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The US national isotope program: Current status and strategy for future success

Mark J. Rivard[a,*], Leo M. Bobek[b], Ralph A. Butler[c], Marc A. Garland[d], David J. Hill[e,1], Jeanne K. Krieger[f], James B. Muckerheide[g], Brad D. Patton[e], Edward B. Silberstein[h]

[a]*Department of Radiation Oncology, Tufts-New England Medical Center, Boston, MA 02111, USA*
[b]*Department of Nuclear Engineering, University of Massachusetts, Lowell, MA 01854, USA*
[c]*University of Missouri Research Reactor, Columbia, MO 65211, USA*
[d]*Department of Mechanical Engineering, Columbia, SC 29208, USA*
[e]*Oak Ridge National Laboratory, Oak Ridge, TN 37831, USA*
[f]*Bristol-Myers Squibb, North Billerica, MA 01862, USA*
[g]*Center for Nuclear Technology and Society, Worcester Polytechnic Institute, Worcester, MA 01609, USA*
[h]*University Hospital, Cincinnati, OH 45219, USA*

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Abstract

Since their introduction in the 1940s, peaceful use of stable isotopes and radioisotopes in the United States has expanded continuously. Today, new isotopes for diagnostic and therapeutic uses are not being developed, critical isotopes for national security are in short supply, and demand for isotopes critical to homeland security exceeds supply. While commercial suppliers, both domestic and foreign, can only meet specific needs, the nation needs a consistent, reliable supply of radioactive and stable isotopes for research, medical, security, and space power applications. The national isotope infrastructure, defined as both facilities and trained staff at national laboratories and universities, is in danger of being lost due to chronic underfunding. With the specific recommendations given herein, the US Department of Energy may realign and refocus its Isotope Program to provide a framework for a successful National Isotope Program.

1. Introduction

The nation needs a consistent, reliable supply of radioactive and stable isotopes for research, medical, security, and space power applications. Today, new isotopes for diagnostic and therapeutic uses are not being developed, critical isotopes for national security are in short supply, and demand for isotopes critical to homeland security exceeds supply. The national isotope infrastructure (The Untold Story: The Economic Benefits of Nuclear Technologies, 1997) at the national laboratories and universities is in danger of being lost due to chronic underfunding. Commercial suppliers, domestic and foreign, can only meet specific needs.

*Corresponding author. Tel.: +1 617 636 1680; fax: +1 617 636 7621.
E-mail address: mrivard@tufts-nemc.org (M.J. Rivard).
[1]Chair, Special Committee on Isotope Assurance, American Nuclear Society.

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Therefore, we are proposing the creation of a *National Isotope Program* for the 21st century to address this issue of national importance.

Why is a national program needed when there are many domestic and international commercial firms that produce isotopes? Simply put, US commercial firms will enter the market only when the endeavor is financially viable. Foreign supplies are impractical for critical short-half-life radionuclides, and inappropriate for those used for national and homeland security missions. In fact, essentially all commercial uses for isotopes were developed through government and university collaboration and then commercialized by both small and large businesses. Furthermore, there are no commercially owned reactor production facilities for isotopes in the United States. A healthy commercial sector requires the existence of a healthy government sector with reactors and large multipurpose accelerators capable of producing these isotopes.

What is the role for science and technology? New science, such as molecular nuclear medicine, is emerging that will require reliable supplies of radionuclides, while the new demands of homeland and national security will spur the development of new technology for radiation detectors and imaging devices, which will ultimately produce new products. Furthermore, the program itself will contribute to the training of a 21st century cadre of radiochemists.

Why now? Over the last 10 years, many studies have identified the need for different components of a National Isotope Program, but their recommendations have never been implemented. We believe that the only way to break the impasse is through coordinated action from the research, provider, and user communities.

What is the goal of the National Isotope Program?
An appropriated program that rejuvenates the current infrastructure and provides core support for

- research and development (R&D) for radioisotopes, applications, and products;
- continuous and reliable radioisotope production for all missions;
- domestic supply of radioactive isotopes to private industry for isotopes unavailable elsewhere, with cost recovery as appropriate;
- training for the next generation of radiochemists; and
- a viable commercial isotope sector.

A National Isotope Program will
Provide for a secure and reliable supply of isotopes for the domestic market by

- establishing national priorities for production, materials management, and radioactive isotope research;
- clarifying government, university, and commercial missions and responsibilities for stable and radioactive isotope production;
- establishing policies and incentives that will encourage future sales, research, and beneficial applications;
- establishing a mechanism for feedback from producers, researchers, and end users to keep the program properly focused;
- guiding the maintenance and modernization of existing capabilities and establishing goals for new production facilities; and
- providing for training and education for the next generation of scientists in the field.

A successful program will not only lead to the restoration of US technical leadership in isotope science, discovery, and innovation but also reduce our over-dependence on foreign sources for critical health care and security uses. This committee recommends realigning and refocusing the US Department of Energy (DOE) Isotope Program to provide a framework for a successful National Isotope Program.

2. The state of isotopes today

Peaceful use of stable and radioactive isotopes in the United States has expanded continuously since their introduction in the 1940s. Traditional industrial use is continuing, and use of radionuclides for food irradiation, sterilization of medical supplies, and other applications is quickly gaining public acceptance. Approximately 15 M diagnostic procedures and several hundred thousand therapeutic treatments using radionuclides are conducted at medical centers each year in the United States. Significant increases in medical research have increased the need for new research isotopes for advanced applications. Isotopes are a significant component of the US economy, with over $300 billion in sales and 4 M jobs related to their use (The Untold Story: The Economic Benefits of Nuclear Technologies, 1997).

2.1. Isotope market

Stable and radioactive isotopes are supplied to the US economy by a largely uncoordinated collaboration among commercial (domestic and foreign), university, and government suppliers. Because of the lack of a National Isotope Program, the roles of these elements are generally uncoordinated, resulting in an ineffective use of limited resources. For discussion of the present supply situation, the isotope market can be divided into a commercial market (proven applications) and the

R&D market (emerging applications). This lack of supply coordination is most pronounced in the area of R&D, where market forces are not present to regulate supply and price. A more detailed description of the present isotope system is provided in Appendix A of this report.

2.1.1. Commercial market

Presently, stable and radioactive isotopes with established markets and profitability are being adequately supplied by a combination of domestic and foreign commercial suppliers. There is also a small role for DOE laboratories and universities in supplying low-volume commercial isotopes in collaboration with private firms. The large volume and established demand have resulted in a stable supply of many such isotopes for established medical and industrial applications. An informal survey conducted by committee members of the Council of Radionuclides and Radiopharmaceuticals, Inc. (CORAR), confirmed that no significant supply issues exist in this established sector of the isotope business.

A major area of business expansion is in the area of nuclear medicine applications. The Society of Nuclear Medicine (SNM) Commission on Radiopharmaceuticals has assembled a comprehensive listing of radioisotopes and radiopharmaceuticals that are available to nuclear medicine practitioners and researchers in 2003 (Silberstein, 2003). These lists (Appendix B) detail radiopharmaceuticals commercially available in the United States as well as radionuclides that can be supplied to North America. However, the current quantity and availability on demand of these radionuclides are unknown. Also provided in Appendix B is a list of radioisotopes available for industrial use.

Although the present global isotope supply system is adequate for established applications, most of the producers are outside the United States. Dependence on foreign suppliers is an issue for isotopes where the use is considered sensitive. This sensitivity may take several forms, including supply interruptions for critical short-life medical isotopes or applications for homeland and national security. This growing dependence on foreign suppliers is not being systematically addressed. The impact to supply interruption and the corresponding need for a US supply are illustrated in Fig. 1. If the impact of supply interruptions is unacceptable, a US supply is essential.

Issue 1: Dependence on foreign suppliers in situations where impacts of supply interruptions are unacceptable is not being systematically addressed.

2.1.2. R&D market

The most demanding isotope supply challenge concerns the isotopes used in R&D, an area in which quantities are small, production techniques are not well established, and costs are high. Isotopes for R&D use without proven markets and profitability are not being adequately supplied. The supply of these stable and radioisotopes for developing new applications has traditionally been the responsibility of DOE. However, the DOE program and its resources have been declining

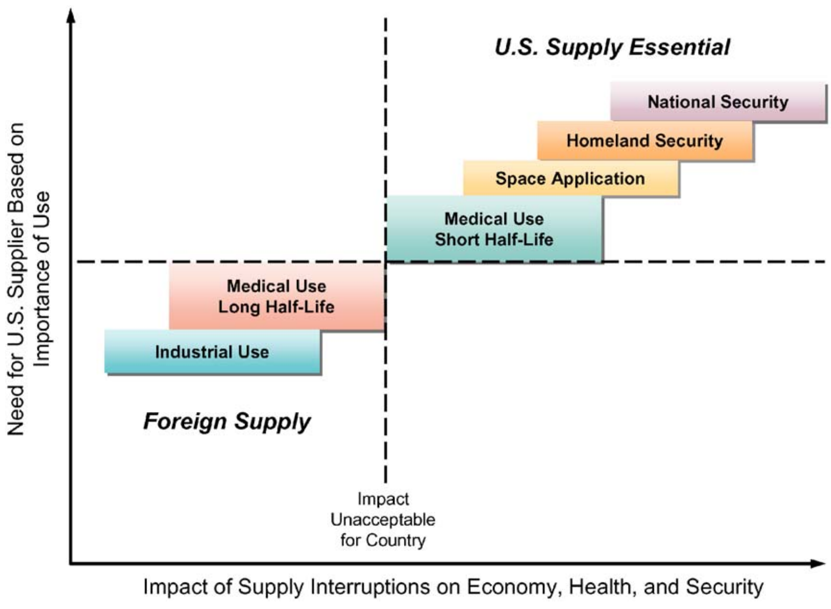

Fig. 1. Areas of critical isotope use in which a US supply is essential.

for two decades, and recent policy changes by DOE have significantly worsened the situation and are impeding the development of new isotope applications. In fact, a recent policy change by DOE eliminated all R&D funding for DOE applications and production.

Although the impact of failing to provide isotopes for the R&D community at a reasonable cost is less obvious than that of not supplying the commercial sector, the lost opportunities to develop new advanced technologies through research enabled by isotopes will have major impacts on pressing needs of US health care and national security.

A few universities have traditionally been suppliers of small quantities of R&D isotopes. However, these contributions have also declined in recent years. Furthermore, where resources are available at universities to produce isotopes, these limited resources are not being coordinated with DOE capabilities.

Issue 2: R&D isotopes at reasonable prices are not available due to declining resources and policy change in the DOE Isotope Program.

Issue 3: Elimination of DOE R&D funding is impacting development of future isotope applications and limiting US isotope business development.

Issue 4: Limited national isotope production resources are not being coordinated to effectively meet the isotope needs of the country.

2.2. Infrastructure status (facilities and trained staff)

Well-equipped facilities and trained staff are critical to a viable isotope supply system. All but a critical few reactor production facilities have been shut down, and the remaining facilities are old and not well maintained. The number of graduates in the radiochemical field has undergone a long-term decline. Significant impacts on isotope applications are expected if trends in isotope infrastructure decline are not addressed.

2.2.1. Facilities

Cyclotrons for isotope production in the commercial sector are being maintained, and new facilities are being added to provide a reliable supply. Because no commercial isotope-producing reactors exist in the US, there is a strong dependence on foreign sources for reactor-produced radioisotopes. The US facilities for reactor-produced isotopes are limited to DOE and one university [University of Missouri Research Reactor Center (MURR)] reactors. The primary issues are with the unique DOE and university production facilities.

The DOE facilities are old, and the funds for upgrading and modernization are generally not available to maintain isotope production due to long-standing budget constraints. All the large DOE isotope production reactors and many of the small-scale research reactors (the High Flux Beam Reactor, the Fast Flux Test Reactor, Experimental Breeder Reactor-II, Savannah River production reactors, etc.) have been irreversibly shut down. Only a small minimum reactor capability remains in DOE for isotope production. Further facility shutdowns will result in major loss of capability for supplying reactor-produced radioisotopes. Of the major remaining operational facilities that support isotope production, the High Flux Isotope Reactor (HFIR) at Oak Ridge National Laboratory (ORNL) was first operated in 1965, the Advanced Test Reactor at the Idaho National Engineering and Environmental Laboratory was first operated in 1970, the ORNL calutrons were first operated in 1944, the Brookhaven Linac (Linear Accelerator) Isotope Producer was first operated in 1972, and the Los Alamos Neutron Source Center was first operated in 1974. Thus, the costs to operate these facilities for isotope production are increasing rapidly because of age-related degradation that must be addressed to ensure the integrity and maintain safety of operations. No strategic approach is in place to address upgrades or replacements of these large expensive facilities, which have long lead times on the order of a decade. Immediate attention is needed to address the infrastructure support of DOE and university isotope production facilities to avoid further loss of capacity. Although this issue has been highlighted in several studies, most recently by the Nuclear Energy Research Advisory Committee (NERAC) report of 2000, DOE has not adequately addressed the concerns or acted on the recommendations.

Issue 5: Lack of infrastructure support for aging production facilities and failure to develop long-term plans for facility replacement have resulted in a loss of capability to produce isotopes at a critical level.

2.2.2. Trained staff

A survey with 19 US universities responding found a continuation of a long-term decline in the number of graduate programs, graduate students, and faculty in the field of radiochemistry. The present trend is 5–10 US Ph.D. graduates each year with a projected demand of several hundred in the next few years at the DOE national laboratories and within nuclear industry and nuclear medicine (Whiteford and Akbarzadeh, 2003; Choppin, in press). In the past, foreign graduates have solved the shortage of nuclear scientists. However, because of a worldwide decline in the number of young scientists in the field, foreign graduates are not available to address the shortage. Immediate action is needed to address the decline in radiochemistry education in the United States to avoid significant impact on radioisotope production and applications R&D due to a shortage of radiochemists.

Issue 6: Decline in radiochemistry education is not being addressed to avoid detrimental impacts on radioisotope production and applications R&D.

2.3. DOE leadership

In the early years of the DOE Isotope Program, the program was highly successful in producing needed isotopes and in developing new applications and transferring these technologies to the private sector of the US economy. In the last 10–15 years, the DOE Isotope Program has been in steady decline. In 1989, Public Law 101–101 (H.R. 2696) was enacted to make the Isotope Program financially self-sufficient. This new requirement for full cost recovery caused DOE to deviate from its original goals for isotope production and distribution by narrowing the range of isotopes produced, concentrating on higher-volume isotopes with profit potential and increasing charges to research users to cover program expenses. This strategy has produced extremely negative results. Despite substantial efforts to operate the Isotope Program on a full-cost-recovery basis, costs have not been met by revenues from sales. The DOE Isotope Program has recently eliminated all R&D funding for radioisotope production and enacted an up-front full and advance prepayment policy. These new policies have resulted in further decline of the DOE Isotope Program and a failure to meet its traditional role in isotope production.

The history of the DOE Isotope Program resources (escalated to FY 2003 dollars) is illustrated in Fig. 2. Declining resources, fueled by the belief that the program can be profitable, has significantly eroded DOE capabilities. Although numerous recommendations have been made to DOE to reverse this negative trend, DOE has failed to implement actions to address the program decline.

Issue 7: DOE has failed to provide the necessary leadership to reverse the decline of the DOE Isotope Program.

3. Need for a national isotope program

3.1. Resolution of issues

A National Isotope Program is needed to address the issues associated with the present isotope system. These issues, identified in Section 2, are as follows:

Issue 1: Dependence on foreign suppliers in situations where impacts of supply interruptions are unacceptable is not being systematically addressed.

Issue 2: R&D isotopes at reasonable prices are not available due to declining resources and policy change in the DOE Isotope Program.

Issue 3: Elimination of DOE R&D funding is impacting development of future isotope applications and limiting US isotope business development.

Issue 4: Limited national isotope production resources are not being coordinated to effectively meet the isotope needs of the country.

Issue 5: Lack of infrastructure support for aging production facilities and failure to develop long-term plans for facility replacement have resulted in a loss of capability to produce isotopes at a critical level.

Issue 6: Decline in radiochemistry education is not being addressed to avoid detrimental impacts on radioisotope production and applications R&D.

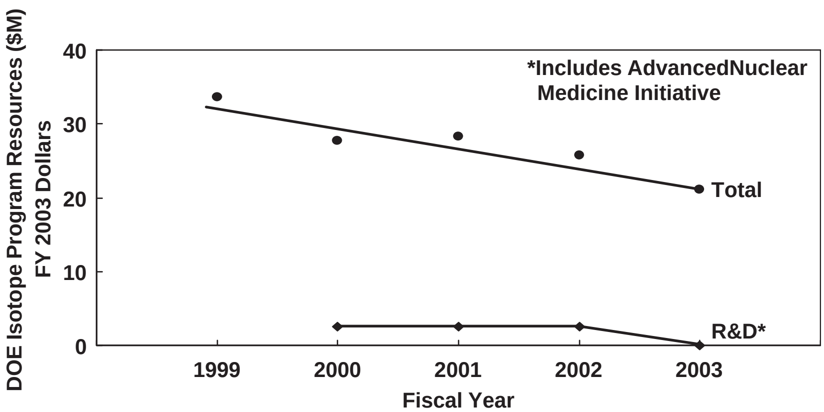

Fig. 2. DOE Isotope Program resources ($M) by fiscal year.

Issue 7: DOE has failed to provide the necessary leadership to reverse the decline of the DOE Isotope Program.

The US isotope program is in a state of crisis, and immediate action is needed to address the major program issues.

3.2. Recommendations from previous studies

Over the last 10 years, a large number of studies have been conducted by expert panels and marketing groups concerning the need for stable and radioactive isotopes in the United States. Most of these studies were commissioned by DOE to guide the existing DOE Isotope Program activities. These studies include the following:

Long-Term Nuclear Technology Research and Development Plan (NERAC Subcommittee on Long-Term Planning for Nuclear Energy Research, June 2000, Long-Term Nuclear Technology Research and Development Plan, 2000).
NERAC Subcommittee for Isotope Research & Production Planning, Dr. Richard Reba, Chairman, April 2000 (Final Report, 2000).
Expert Panel: *Forecast Future Demand for Medical Isotopes*, Medical University of South Carolina, March 1999 (Expert Panel, 1999).
Report on Isotope Production and Distribution, ORNL, September 1995 (Report on Isotope Production and Distribution, 1995).
Isotopes for Medicine and the Life Sciences, Institute of Medicine, Division of Health Sciences Policy, January 1995 (Institute of Medicine, 1995)
US DOE National Isotope Strategy, August 1994 (US Department of Energy National Isotope Strategy, 1994).

Abridged conclusions and recommendations of these previous studies are provided in Appendix C.

Major highlights of the recommendations follow:

- Establish a program organized to meet the national need for isotopes with the stewardship for the national resource of materials. The program should be supported at the Secretary of Energy level with the director reporting at a high level in DOE.
- Establish an organization to provide effective delivery of products and services.
- Establish a national advisory committee to assist the program director on R&D, production, and education programs.
- Establish a mechanism to foster partnerships with R&D, medical, and industrial users to assess isotope needs and transfer technologies to accelerate applications.
- Establish a capacity to produce a diverse supply of stable and radioactive isotopes and provide infrastructure stewardship to ensure continued viability of the capacity.
- Invest in R&D to improve isotope production, processing, and utilization with a focus on isotope applications not being supported by other government programs.
- Establish an education and training program to ensure that the next generation of radiochemists are trained and available to support the nation's needs.

While the recommendations from these previous studies have largely not been implemented, these recommendations are consistent in their general direction and would be effective in addressing the present issues if implemented. The key is to establish a framework for implementing needed changes to the DOE Isotope Program. Although the present DOE Isotope Program structure has been in place for 15 years and recommendations for program improvement have been available for most of this period, the effectiveness of the program has declined. Therefore, it is the recommendation of this committee to significantly realign and refocus the present DOE Isotope Program to form a National Isotope Program, which provides a framework for implementing program improvement.

4. National isotope program fundamentals

A National Isotope Program is needed to coordinate all the previously addressed required elements such that available resources are used to their greatest advantage to carry out the essential program functions (Fig. 3). The present program is missing several elements, and realignment and refocusing are needed to embrace the fundamental principles of a successful program.

The fundamental principles of a National Isotope Program are as follows:

(1) *Provide strong management and leadership*: A single program office must provide effective management, coordinating the efforts of disparate organizations in the federal government. The program would monitor universities and the commercial isotope supply. This office must also have the leadership capabilities required to influence these disparate organizations to act for the common good and to garner Congressional and administration support for the program.
(2) *Facilitate collaboration among all interested parties*: A successful, sustainable National Isotope Program is possible only if all organizations involved in the

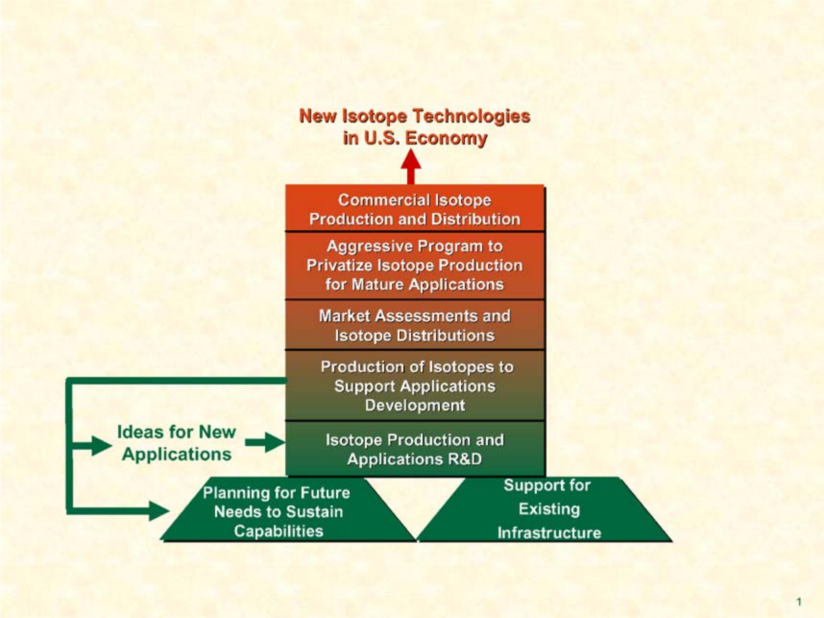

Fig. 3. Functions of a National Isotope Program.

production and use of radioisotopes routinely communicate to shape policy. DOE and the Department of Health and Human Services must coordinate their efforts and interact with organizations such as the SNM; CORAR; the National Organization of Test, Research, and Training Reactors; and organizations representing various university programs.

(3) *Provide adequate resources for the production of R&D isotopes*: Isotopes for research are usually unavailable from commercial suppliers due to insufficient revenues and are typically very expensive due to high unit costs associated with smaller quantities. Government subsidies are required to ensure availability to researchers.

(4) *Continuously monitor the needs of researchers and clinicians*: Ensure that all reactor, accelerator, and cyclotron resources are optimally used to meet the needs of researchers and clinicians. In the short term, this requires coordinating the efforts of existing government resources. In the long term, this must address the construction of one or more reactors, accelerators, and/or cyclotrons to meet the growing demand for radioisotopes. Infrastructure for these government isotope production facilities must be maintained.

(5) *Facilitate the transfer of commercially viable isotope programs to the private sector*: The government should not be in the business of commercial supply of radioisotopes, and, indeed, DOE has policies prohibiting competition with private companies. However, there can be significant barriers to the commercialization of isotope production, particularly the high capital costs of production facilities, and federal support will be required to overcome these barriers.

The successful implementation of these fundamental principles will transform the critically inadequate status of the US isotope system into a modern, self-reliant and productive system. Significant management and programmatic changes are necessary to create a National Isotope Program within which research and commercialization can flourish.

5. Recommendations for action

Substantial changes are needed to realign and refocus the federal government's role in isotope research, development, and production. Cooperation and collaboration among DOE and other federal departments and agencies as well as universities and private industry need to be strengthened. Recommendations to accomplish these changes have been identified.

Cooperative effort is crucial for the success of this plan to provide for reliable supplies of isotopes and fully developed radioisotope applications. The involvement of such diverse agencies, organizations, institutions, and enterprises will substantially broaden the constituent base of support for isotope programs. With consensus achieved among such a broad base, implementation of these programs will be greatly facilitated through broad support in Congress and the administration. Implementation of these recommendations will require an increase of approximately $30 M from the FY 2003 appropriation for the DOE Isotope Program (see Appendix D).

(1) *The government should establish a new national isotope policy and develop a long-term strategic plan*: This strategic plan must systematically address dependence on foreign suppliers.
(2) *Establish a National Isotope Program organization* (Fig. 4) *to implement the national isotope policy and long-term strategic plan*: The scope of the National Isotope Program includes all stable and radioactive isotope R&D and production programs except weapons materials, ^{238}Pu production, and special heavy actinides. The new organization will have two functions: Isotope Management and Technology Transfer and DOE Production and R&D. Both functions will report to the National Isotope Program Director. The National Isotope Program will contract the Isotope Management and Technology Transfer to a company with experience in the commercial isotope business and DOE operations. This new organization will conduct supply tracking and demand forecasting, distribute stable and radioactive isotope products, coordinate DOE production, market products, and manage potential DOE technologies. The DOE Production and R&D organization will manage the traditional production and R&D operations at the DOE national laboratories.
(3) *Establish an independent scientific advisory board for the National Isotope Program to provide oversight and guidance for the program director*: The board should have representatives from all sectors involved in the production and use of radioisotopes including private industry, universities, DOE, the National Institutes of Health (NIH), other federal laboratories, and research institutions. Organizations that could be represented include the SNM, the American College of Nuclear Physicians, the American Chemical Society Division of Nuclear Chemistry and Technology, the American Nuclear Society, CORAR, DOD, and NASA.
(4) *Ensure that the National Isotope Program office is adequately staffed*: Perform an analysis of the roles and responsibilities of the office and ensure that the staff is adequate, both from the standpoint

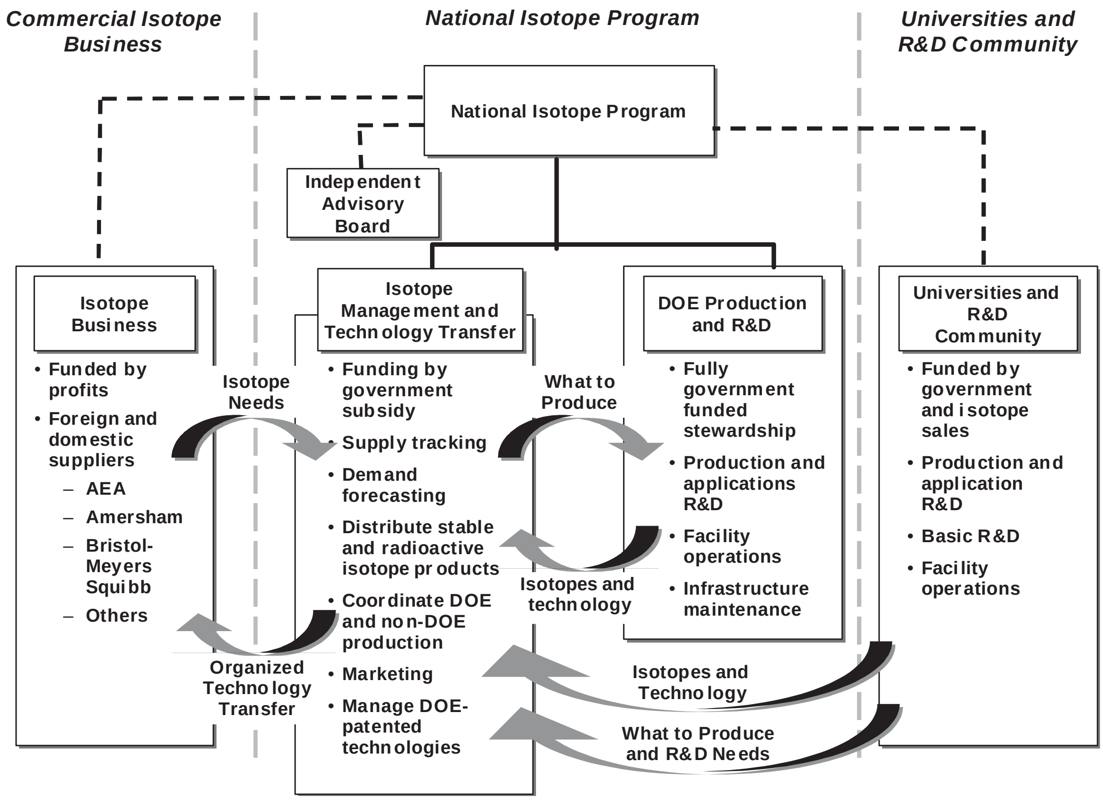

Fig. 4. Structure of a National Isotope Program.

of staff size and capabilities (technical and administrative). The first action is to select a Director for the National Isotope Program. The Director must have the technical and administrative skills necessary to fully understand the complex issues and interrelationships involved in radioisotope production and end use, and must be capable of developing innovative strategies to enhance these programs. The Director must also have leadership and communications skills to foster cooperation among all isotope production and application programs. Most importantly, this involves close consultation with the scientific advisory board.

(5) *Promote technology transfer to the private sector*: As R&D leads to successful applications, markets for radioisotope products will grow to the point where products become commercially viable. The National Isotope Program office should facilitate the transition from federally supported production of research quantities to private-sector production of commercial quantities of isotopes and isotope products. The National Isotope Program must understand its role in supporting the production of isotopes that are not profitable and helping private industry take over the production and supply of isotopes when they become commercially viable. The National Isotope Program should place special emphasis on encouraging small business involvement in isotope business initiatives.

(6) *Ensure adequate resource allocation to support the programs*:
   (a) *Evaluate Public Law 101-101 (H.R. 2696) for impact on the program*: If the provisions of Public Law 101-101 will not allow proper funding of the programs, propose Congressional revision of the law. A consequence of the inevitable transfer of profitable programs to the private sector is that federal programs, by definition, will not be profitable. Thus, operating federal isotope programs on a full-cost-recovery basis is untenable.
   (b) *Essential isotope production* (*both research isotopes and other isotopes that are not commercially available*): If research isotopes are not available at a reasonable cost, R&D will not be possible. Since research isotopes are usually expensive (because production costs are being allocated to small quantities of isotopes), subsidies are required to reduce costs to researchers. This latter concern often applies to non-research isotopes as well as to isotopes with applications in aerospace and medicine.
   (c) *Stable and radioactive isotope production R&D*: Isotope production and separation research is not supported by existing government programs. The program will assess needs and provide funding for needed R&D.
   (d) *Radioisotope applications and radioisotope products R&D*: Radioisotope applications research is supported by many departments and agencies (e.g., NIH, National Aeronautics and Space Administration, Department of Homeland Security). The National Isotope Program office should support applications not supported by other programs and should ensure the availability of isotopes for research and applications that are funded by other programs.
   (e) *Radiochemistry and nuclear technology personnel development*: Faculty positions, scholarships, and fellowships must be supported to reverse the significant decline in appropriately trained personnel.
   (f) Assess isotope production infrastructure needs, both short term and long term, and develop a plan to ensure that these needs are met. Infrastructure, in this sense, includes reactors, accelerators, cyclotrons, enrichment devices, hot cells, radiochemical processing facilities, laboratories, and associated supporting facilities. The National Isotope Program will provide stewardship funding of the DOE production and R&D facilities. The plan will ensure that awards be made on a competitive basis to non-DOE facilities and organizations to establish and maintain critical infrastructure.

Appendix A. The present isotope system

The present isotope supply and-use system is made up of the commercial sector, government sector, university community, and medical R&D community. Perhaps the single most important element of this system for ensuring the continuing use and development of radioisotopes is our nation's education and research infrastructure. Collectively, this includes all the sectors of the isotope system. These sectors work in a synergistic fashion to create a talented workforce of technicians and research scientists to make essential new discoveries and to develop useful products. The role of each of these sectors is discussed in the following sections. The roles of and the relationships between these elements of the isotope system vary by isotope and change as isotope applications are developed or as use declines.

A.1. Role of commercial sector—domestic and foreign

For discussion of the present roles, the commercial sector is divided into medical and industrial markets. These two markets have in common the established nature of use and the developed market forces to self-regulate supply and price.

A.1.1. Medical market

The "medical market" relies on two types of supplies: routine commercial supply of radioisotopes for established products or services and smaller quantities of radioisotopes for R&D, including clinical trials. The keys to supplying the medical isotope market are consistent product quality and extremely reliable, on-time delivery. The medical market also has two categories of use: diagnostic and therapeutic. While the supply of the chief diagnostic radioisotope in the United States ^{99m}Tc is well served by relationships with foreign producers, radioisotopes for therapy, both established and those in the R&D phase, have a very different profile.

Significant investment in people and facilities is required to move from the prototypes in the research laboratory to the scale of commercial supply. Factors influencing commercial radioisotope and radiopharmaceutical manufacture include the following:

- *Dose:* The large scale of commercial operations requires sophisticated automation and extensive shielding to ensure that operators are remote from sources of radiation. Dose considerations may inhibit preventive and non-routine maintenance, necessitating redundant facilities to ensure uninterrupted production.
- *Processing time:* The steps of pharmaceutical manufacturing that are normally conducted on the time scale of days or weeks (i.e., formulation, filling, sterilization, packaging, quality testing, and release) are conducted within hours for radiopharmaceuticals to minimize decay. Automation and a highly skilled workforce address constraints of time.
- *Availability:* Patient needs require a daily, continuous supply of isotopes and radiopharmaceuticals. Frequent manufacturing and a robust distribution system address such demand. Facilities and personnel dedicated solely to commercial supply ensure prioritization of medical requirements.
- *Controls:* Radiopharmaceutical manufacture is regulated by the FDA and governed by the controls of cGMP's (current good manufacturing practices). The pharmaceutical regulatory infrastructure is additive to those required to control radiation exposure and transportation. Additionally, dedicated process equipment is required for each isotope to prevent cross-contamination. Waste processes specific to the isotope are developed to accommodate the large volumes associated with commercial manufacture.

Nearly 15 M diagnostic ^{99m}Tc-based procedures are conducted annually in the United States. There are three major supplies of diagnostic radiopharmaceuticals with operations in the United States, two of which are supplied with reactor-produced radioisotopes from Canada, augmented by secondary suppliers from South Africa and Belgium. This supply arrangement affords security and responsiveness in the case of unforeseen demand and events. The third radiopharmaceutical producer supplies its US operations with reactor-produced isotopes from in-house processing in the Netherlands and from Belgium.

Barriers to entry into reactor isotope production are significant. In 1996 MDS Nordion announced the construction of two new 10 MW MAPLE reactors and a processing facility at Atomic Energy of Canada Ltd.'s Chalk River Laboratories site. Investment in the project to date is approximately $200 M.

Cyclotron isotope production is associated with significantly lower capital costs. Operational expertise to run cyclotron facilities is less of a burden, and waste products are less onerous. As a result, major radiopharmaceutical and medical device companies have purchased cyclotrons and have moved into cyclotron isotope production. Although all three US producers of cyclotron products have installed US capability, all rely on Canadian and European supply for back-up capacity.

In the past 5 years, a number of new therapeutic applications have stimulated the demand for existing isotopes and created a market for new isotopes. The use of ^{125}I and ^{103}Pd in the treatment of early stage (localized) prostate cancer is an example of a new market of considerable size. Eight multinational pharmaceutical companies manufacture these brachytherapy sources. The annual prostate brachytherapy market is currently valued around $200 M (US).

Iodine-131 is used primarily in capsule form for treatment of thyroid cancer. Several companies, both US and international, market capsules in the United States through a network of central radiopharmacies. MDS Nordion and Instituit (National) des Radio-Elements (IRE, Belgium) supply ^{131}I to these companies.

As new radioimmunotherapies have made their way through clinical trials, demand for ^{131}I (reactor produced) and for ^{90}Y (produced from a ^{90}Sr/^{90}Y generator, the ^{90}Sr being produced in a reactor) has grown. These trials have spurred experimental interest in other therapeutic isotopes, such as ^{177}Lu, ^{186}Re, and ^{188}Re.

Yttrium-90 is supplied by a United States radioisotope producer under license from DOE as well as a Canadian firm from a ^{90}Y facility in Belgium, which will integrate production from a back-up facility in South Africa in the coming months. US demand for ^{177}Lu is currently met primarily by the MURR. MURR also supplies ^{90}Y glass microspheres (marketed as TheraSpheres®) for the treatment of liver cancer. Rhenium-186 is available from MURR and DOE. DOE also supplies tungsten-rhenium generators for the production of ^{188}Re at ORNL.

Bone-pain palliation reagents are a promising therapeutic application. Samarium-153 is supplied by MURR for production of Quadramet®. Strontium-89 produced in Europe is marketed in the United States. MURR is the sole US supplier of ^{33}P, ^{32}P, and ^{35}S, which have biomedical applications for DNA analysis, protein analysis, and labeling.

The US demand for PET isotopes is supplied by a varied set of regional cyclotron operators. The majority of medical PET isotopes are very short-lived. With half-lives ranging from a few minutes to about $1\frac{1}{2}$ h, manufacturers must be located very close to their patient base. In general, research-oriented PET procedures are performed by university medical centers that operate their own cyclotrons. Most clinical PET procedures utilize ^{18}F fluorodeoxyglucose (FDG), a modified sugar molecule that is readily available from many independent and chain radiopharmacies throughout the United States.

Some specialized cardiac PET procedures are performed using ^{82}Rb, produced in an ^{82}Sr/^{82}Rb generator system. Strontium-82 is produced in Canada and by DOE. DOE secures some of its supply of ^{82}Sr from Russian producers.

Tritium for labeling compounds for receptor assays and related studies is available from Ontario-Hydro. Carbon-14, which is incorporated into labeled compounds for metabolic and tracer studies, will soon be available only from Russia.

Barriers to entry are high to meet the stringent requirements of commercial supply. Despite these barriers and the constraints of operating in a highly regulated environment, the U.S isotope supply is robust and there are no significant commercial radionuclide supply issues in the United States.

A.1.2. Industrial market

The industrial isotope market represents a diverse range of applications involving many radioisotopes, generally in the form of sealed sources. Many applications involve only small amounts of material; however, there are market areas (product sterilization and food irradiation) that require large quantities of radioisotopes. The industrial applications can be categorized as four types: instrument applications, irradiation applications (product sterilization and food irradiation), radioactive tracer applications, and non-destructive radiography.

Instrumentation applications include analysis, measurement, and control, using sealed radioactive sources. These applications involve a large number of radioisotopes, and applications are found in a large number of industrial sectors (A.1.) The radioisotope applications in this area are as follows:

- weight, level, or density gauges by gamma absorptiometry incorporating ^{60}Co, ^{137}Cs, or ^{241}Am sealed sources;
- thickness and mass gauges by beta-particle or gamma photon absorptiometry incorporating ^{85}Kr, ^{90}Sr, ^{137}Cs, ^{147}Pm, or ^{241}Am;
- thickness gauges for thin coatings by beta-particle back-scattering incorporating ^{14}C, ^{90}Sr, ^{147}Pm, or ^{204}Tl;
- on-line analytical instruments by neutron-gamma reaction incorporating ^{241}Am or ^{252}Cf;
- pollution measurement instruments using beta sources incorporating ^{14}C, ^{63}Ni, and ^{147}Pm;
- luminous points for exit lights incorporating tritium (^{3}H);
- X-ray fluorescence analyzers incorporating ^{55}Fe, ^{57}Co, ^{109}Cd, and ^{241}Am;
- density, parsity, water, and oil saturation of rock by neutron/gamma interactions incorporating ^{137}Cs, ^{241}Am-Be, or ^{252}Cf; and
- smoke detection using ^{241}Am sealed sources.

Irradiation applications include sterilization of medical supplies, pharmaceutical and food packaging, food irradiation, and material curing (cross-linking). This application involves large quantities of material, but the only radioisotope in widespread use is ^{60}Co. Because of the high volume used (estimated \$33–44 M wholesale in 1992) [A.3], the demand for ^{60}Co is very price sensitive. Currently, the two primary sources of this material are reactors in Canada and the former Soviet Union, both of which are within a decade of their end-of-life operations. Because of the limited number of suppliers (all foreign) and the importance of the radioisotope for sterilization of medical supplies, there is a concern for the stability of supply and price of this material.

Radioactive tracers are used in small quantities to check performance, optimize processes, calibrate models, and test prototype installations. A large number of radioisotopes are employed in various chemical and physical forms.

Non-destructive radiography is used in a variety of fields; 90% of all gamma radiography utilizes ^{192}I sources, although ^{60}Co, ^{75}Se, and ^{169}Tb are also used. Neutron radiography uses ^{252}Cf-sealed sources.

Enhanced security requirements are increasing the demand for some radioisotopes. One example is ^{63}Ni. This isotope has been used for a number of years as a key component of electron capture technology but recently is being utilized in devices that have the ability to detect explosives and drugs, especially at airport checkpoints to enhance homeland security. Nickel-63 is a reactor-produced radioisotope that requires 2 years of irradiation to produce in the DOE's HFIR; thus, there is a significant time delay in increasing the supply. Rubidium-87 is another "stable" (naturally occurring radioisotope with a long half-life) that is in short supply. Rubidium-87 is used as an "atomic clock" in satellites for national security.

A.2. Role of universities

Perhaps the single most important national asset needed to ensure the continuing use and development of radioisotopes is our nation's education and research infrastructure. Collectively, this includes our universities, national laboratories, hospitals, and private industries. The unique combination of people and facilities available at universities is critical to success in radioisotope use and development. However, a long-term downward trend in the education and research infrastructure, both in funding and enrollment in nuclear-related university programs, has negatively impacted our national capacity to use and develop radioisotopes both in research and applied technology.

Most of the US nuclear engineering and radiological science programs were formed in the 1960s in response to the growth of nuclear power and the applications of nuclear technologies. Concurrent with these programs of higher education were the construction and use of over 60 university research reactors for training and research. With the nuclear power industry at a plateau for nearly 20 years, the number of nuclear engineering and radiological sciences programs and university research reactors has declined to less than half the original number.

The role of the university is to bring together the resources of a broad spectrum of research resources, from a research reactor to a teaching hospital; a college of veterinary medicine; a cancer hospital; and distinguished university programs in biosciences, chemistry, and engineering. The objective is collaboration from concept to commerce—from helping physicians, scientists, and enterprises not only to imagine but also to achieve and bring to market new products and services. Universities provide invaluable support to the R&D community by supporting educational programs for promising research scientists in a great variety of fields including archeology, biology, radiochemistry, physics, medicine, and veterinary medicine. As university funding and support for these programs decline, the R&D community will suffer the loss of these resources.

University research reactors are also a critical casualty of the downward trend in funding and support for radiological science programs. Their unique sizes and flexible operating schedules allow them to support a wide variety of R&D activities including radioisotopes for research, clinical trials, and treatments. However, due to lack of support by host institutions and government agencies, the ever-shrinking circle of university research reactors that is available for research infrastructure damages the health of university systems essential to support research and industrial applications of radioisotopes.

University reactors currently educate many of the nation's new nuclear engineers and train a talented workforce of technicians to respond appropriately to the ever-evolving demands of research science. Skilled technicians and cutting-edge scientists provide inspiration and resources to one another; the products of such partnerships enable unique R&D and preliminary work for production, filling a vital niche in the progression from research to market. These technicians and engineers are crucial to ensuring the continuing contribution of the nuclear sciences to mankind. The National Research Council's *University Research Reactors in the United States—Their Role and Value* summarizes the university role (A.2).

> The flexible, informal, and creative atmosphere of research reactor facilities together with medical schools and teaching hospitals in the university environment have contributed to development of new and innovative procedures in nuclear medicine. The synergism between the URR centers and the teaching hospitals and medical schools and the wide variety of skills available at these facilities are effective in training students and researchers.

By focusing on interdisciplinary R&D using its unique facilities, a university research reactor contributes not only to the educational mission of the host university but also to discovery and innovation in nuclear sciences.

In addition, university research reactors supply isotopes and provide research infrastructure that the national labs cannot. Thus, the university research reactor complements, rather than supplants, the national lab system. The capabilities and products of a university research reactor differ greatly from those of a national lab. However, together they have the responsibility to supply researchers with a wide range of beneficial isotopes in the quantities and time frames required.

A.3. Role of DOE sector

DOE and its predecessors, the Atomic Energy Commission and the Energy Research and Development Agency, have been major suppliers of critical isotopes to the world since August 2, 1946, when the first shipment of ^{14}C was made to a civilian laboratory from ORNL. The DOE mission in supplying isotopes was further authorized by the Atomic Energy Act of 1954. The act authorized the Atomic Energy Commission [now DOE] to

> … distribute, sell, loan, or lease such byproduct material as it owns to qualified applicants with or without charge: Provided, however, that, for byproduct material to be distributed by the Commission for a charge, the Commission shall establish prices on such an equitable basis as, in the opinion of the Commission, (a) will provide reasonable

compensation to the Government for such material, (b) will not discourage the use of such material or the development of sources of supply of such material independent of the Commission, and, (c) will encourage research and development. In distributing such material, the Commission shall give preference to applicants proposing to use such material either in the conduct of research and development or in medical therapy.

The early DOE program was very successful in "technology transfer" of peaceful uses of isotopes. The unique facilities within DOE have been critical to making isotopes available for development of commercial applications. Isotope production has always been a secondary mission at the DOE laboratories, and this mission has suffered as support for the laboratories' primary missions of research in nuclear and particle physics, nuclear weapons, and nuclear power has declined with the end of the Cold War.

DOE's most important role is the production of stable and radioactive isotopes for research and clinical trials when final applications are unproven and production levels are low. Critical to the success of future development of isotope applications is the ability to provide these materials before production is profitable.

Although the DOE facilities are aging and are underfunded, they continue to be the only source of many stable and radioisotopes. Because of the high up-front investment, operational risks, and lack of profitability, DOE is the only viable provider of this facility capability. DOE's Advanced Test Reactor at the Idaho National Engineering and Environmental Laboratory and the HFIR at ORNL provide a unique capability for reactor-produced radioisotopes. The electromagnetic separation capacity (presently in standby mode) represents a crucial capability within DOE for enriched stable isotopes for research, therapy, diagnosis, and other applications. DOE provides unique higher-energy accelerator-produced radioisotopes in its Brookhaven Linac Isotope Producer at Brookhaven National Laboratory and the Los Alamos Neutron Source Center at the Los Alamos National Laboratory. DOE also has numerous radiochemical hot cell and glove-box facilities to facilitate handling, separation, and purification of radioisotopes.

A.4. Role of R&D medical community

The medical R&D community is the end user of a variety of isotopes and represents the most challenging market to supply because of the ever-shifting demand for small quantities of specialty isotopes to enable research and develop new isotope applications. Because of the small quantities of isotopes used and the ever-changing demand, these isotopes are very expensive. Such diversity also makes it very difficult to group or list the individual isotopes and their applications.

There are isotope supply issues in this critical R&D area. Tables A1 and A2 list isotopes that are presently of supply concern because (1) they are unavailable at a reasonable cost, on a routine basis, in acceptable quality, and/or in sufficient quantity or (2) they are available only through limited or unreliable domestic sources.

In addition to the use of isotopes, the R&D community has a role in training the next generation of radiochemists. Both the technology and the trained professionals are essential to the transfer of new applications to the commercial sector. Specific roles for the R&D community are as follows:

(1) Provide input on a regular basis concerning isotope use and future needs.
(2) Provide input on the impact of future implementation, application, and products to support funding and appropriation for isotope production and production R&D.
(3) Train the next generation of radiochemists to implement new technologies.

A.5. References for Appendix A

A.1. Beneficial Uses and Production of Isotopes: 2000. Update, Nuclear Energy Agency, Organization for Economic Co-operation and Development.

A.2. Committee on University Research Reactors, 1988. National Research Council, University Research

Table A1
Isotopes unavailable at reasonable cost or on a routine basis in acceptable quality and/or sufficient quantity

Isotope	Major use
$^{225}Ac/^{213}B$	Cancer therapy
^{211}At	Cancer therapy
^{76}Br	PET imaging
^{55}Co	PET imaging
^{64}Cu	Label for biodistribution
^{67}Cu	Cancer therapy
^{52}Fe	Iron tracer
^{195m}Hg	Source ^{195m}Au for cardiac blood studies
^{122}I	PET imaging
^{124}I	PET imaging
$^{212}Pb/^{212}Bi$	Cancer therapy
^{177}Lu	Cancer therapy
^{195m}Pt	Labeled compounds, cancer therapy
$^{223}Ra/^{224}Ra$	Source $^{212}Pb/^{212}Bi$ for cancer therapy
^{47}Sc	Cancer therapy
^{117m}Sn	Pain palliation: prostate, breast, lung malignancies
^{86}Y	PET imaging

Table A2
Isotopes available but at risk because of limited/unreliable domestic supply sources

Isotope	Major use
^{99}Mo/^{99m}Tc	Multiple diagnostic applications
^{123}I	SPECT imaging applications
^{68}Ge	PET calibration source
^{68}Ga	PET calibration source
^{82}Sr	PET myocardial perfusion tracer
^{188}W/^{188}Re	Cancer/arthritis therapy; prevent restenosis; bone-pain palliation
^{90}Y	Cancer therapy

Reactors in the United States—Their Role and Value, National Academy Press, Washington, DC.

A.3. Institute of Medicine (1995). Isotopes for Medicine and the Life Sciences, ed. S. J. Adelstein and F. J. Manning, National Academy Press, Washington, DC.

Appendix B

Information about commercially available radiopharmaceuticals (2003), Radioisotopes for medical use in the United States (2003) and Radioisotopes for industrial use available in the United States (2003) are presented in Tables B1, B2 and B3, respectively.

Appendix C. Abridged conclusions and recommendations of previous studies

C.1. Long-term nuclear technology research and development plan, NERAC (June 2000)

C.1.1. Conclusions

- Isotopes, both radioactive and stable, are essential for several critical areas of national importance to health, safety, and industrial development and international competitiveness.
- The use of isotopes is estimated to be growing at 7–15% per year, faces major challenges; institutional complexity; difficulty in measuring economics and benefits; lack of central leadership; public perception of risks, benefits, and reliability; maintenance of technical expertise; and deteriorating infrastructures.
- DOE-NE's roles will include (1) production and inventory of isotopes for research, medicine and industry, (2) research and development on isotopes, (3) fostering the application of isotopes, and (4) management of national resource isotopes.

Table B1
Commercially available radiopharmaceuticals, 2003

^{14}C-urea	^{153}Sm-samarium lexidronam
^{57}Co-cyanocobalamin	^{89}Sr-strontium chloride
^{51}Cr-sodium chromate	^{99m}Tc-apcitide (GPlla/lllb)[a]
^{18}F-sodium fluoride	^{99m}Tc-arcitumomab (CEA)[a]
^{18}F-fluorodeoxyglucose (FDG)	^{99m}Tc-bicisate dihydrochloride (ECD)[b]
^{67}Ga-gallium citrate	^{99m}Tc-disofenin
^{111}In-capromab pendetide (PMSA)[a]	^{99m}Tc-exametazime (HMPAO)[c]
^{111}In-ibritumomab tiuxetan (CD20)[a]	^{99m}Tc-gluceptate
^{111}In-indium chloride	^{99m}Tc-lidofenin
^{111}In-indium oxyquinoline (oxine)[b]	^{99m}Tc-macroaggregated albumin (MAA)[c]
^{111}In-pentetate (DTPA)[b]	^{99m}Tc-mebrofenin
^{111}In-pentetreotide (SRS)[a]	^{99m}Tc-medronate (MDP)[c]
^{123}I-lobenguane	^{99m}Tc-mertiatide (MAGS)[c]
^{123}I-iodohippurate sodium	^{99m}Tc-oxidronate (HDP)[c]
^{123}I-sodium iodide	^{99m}Tc-pentetate (DTPA)[c]
^{125}I-iodinated albumin	^{99m}Tc-sodium pertechnetate
^{125}I-sodium iothalamate	^{99m}Tc-pyrophosphate
^{131}I-iobenguane	^{99m}Tc-red blood cells[d]
^{131}I-iodinated albumin	^{99m}Tc-sestamibi
^{131}I-iodohippurate sodium	^{99m}Tc-succimer (DMSA)[b]
^{131}I-sodium iodide	^{99m}Tc-sulfur colloid
^{131}I-6-β-iodomethyl-19-norcholesterol[c]	^{99m}Tc-tetrofosmin
^{32}P-chromic phosphate (suspension)	^{201}Tc-thallous chloride
^{32}P-sodium phosphate	^{133}Xe-xenon gas
^{82}Rb-rubidium chloride	^{90}Y-ibritumomab tiuxetan (CD20)[a]

[a]Antigen or receptor with which interaction occurs.
[b]Common chemical abbreviation.
[c]IND with the University of Michigan required.
[d]Red cells labeled with commercially available kit.

C.1.2. Recommendations

C.1.2.1. Isotope research

- Focus on isotope applications not being supported by other Federal programs. It is recognized that there is a large amount of medical research (both basic and applied) on diagnostic and therapeutic modalities, which are typically funded by NIH and/or DOE-SC. The DOE needs to balance this medical emphasis with research into a number of areas which can complement the ongoing medical research, stimulate new and beneficial applications for industry, and enhance environmental, life sciences, agricultural and food safety research.
- Invest in R&D to improve isotope production, processing, and utilization. This includes improving both the technical aspects of isotope production

Table B2
Radioisotopes for medical use available in the United States, 2003

Radioisotope	Radioisotope
$^{225}Ac/^{213}Bi$	^{24}Na
^{241}Am	^{95}Nb
^{41}Ar	^{63}Ni
^{73}As	^{191}Os
^{198}Au	^{32}P
^{207}Bi	^{33}P
^{212}Bi	^{103}Pd
^{213}Bi	^{109}Pd
^{76}Br	^{149}Pm
^{77}Br	^{191}Pt
^{45}Ca	^{195m}Pt
^{109}Cd	$^{224}Ra/^{212}Pb/^{212}Bi$
^{141}Ce	^{86}Rb
^{252}Cf	^{186}Re
^{36}Cl	^{188}Re
^{57}Co	^{105}Rh
^{60}Co	^{103}Ru
^{51}Cr	^{35}S
^{60}Cu	^{122}Sb
^{61}Cu	^{46}Sc
^{64}Cu	^{47}Sc
^{67}Cu	^{75}Se
$^{166}Dy/^{166}Ho$	^{153}Sm
^{55}Fe	^{113}Sn
^{59}Fe	^{117m}Sn
^{66}Ga	^{82}Sr
^{67}Ga	^{85}Sr
^{68}Ga	^{89}Sr
^{153}Gd	^{160}Tb
^{68}Ge	^{94m}Tc
^{165m}Ho	^{99}Tc
^{166}Ho	^{99m}Tc
^{123}I	^{123m}Te
^{124}I	^{125m}Te
^{125}I	^{129m}Te
^{131}I	^{201}Tl
^{111}In	$^{188}W/^{188}Re$
^{114}In	^{133}Xe
^{192}Ir	^{86}Y
^{42}K	^{88}Y
^{177}Lu	^{90}Y
^{54}Mn	^{169}Yb
^{99}Mo	^{65}Zn
^{22}Na	^{88}Zr

(e.g., target design and fabrication, processing, transportation) as well as the systems that enable isotope generation and utilization (e.g., safety systems).

C.1.2.2. Production and inventory

- DOE-NE should be responsible for managing US national resource materials. These materials, some of which are difficult or impossible to replicate but which have no current use, are vital to the future of beneficially using isotopes.
- DOE-NE should lead a multi-program effort to assess responsibilities for the current isotope and radiation source infrastructure with the goal of streamlining responsibilities. Currently, isotope production depends on facilities within the purview of multiple DOE programs (NE, SC, and DP) and some facilities are funded by one program but managed by another. In addition considerable relevant university, commercial, and international infrastructure must be considered.
- Invest and organize to meet the needs of isotope researchers. The current supply is not able to meet the needs of the research community for promising, yet rare or difficult to produce radioisotopes, such as iodine-124, bismuth-212 and -213 and copper-67. In addition, long-term supplies of stable isotopes are not assured since the DOE has halted production.

Table B3
Radioisotopes for industrial use available in the United States, 2003

Radioisotope
^{241}Am
^{14}C
^{109}Cd
^{252}Cf
^{57}Co
^{60}Co
^{137}Cs
^{55}Fe
^{3}H
^{192}Ir
^{85}Kr
^{63}Ni
^{147}Pm
^{238}Pu
^{75}Se
^{90}Sr
^{204}Tl
^{179}Ta
^{234}U

C.1.2.3. Infrastructure

- Maintain current infrastructure while planning for new capability within the next two decades.
- Increase investments in maintaining and improving the capabilities of existing infrastructure.
- Build new, dedicated isotope production capability and/or undertake major upgrades to existing facilities

to meet changing demands, and national and regional needs. DOE-NE should perform a comprehensive assessment of university, laboratory, and international infrastructure as a basis for planning future upgrades or new capacity.
- Establish an appropriately sized, flexible facility for enriching small quantities of stable and radioactive isotopes.

C.2. Report of the NERAC isotope research and production planning subcommittee (April 2000)

C.2.1. Conclusions

- DOE is not meeting the demand for research isotopes and needs to refocus its efforts.

C.2.2. Recommendations

- The production system must be viewed as an integrated set of federal, university and commercial suppliers.
- A dedicated research isotope production capability (including both a cyclotron and small reactor) is needed in the long term.

C.3. Expert panel: Forecast future demand for medical isotopes (March 1999)

C.3.1. Conclusions

The DOE and NIH must develop the capability to produce a diverse supply of radioisotopes for medical use in quantities sufficient to support research and clinical activities. Such a capacity would prevent shortages of isotopes, reduce American dependence on foreign radionuclide sources and stimulate homeland research.

Though the cost of providing a reliable and diverse supply of isotopes for medical use may seem expensive, it will surely pay for itself in reduced patient care costs, improved treatment and improved quality of life for the millions of patients that take advantage of this technology.

C.3.2. Recommendations

- The US government builds its capacity to produce a diverse supply of radioisotopes around either a reactor, an accelerator, or a combination of both technologies as long as isotopes for clinical and research applications can be supplied reliably, with diversity in adequate quantity and quality.

C.4. Report on isotope production and distribution (September 1995)

C.4.1. Conclusions

- There is an increasing need for DOE to assume a leadership position as the primary supplier of isotopic materials (enriched stable and radioiodine isotopes).
- There is a need to continue support of basic research and development with the view toward enhanced medical and industrial applications.
- There appears to be lacking a thorough and comprehensive study of the global situation, an analysis of the challenges, and an analysis of the legal issues involved.

C.4.2. Recommendations

- Decide at the Secretary of Energy level to support the national health care delivery and provide a central role for the DOE isotope program.
  - Establish strong centralized program leadership.
  - Coordinate the various programs within the Department.
  - Coordinate all interfacing federal agencies.
  - Foster international cooperation and understanding.
- Establish a DOE/commercial industry partnership in the production/distribution of isotope products.
  - The production and processing facilities are primarily US government owned and operated.
  - The business and supply expertise is provided by industry.
- Commit to subsidize isotope production facility construction and upgrade.
  - Reactivate facilities and provide start up funding.
  - Upgrade existing facilities to ensure compliance with current regulations.
  - Construct new facilities as needed.
- Commit to strong research & development and training programs.
  - Develop new medical isotopes, procedures, and instrumentation.
  - Develop new industrial applications and techniques.
  - Support basic physical, chemical, and materials research.
  - Support education and training in the use of isotopes.
- A systematic and comprehensive isotope market supply/demand and strategic planning analysis should be conducted to guide the decisions and actions required for the development of any future program initiatives. This market strategic plan builds upon the most recent studies and address the

following issues at a minimum:

- ○ Domestic and world-wide supply/demand projection.
- ○ Stability/reliability of production facilities.
- ○ Market strategy—production and distribution by market segment.
- ○ Environmental and business legal issues.
- ○ National and international economic impact.
- ○ Future sources of technically trained personnel.

C.5. Isotopes for medicine and the life sciences, Institute of Medicine (1995)

C.5.1. Conclusions

- On the basis of its congressional mandate, its historic role, and its technical expertise and resources, DOE has important roles to play in all aspects of isotope production, research, and education.
- Although the full cost recovery provision of Public Law 101-101 has hindered rather than helped DOE in promoting isotope research and application, the concept of centralized management is not without merit. The important research, development, and education activities associated with isotope production and distribution are, however, still spread throughout DOE.

C.5.2. Recommendations

- A National Isotope Program, reporting directly to the director of the Office of Energy Research of DOE, should be created to consolidate the administration of all biomedical isotope-related activities: production and distribution, research and development, and education and training.
- A national advisory committee should be formed to assist the National Isotope Program Director in prioritizing critical needs in technology development and in choosing among applicants wishing to use the reactor and accelerator isotope production facilities or obtain their products. This National Isotope Program Advisory Committee should also provide advice on the development and execution of the several educational programs associated with isotope production and use.

C.6. US DOE national isotope strategy (August 1994)

C.6.1. Conclusions

- Public Law 101-101
  - ○ In 1989, Public Law 101-101 was enacted to change the financing of the operation of the Isotope Production and Distribution Program. Public Law 101-101 established a revolving fund with the objective of making the Isotope Program financially self-sufficient. It is clear that financing the Isotope Production and Distribution Program on a self-supporting basis does not meet the country's needs. Instead, it encourages the production of isotopes that can be sold in the world market at a profit and discourages production of the wide array of unprofitable isotopes that are needed for applications such as in research to lower health care costs and improve the country's economic competitiveness.
- Serve isotope customers and stakeholders
  - ○ *Continue current operations*: The Department will continue to serve its customers in the short term by delivering products and services from our production facilities at six locations: the Brookhaven National Laboratory, EG&G Mound Applied Technologies, Idaho National Laboratory, Los Alamos National Laboratory, ORNL, and the Westinghouse Hanford Company.
  - ○ *Respond to our customers' needs for isotopes*: In keeping with the National Performance Review objective of putting customers first, the Department will respond to the need for isotopes that the Department, in consultation with its customers and stakeholders, determines to be important for medical, industrial, and research applications, first by encouraging private sector sources, and second, when no private sector source is available, by producing the isotope.
  - ○ *Support selected process development research projects*: The Department, also in consultation with its customers and stakeholders, will identify isotopes that are needed to support research projects and that are not currently available. The Department will support research to produce, separate, and refine such isotopes. Proposals by Government organizations or private researchers will be considered. The Department will seek appropriations to support selected process development research projects.
  - ○ *Organize for effective delivery of products and services*: The Isotope Production and Distribution Program will enhance its effectiveness in product and service delivery. The Headquarters staff will be increased and organized into functional units for production, product delivery, marketing and customer services, and business management. In addition, the Headquarters Isotope Program will reach new mutual understandings with the management and operating contractors of its production sites on the need for and was to improve the efficiency and reliability of production activities and ensure excellent customer service.
- Involve customers and stakeholders in the Isotope Program

- *Share current technology with the Department's customers and stakeholders*: The Department of Energy has strong intellectual resources and unique facilities for providing isotope products and services. Non-Department of Energy organizations also have substantial capabilities to separate and process isotopes, perform research, develop beneficial applications, and deliver isotope-related products and serves to the world market. These capabilities, which are at least partially complementary, will need to be better coordinated and enhanced. The Department will develop and use an array of mechanisms to share resources with non-Department participants.
- *Provide isotopes for research*: Research is needed to explore new isotope applications that may have societal benefit and market potential. In many cases, research organizations outside the Department are well positioned to identify beneficial uses of isotopes. The Department, in consultation with its isotope customers and stakeholders, will identify isotopes needed for selected research projects and seek appropriations to provide them at a nominal cost to the researchers.
- *Encourage private sector production isotopes*: The Department will encourage private sector production of isotopes by working with potential producers to identify barriers to their entry into the market. If, after careful analysis determines that it is possible, legal, and appropriate, Government support might include Federal-private cost sharing of up-front capital costs through cooperative arrangements that may provide for the return of the Federal investment from future profits; sharing of costs associated with reactor operations; and treatment of nuclear waste for ultimate disposal. Where consultation with the Department's customers and stakeholders determines that Government support is appropriate, the Department will seek authorities and/or appropriations to support selected projects.

C.6.1. Recommendations

- Change Public Law 101-101
  - *Propose legislation*: To return financing of the Isotope Program to a basis that is consistent with its mission, the Department will seek legislation that provides, in addition to revenues generated from the sales of isotope products and services, a second source of revenue for the revolving fund through annual appropriations. Annual appropriations for the Isotope Production and Distribution Program would be identified in a new decision unit in the Energy Supply, Research and Development appropriation called "Isotope Support". The Isotope Support decision unit will fund a payment into the Isotope Production and Distribution Fund for the production and processing of those isotopes which, although unprofitable, are in the national interest.
- Serve isotope customers and stakeholders
  - *Molybdenum-99 production*: The Department's plan to assure domestic production of molybdenum-99 is an example of its commitment to respond to the needs of its isotope customers and stakeholders in a way that reflects post-Cold War national priorities. Therefore, the Department is planning to convert an existing reactor and adjacent processing facilities within its complex to produce molybdenum-99 and related medical isotopes to ensure that there are no inadequacies of supply for domestic use.
  - *Learn the needs of the Department of Energy's customers*: Beginning immediately, with more aggressive solicitation of customer feedback, the Department will seek to better determine the short- and long-term needs of its customers and stakeholders consistent with the National Performance Review principle of putting customers first. Also beginning immediately, the Department will encourage informal dialogue with experts among its customers and stakeholders to encourage them to express their needs. Working with the Office of Science and Technology Policy, the Department will develop an implementation plan that describes the process for obtaining information about current and future isotope needs, criteria for selecting which isotopes to produce, and a system for setting development and production priorities. Professional societies and trade associations, including the American Nuclear Society, the American College of Nuclear Physicians, and the Society for Nuclear Medicine, the Council on Radionuclides and Radiopharmaceuticals, and the Alliance for American Isotope Production, have offered to support this dialogue.

    Beginning in fiscal year 1995, the Department will convene an annual meeting of its customers and stakeholders, research community representatives, other isotopes producers, and all other interested parties. At this event, representatives of the Department, suppliers of products and services to the Department, and Department-sponsored researchers will describe the Isotope Program to the Department's customers and stakeholders using, among other information, quantitative performance measurements based on the requirements of the Government Performance and Results Act of 1993. Representatives of the isotope user community will be encouraged to present their needs, help the Department develop its future plans, and provide feedback on the Department's performance. Notice of this meeting will be provided by the Department by letter to its customers and stakeholders.

- *Continue current services*: The Department recognizes that many of its customers, particularly those conducting research, are critically dependent on a continuing supply of isotopes. Any decision to produce a new isotope or to cease producing an isotope or providing a service or to withdraw from any of the production facilities will be made in consultation with the Department's customers and with the advice of its customers and stakeholders. Although many of the Department's facilities have unique capabilities to deliver products to rigorous specifications, for example at high specific activities and purity, alternate sources and production processes within the Department, other Government organizations, the US private sector and throughout the world will be considered in making this decision. The Department will consult with its customers before changing its product and service mix to assure that they receive sufficient notice of planned changes to avoid causing trauma to the customer and to the existing marketplace.
  The Department of Energy will continue to serve its customers in the short term by delivering products and serve its customers in the short term by delivering products and services from its major production facilities. Many of these facilities have production capabilities that are unique in the United States. The Department will also continue to exploit the inventory of isotopes at these facilities. Each of these facilities, except the calutrons, actively produced isotopes in 1993 for the Isotope Program. The calutrons were maintained in standby, ready to renew the available inventory of enriched stable isotopes. The Department recognizes that the inventory of certain stable isotopes needed for research is very low. There is a strong need to run the calutrons to replenish supply in the near future. Pending a thorough review of its current operations, the Department will continue to provide unique capabilities and capacities on which its customers depend.
- *Long-term plans for Department of Energy facilities*: Consistent with the Department's commitment to respond to its customers' and stakeholders' needs for essential isotopes, the long-term plan for use of Department facilities will include delivery of products and services that are unavailable outside the Department of Energy.
  Two major reactors and two accelerators currently produce isotope products and services that cannot be produced elsewhere in the country. These are the HFIR at ORNL and the Advanced Test Reactor at Idaho National Laboratory, and the Brookhaven Linear Accelerator Isotope Producer at Brookhaven National Laboratory and Los Alamos Meson Physics Facility at Los Alamos National Laboratory, respectively. Based on its current understanding of its customers' needs, the Department will continue to produce isotopes at both reactors and at least one of the accelerators.
  In anticipation of the eventual end of life for the HFIR and potential changes in the host program support for the HFIR and other facilities, the Department will identify potential substitute facilities among Department, university, industry, and foreign facilities. The Department will evaluate the need for new or upgraded facilities, including the potential isotope production capability of the Advanced Neutron Source, seek new processes to replace inefficient operations, and develop a mechanism to assure the consideration of isotope production needs as the Department develops plans for new facilities and facility modifications. These deliberations will include the user community and will be documented in the fiscal year 1995 update to the National Isotope Strategy.
  For batch processes such as the production of enriched stable isotopes using for example, the calutrons at Oak Ridge for electromagnetic separation and the thermal and chemical separation capabilities at Mound, the Department will consult with its customers and stakeholders to determine needs and operate the facilities to build inventories in response to research and market demands. In the long-range planning process, the Department will seek expressions of need from its customers and stakeholders for continued availability of existing facilities or development of alternate processes. The Department will also identify complementary uses of university, industry, and foreign facilities and encourage non-Department participants to construct replacement facilities as separation technology progresses.
- *Respond to our customers' needs for new isotopes*: The Department will respond to the greatest extent possible to the needs for new isotopes that the Department's customers determine to be essential for medical, industrial, and research applications. When there is an agreed upon need for an isotope not currently produced by the Department, the Department will first determine if it is reliably available from sources

elsewhere in the world, then evaluate the capability of non-Department organizations to produce it. If needed, the Department may assist a non-Department source to begin producing the isotope. When on other source is available, the Department will allocate currently appropriated money, seek support from other Government agencies, or seek appropriations to begin producing the isotope, either by using existing capabilities or exploiting current inventories, including surplus stockpiles and waste products.

- ○ *Support selected process development research projects*: The Department, also in consultation with its customers and stakeholders, will identify isotopes needed to support research projects that are not available in chemical form, specific activity, or purity needed for specific applications. Research cannot be conducted unless these isotopes are available. Once they are available, using them in research applications may lead to the development of new ways to improve targeted cancer therapies.

  After consultation with its customers and stakeholders, the Department may choose to support research to produce, separate, and refine isotopes that are needed for research projects similar to the example described above. Proposals by Government and non-Government organizations will be considered. The Department will request appropriated funds for the Isotope Program to support selected process development research projects.
- ○ Organize for Effective Delivery of Products and Services

  Strengthen the headquarters organization: The Department's Isotope Production and Distribution Program was reorganized in December 1993. A new director was appointed to manage and oversee restructuring efforts and to implement Isotope Program changes. Production, distribution, and business managers have been appointed. The position of marketing manager will be filled with a Federal employee as soon as possible. In the interim, a plan for integration of the marketing function, in close cooperation with the Isotope Program Director, is being developed at one of the production sites. Further changes are planned to assure that production and distribution problems are identified immediately and corrective actions set in place. The marketing function will maintain a continuing interaction with customers to assure that customer concerns receive immediate attention and that isotope products are being delivered in accordance with product quality and schedule commitments. In addition, the marketing function will seek to expand current markets and identify new business opportunities. Initially, the Department will retain market experts from the private sector to help characterize the domestic and international isotope markets and provide a pricing structure that, consistent with the Department of Energy's mission, assures maximum income to the Department from the sale of products and services. A comprehensive marketing plan will be developed by September 30, 1994.

  Strengthen production agreements: Isotope production and service delivery are not large dollar activities. In the past, they have been dependent on other major programs including, particularly, defense and energy research. Thus, they have not received priority attention from either the Department of Energy field organizations or the management and operating contractors. Working with the field organizations, the Department will begin immediately to review the field organization and contractor performance in this area in order to seek new mutual understanding of methods of improving the efficiency and reliability of production activities and ensure improved customer service consistent with the Department's renewed commitment to provide isotope production and distribution services. Consistent with the goals of the Government Performance and Results Act of 1993, essential elements of this understanding are performance incentives and measures for the Department organizations and the contractors, empowerment of isotope production managers, new commitments to honor customer contracts and schedule needs, longer term commitments for production and delivery of isotope products and services, and establishment of performance standards for key personnel. These understandings between the Department and its management and operating contractors will be included, if appropriate, in the management and operating contracts.

  Organize for effective delivery of products and services: The Department will improve the Isotope Production and Distribution Program for more effective product and service delivery. The Department's Isotope Production Program staff will be increased and organized into functional units for production, product delivery, marketing and customer services, and business management. In addition, the Department's Isotope Production Program staff will reach new mutual understandings with the management and operating contractors for our production sites on the need for and ways to improve the efficiency and reliability of production activities and ensure improved customer service.

- ● Involve customers and stakeholders in the Isotope Program.

- *Share current technology with the Department's customers and stakeholders*: The Department has strong intellectual resources and unique facilities for providing isotope products and services. The Department's customers and stakeholders also have strong capabilities to irradiate separate and process isotopes, perform research, develop beneficial applications, and deliver isotope-related products and services to the world market. These complementary capabilities will be coordinated and developed to help assure full beneficial applications of isotope products and services.
- *Seek appropriations to provide isotopes for customer and stakeholder research*: Research is needed to explore new isotope applications that may have societal benefit and market potential. In many cases, non-Department of Energy organizations, particularly universities, are well positioned to identify beneficial uses of isotopes but lack even the small quantities of isotopes needed to pursue their research. They do not have the capacity to produce separate, or refine the isotopes they need and have depended on the Department in the past to give, lend, or lease isotopes to them. Small quantities of an array of research isotopes are very inefficient to produce. The researchers cannot afford to pay the Department the full cost of producing these isotopes. The Department, in consultation with its customers and stakeholders, will identify candidate research projects and the isotopes needed for this research. For selected research projects, the Department will seek appropriations to provide the needed isotopes at a nominal cost to the researchers.
- *Encourage private sector production of isotopes*: The Department will encourage competitive private sector production of isotope products and services by working with potential producers to identify and overcome barriers to their entry into the market. The Department will withdraw from competitive, reliable markets. Government support might include Federal-private cost sharing of upfront capital costs through cooperative arrangements that may provide for return of Federal investment from future profits, sharing of costs associated with reactor operations, and treatment of nuclear waste for ultimate disposal.

Appendix D. Cost of program implementation

As discussed in Section 2 of the report, total resources for the DOE Isotope Program have been in decline for several years. The resource history and the declining trend are illustrated in Table D1. All data presented in Table D1 have been escalated and presented in FY 2003 dollars. The resource categories presented in Table D2 are defined as follows:

Operations	Resources to operate and maintain facilities to produce isotopes. In FY 1996 through FY 1999, any funding available for production and applications R&D was included in the operations category.
R&D	Both R&D resources for new production techniques and isotope applications.
Special projects	Resources for new facilities or significant modification to existing facilities to enhance capabilities.
Total resource	Total resources available to the program, which include Congressional appropriations and revenue from isotope sales.

The proposed National Isotope Program will require and include in its projections resources of approximately \$25 M. These resources will be used to produce essential isotopes, reestablish R&D for production and isotope applications, establish nuclear technology education

Table D1
History of DOE isotope resources

Resources by fiscal year (\$M, in FY 2003 dollars)								
	1996	1997	1998	1999	2000	2001	2002	2003
Operations[a]	35.2	21.2	25.3	21.3	17.9	20.2	13.8	18.6
R&D	ND[b]	ND[b]	ND[b]	ND[b]	2.6	2.6	2.6	0
Special projects	14.4	5.8	10.3	12.3	7.2	5.5	9.3	2.5
Total resources[c]	49.6	27.0	35.6	33.6	27.7	28.3	25.7	21.1

[a]\$6.5 M in FY 2003 provided to support ORNL Bethel Valley Facilities (one isotope facility) not included.
[b]No separate data available for R&D resources; any R&D resources are included in operations.
[c]Total requirement resources will be offset by any sales revenues (nominally \$8–10 M/yr).

Table D2
National Isotope Program implementation cost

Funding category	Projected annual resource needs ($M)
Operations	15
R&D	9
Nuclear technology education initiative	1
Facility stewardship	15
Special infrastructure improvement projects	10
Total resources[a]	50

[a]Total resource needs will be offset by any sales revenue (nominally $8–10 M, FY 2003).

activity, and support isotope production infrastructure (new and existing facilities). Table D2 provides the resource breakdown for the National Isotope Program. Also shown are candidate special projects to enhance the production capabilities. Prioritization of the special projects based on limited resources is left to the National Isotope Program Director and Advisory Committee.

Candidate Special Infrastructure Improvement Projects

Stable Isotope Separator	$10M
70-MeV Cyclotron	$30M
MURR Upgrade	$9M

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