium mined, milled, and enriched as reactor fuel. Section 651 of the Energy Policy Act of 2005 defined byproduct material and extended the definition to include any discrete source of radium-226 that is used for a commercial, medical, or research activity, any material that has been made radioactive using a particle accelerator (including PET isotopes), and any other discrete source of radioactive material

The Energy Policy Act of 2005 added discrete sources of radium-226 and accelerator-produced radioisotopes to the category of “byproduct materials” now regulated by the U.S. Nuclear Regulatory Commission.

would pose a threat similar to that of a discrete radium-226 source. New regulations under the act for naturally occurring and accelerator-produced radioactive material (NARM) were introduced in the *Federal Register* on October 1, 2007 (72 FR 55864) and became final on November 30, 2007. The major impact of this redefinition was that it gave the Nuclear Regulatory Commission authority to regulate accelerator production of medical isotopes, and the use and handling of those isotopes. The Energy Policy Act asked the Nuclear Regulatory Commission to consider the impact of its regulations on the availability of radiopharmaceuticals to physicians and patients whose medical treatment relies on radiopharmaceuticals (although no further interpretation was given as to what was meant by “to consider”).

Nuclear Infrastructure. Section 955 of the Act required the Secretary of Energy to operate and maintain the federal nuclear infrastructure and facilities needed to support isotope production for commercial applications. The goal of this specification was to ensure that Department programs under Section 955 will be funded sufficiently to ensure that they are generally recognized to be among the best in the world.

Status of Medical Isotope Production in the U.S.

As stated above, the U.S. imports most of the medical isotopes used in the U.S. (such as molybdenum-99 for technetium-99m generators, iodine-125, iodine-131, and xenon-133), with the exception of very short-lived positron emitters for diagnostic imaging that must be produced in close proximity to the imaging center (fluorine-18, carbon-11, nitrogen-13, and oxygen-15). The U.S. also imports most of the yttrium-90 and indium-111 used in the U.S. for radioimmunotherapy of lymphoma and as microspheres for treating liver cancer.

Commercial isotope suppliers in the U.S. produce thallium-201 for heart imaging and palladium-103 for prostate seed implants. The University of Missouri Research Reactor in Columbia, Missouri, produces lutetium-177, holmium-166, rhenium-186, and promethium-149 for applications in cancer treatment research.

The Department of Energy is the single federal agency with responsibility and authority, mandated by Congress, to produce isotopes for scientific and medical purposes. The Department of Energy's isotope program produces germanium-68 for gallium-68 generators, and strontium-82 for rubidium-82 generators used in heart imaging. The High Flux Isotope Reactor (HFIR) at Oak Ridge, Tennessee, produces tungsten-188 for rhenium-188 generators used in radioimmunotherapy research. Other medical isotopes produced at the HFIR reactor include carbon-14, phosphorus-32, sulfur-35, iron-55, lutetium-177, strontium-89, and californium-252, and some industrial isotopes such as nickel-63, among others. Oak Ridge also produces small amounts of actinium-225 and bismuth-213 from thorium-229 by radiochemical separation. The Idaho National Laboratory's Advanced Test Reactor (ATR) produces cobalt-60, iridium-192, and barium-131 for cesium-131 brachytherapy seeds in partnership with private industry. The Pacific Northwest National Laboratory produces bismuth-212 generators in partnership with private industry for radioimmunotherapy of cancer, and cesium-137 for gynecological brachytherapy sources.

In the U.S., the shortage of research isotopes is particularly acute. The Department of Energy's isotope program is unable to meet national needs for isotopes such as silicon-32, cobalt-55 and cobalt-57, accelerator-produced tin-117m, copper-62, copper-64, and copper-67, iron-52, magnesium-28, arsenic-72, titanium-44, and zinc-62, zinc-65, zirconium-89, radium-223, and actinium-225, among others. The Congress has not provided funds to the Department to produce research isotopes. Although the Department of Energy strives to maintain an aging infrastructure, it has not taken initiative to secure funding for research isotope production or to lead in the construction of new isotope production capabilities.

Other federal agencies, such as the National Cancer Institute of the National Institutes of Health, have begun to investigate other sources, such as a dedicated 70-MeV cyclotron, for isotopes to support cancer imaging and treatment research and new radiopharmaceutical development.

The current shortage of some research isotopes is particularly acute.

The state of the science in nuclear medicine was the subject of a report released recently by the National Academy of Sciences. In its September 2007 report on *Advancing Nuclear Medicine Through Innovation*, the National Research Council and the Institute of Medicine stated that

“There is no domestic source for most of the medical radionuclides used in day-to-day nuclear medicine practice. Furthermore, the lack of a dedicated domestic accelerator and reactor facilities for year-round uninterrupted production of medical radionuclides for research is discouraging the development and evaluation of new radiopharmaceuticals. The parasitic use of high-energy physics machines has failed to meet the needs of the medical research community with regard to radionuclide type, quantity, timeliness of production, and affordability.” (National Research Council, 2007, page 6, and chapter 4, 5, and 6).

The National Academies and Institute of Medicine echoed prior recommendations (Institute of Medicine, 1995) in advising that the Department of Energy, together with the Department of Health and Human Services, the National Institutes of Health and the National Cancer Institute should work cooperatively on joint solutions to the shortages of medical isotopes. In particular, the agencies should

“... enhance the federal commitment to nuclear medicine research. Given the somewhat different orientations of the DOE and the NIH toward nuclear medicine research, the two agencies should find some cooperative mechanism to support radionuclide production and distribution.” (National Research Council, 2007, page 5 and chapter 6).

The Department of Energy and National Institutes of Health must work together to develop new capabilities for isotope production.

The solution to improved availability of radioisotopes in the U.S. is for Congress to establish funding for a joint federal agency program focused specifically on meeting current needs for medical and industrial radioisotopes.

CONCLUSIONS

The threat of radiological terrorism has resulted in a cascade of federal regulations designed to prevent illegal international trafficking of nuclear materials and radioisotopes, to safeguard both foreign and domestic nuclear materials used for legitimate purposes, and to reduce opportunities for theft and illicit use. Nuclear nonproliferation activist organizations, in partnership with governments, have greatly limited the use of highly enriched uranium in research reactors, but the drive toward replacement of highly enriched fuel and targets in radioisotope-producing reactors is challenging. Conversion, if feasible, will lead to higher costs of medical isotopes, supply disruptions, and increased production of nuclear waste.

Medical isotope availability in the U.S. is good for most commercial products, but we are highly dependent on imports from foreign producers. The availability of research isotopes for developing new radiopharmaceutical is poor, and the National Academy of Sciences recommends strong federal action and interagency cooperation to develop new production capabilities and sponsor radioisotope production research.

As professionals responsible for the safe use of radiation and radioactive materials, we must ensure that nuclear materials are used properly, handled safely, and protected against theft or diversion. However, we should also be active in supporting efforts to find an appropriate balance between necessary safeguards and radioisotope availability. The Energy Policy Act of 2005 strengthened safeguards but weakened domestic capability to produce medical isotopes. Congress will need to remedy this situation, recognizing that the modern practice of nuclear medicine relies on an affordable, continuous supply of medical isotopes.

ACKNOWLEDGEMENTS

This work was sponsored by the U.S. Department of Energy under Contract No. DE-AC05-76RL01830. Pacific Northwest National Laboratory is operated by Battelle for the U.S. Department of Energy. The author is scientific director of the Office of National Isotope Programs.

REFERENCES

Energy Policy Act of 2005, Public Law 109-58, August 8, 2005. 42 USC 15801. Government Printing Office, Washington, DC.

International Atomic Energy Agency, *Code of Conduct on the Safety and Security of Radioactive Sources*, Vienna, Austria: IAEA, December 2000 (approved by the Board of Governors of IAEA on September 8, 2003). Also: IAEA Safety Standards for Protecting People and the Environment, *Categorization of Radioactive Sources*, Safety Guide No. RS-G-1.9, Vienna, Austria: IAEA, 2005.

International Atomic Energy Agency, *Advisory Material for the IAEA Regulations for the Safe Transport of Radioactive Material*, Safety Guide No. TS-G-1.1 (ST-2), Vienna, Austria: IAEA, June 2002. Also: *Regulations for the Safe Transport of Radioactive Material*, IAEA Safety Standards Series No. TS-R-1 (ST-1), Vienna, Austria: IAEA, 1996).

National Research Council and Institute of Medicine, *Advancing Nuclear Medicine Through Innovation*. Washington, DC: The National Academies Press; 2007.

National Research Council, *Radiation Source Use and Replacement*. Washington, DC: The National Academies Press; 2008.

Institute of Medicine, *Isotopes for Medicine and the Life Sciences*, Washington, DC: National Academy Press; 1995

ASSESSMENT QUESTIONS

1. What is the single most important challenge facing researchers involved in development and testing of new radiopharmaceuticals?
 - a. The threat of radiological or nuclear terrorism.
 - b. The potential shut-down of the NRU Reactor in Canada.
 - c. The shortage, non-availability, or high cost of research isotopes in the U.S.
 - d. The ability to apply for new drug approval for exciting new concepts.

2. During recent years, several incidents of deliberate (criminal) misuse of radioactive materials at prominent university or medical research institutions in the U.S. have been investigated by the Federal Bureau of Investigation. What was the most common radioisotope involved in these events?
 - a. Uranium-235
 - b. Phosphorus-32
 - c. Cesium-137
 - d. Technetium-99m.

3. Which government agency is primarily responsible for the security and accountability of radioactive materials in a radiopharmacy setting?
 - a. The Nuclear Regulatory Commission and the Agreement States
 - b. The Department of Homeland Security
 - c. The Department of Energy and the National Nuclear Security Administration
 - d. The Food and Drug Administration of the Department of Health and Human Services

4. The Energy Policy Act of 2005 further restricted the use of highly enriched uranium for research reactors and medical isotope-producing reactors. What might be the most critical impact of the switch from use of highly enriched uranium to low-enriched uranium?
 - a. University researchers will not be able to conduct neutron scattering experiments in research reactors.
 - b. The production of fission-product molybdenum-99 and other medical isotopes will become less efficient and more costly.
 - c. It will not be possible to develop low-enriched uranium fuels for isotope-producing reactors.
 - d. Terrorists will no longer be able to acquire highly enriched uranium for constructing a crude, improvised nuclear weapon.

5. The Energy Policy Act of 2005 requires fingerprinting and background checks for healthcare workers with access to which types of radioactive materials?
 - a. Nuclear medicine imaging and therapy agents.
 - b. Research isotopes, including P-32, C-14, S-35, and I-125.
 - c. Calibration sources.
 - d. Blood irradiators, teletherapy sources, and gamma-knife systems.

6. The Nuclear Regulatory Commission's expanded definition of by-product material, required by the Energy Policy Act of 2005, includes which radioactive materials?
 - a. Any material made radioactive by an accelerator and discrete sources of radium-226.
 - b. Any alpha-emitter, including radium-226.
 - c. Highly enriched uranium.
 - d. Daughter products of radioactive materials produced in radioisotope generators.

7. Isotope production in the U.S. can best be improved by what action?
 - a. Repeal of the Energy Policy Act of 2005.
 - b. Congressional support for research isotope production and cooperation by the Department of Energy and the National Institutes of Health.
 - c. Funding for a National Academy of Sciences study on the causes of current isotope shortages.
 - d. Converting isotope production reactor targets from highly enriched uranium to low-enriched uranium.