Nuclear Energy Research Advisory Committee (NERAC)

Subcommittee for Isotope Research & Production Planning

Final Report

April 2000

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May 19, 2000

James J. Duderstadt, Ph.D.,
Chairman, Nuclear Energy Research Advisory Committee
Office of Nuclear Energy, Science and Technology
U.S. Department of Energy
Washington, D.C 20585

Dear Dr. Duderstadt:

On behalf of the NERAC Subcommittee For Isotope Research And Production Planning, I am pleased to submit to you the enclosed final report. This report is in response to the charge outlined in the January 11, 1999 letter from Mr. William D. Magwood, IV, Director, Office of Nuclear Energy, Science and Technology, requesting advice regarding "the creation of a comprehensive Long-term Isotope Research and Production Plan to guide the Department's isotope-related activities over the next ten years".

The subcommittee reaffirms that the Department of Energy is the custodian of unique physical facilities and addressed many of the important issues regarding the Department's role in the important area of isotope availability.

The Subcommittee believes that planning should be initiated now to ensure that appropriate responses would be made regarding the long-term reliable availability of stable and radioactive isotopes and other issues that will need to be addressed in the near future.

In the short term, the Subcommittee strongly recommended that an immediate goal must be to make optimal use of the existing facilities and opportunities. Consequently, several specific recommendations were made in this regard. We believe the Centers of Excellence concept, which will concentrate expertise in particular areas, is something that should be considered strongly by the DOE.

There is a large benefit to be realized from ongoing technical advances. The radiotracer technique provides a strong signal on a very small mass utilized to measure kinetic functions without directly disturbing the fundamental function one wants to assess. As the proprietor and overseer of large physical facilities that offer the unique opportunity to provide isotopes critical to gain extremely important information regarding the function of biological molecules, the Department of Energy is in position to make extraordinarily important contributions to biology and medicine. The scientific research contributions are already extended to advances in industry, availability of consumer products, the space program and agriculture.

The Subcommittee is comprised of ten members, selected for their expertise and experience in the production, processing, distribution and application of stable and radioactive isotopes in the biological and physical sciences and in medicine. The members included basic and clinical scientists, administrators and users of isotopes, from the federal government, academia and industry. Subgroups made one day site visits to isotope production and processing facilities at the Brookhaven National Laboratory, Oak Ridge National Laboratory, Loa Alamos National Laboratory, and Pacific Northwest National Laboratory, to an academic facility, the Missouri University Research Reactor (MURR) and to a commercial company, International Isotopes, Inc (I^3). Detailed site visit reports of our observations and judgments of the operations at these facilities are included as appendices to the report. The full subcommittee met over a 2 day period, June 22-23, 1999, to review the six site-visit reports, agree on the recommendations and draft the report, for which there is unanimous agreement.

I am grateful to all members of the Subcommittee for their dedicated commitment to completing this project and to their intellectual contributions to the final report. Mr. Owen Lowe, director of the DOE Isotope Production and Distribution Program was an important resource who contributed significantly to our efforts. I am particularly indebted to Dr. Ralph Bennett for his insightful comments and critique and for his expert assistance with the final editing and presentation of the final report.

Sincerely yours,

Richard C. Reba, M.D.
Chairman, NERAC Sub-Committee for
Isotope Research and Production Planning

Encl:

Department of Energy
Washington, DC 20585

January 11, 1999

Dr. Richard D. Reba
University of Chicago Hospital
5841 South Maryland Avenue
Chicago, Illinois 60637

Dear Dr. Reba:

Thank you for agreeing to chair the Nuclear Energy Research Advisory Committee (NERAC) Subcommittee for Isotope Research and Production Planning. As you are aware from your participation in many isotope studies, including cochairing the NERAC Expert Panel to Forecast Future Demand For Medical Isotopes, the issue of isotope availability now and in the future is of considerable importance to the Nation. As a result, the manner in which the Department of Energy manages its unique resources and capabilities to provide for the future isotope and isotope-based technology needs of the American people is an appropriate subject of consideration of NERAC. As anticipated by the recent letter issued by the chairman of the full NERAC, Dr. James Duderstadt, this subcommittee provides the Department with the opportunity to receive expert, objective advice regarding the future form of its isotope research and production activities.

We believe that the first order of business for the subcommittee should be the creation of a comprehensive Long-term Isotope Research and Production Plan to guide the Department's isotope-related activities over the next ten years. This plan should consider the following questions:

- How well does the Department's existing five-site production infrastructure serve the current need for commercial and research isotopes?
- What should be the long-term role of Government in providing commercial and research isotopes?
- What long-term research should be conducted by the Department to support the production and use of medical isotopes?
- The Department believes that the private sector is best suited to produce commercial quantities of isotopes and has established a plan to privatize seven aspects of its isotope activities by October 2000. How can the Department best utilize private sector strengths to assure the future production of sufficient quantities of research isotopes?

- Should the Department establish public/private joint ventures, Government corporations, or other innovative arrangements to accommodate both the projected growth in demand for commercial isotopes and the need for inexpensive, plentiful research isotopes?

Other issues may be appropriately addressed by such a Long-term Isotope Research and Production Plan, and we look forward to NERAC's input as to the range of subjects that should be included in such a plan. The Department requests that the committee issue an interim plan by August 31, 1999, with a final plan completed by December 31, 1999.

The deliberations of NERAC and your subcommittee are very important to the success of a Long-term Isotope Research and Production Plan. Indeed, we believe that only NERAC can author a credible strategy that will successfully represent the needs and interests of the Nation. As we recently discussed, the Department stands ready to support early convening of this subcommittee. Please contact me, Dr. Norton Haberman, or Mr. Owen Lowe if you have any questions or comments.

Sincerely,

William D. Magwood, IV, Director
Office of Nuclear Energy,
Science and Technology

cc: Dr. James Duderstadt, Chairman, NERAC
Dr. Ernest Moniz, Under Secretary

EXECUTIVE SUMMARY

Isotopes, including both radioactive and stable isotopes, make important contributions to research, medicine, and industry in the United States and throughout the world. For nearly fifty years, the Department of Energy (DOE) has actively promoted the use of isotopes by funding (a) production of isotopes at a number of national laboratories with unique nuclear reactors or particle accelerators, (b) nuclear medicine research at the laboratories and in academia, (c) research into industrial applications of isotopes, and (d) research into isotope production and processing methods. The radiopharmaceutical and radiopharmacy industries have their origin in these DOE-funded programs. Currently, more than 12 million nuclear medicine procedures are performed each year in the United States, and it is estimated that one in every three hospitalized patients has a nuclear medicine procedure performed in the management of his or her illness.

Short-Term Recommendations (the next five years)

1. Refocus the Office of Isotope Programs on the supply of radioisotopes and stable enriched isotopes for research within its mission to serve the national need for a reliable supply of isotope products and services for research, medicine, and industry.
2. Limit commercial isotope production to products where the DOE has a unique production capability and where other market supplies are not sufficient to meet U.S. demand.
3. Establish an Isotope Review Panel to review and recommend proposals to produce isotopes to the Director of Isotope Programs. The Panel should identify isotopes of interest and preferred sites for production, including alternative supply options, and provide other advice as requested.
4. Consolidate existing radioisotope processing capabilities.
5. Contract with the academic and private sectors to accomplish the primary focus and mission.
6. Expand innovative research in diagnostic and therapeutic nuclear medicine by increasing funding for the Advanced Nuclear Medicine Initiative.
7. Increase the funding for academic training to support the primary focus and mission.
8. Begin conceptual design of a dedicated cyclotron to support the mission to serve the national need for a reliable supply of isotope products and services for research, medicine, and industry.

All of this is enabled by an abundant supply of isotopes that can meet the changing needs of a vigorous and growing research community. If the widespread uses of radioactive materials are not maintained through research, it will not be possible for this country to sustain, much less expand, our high standard of living and advanced industrial economy.

Recent levels of federal appropriations, averaging about $20 million per year, have not permitted the DOE's isotope supply to adequately keep pace with the changing needs of the research community. It is now widely conceded that limited availability of specific radionuclides is a constraint on the progress of research. The problem is especially apparent in a number of medical research programs that have been terminated, deferred, or seriously delayed by a lack of isotope availability.

The Nuclear Energy Research Advisory Committee (NERAC) convened a Subcommittee for Isotope Research and Production Planning in January 1999 to study the issue of isotope availability. The Subcommittee visited seven isotope production sites: five within the national laboratory system and two outside producers. A number of recommendations, both short- and long-term, were made regarding the supply of isotopes:

Long-Term Recommendations (the next ten years)

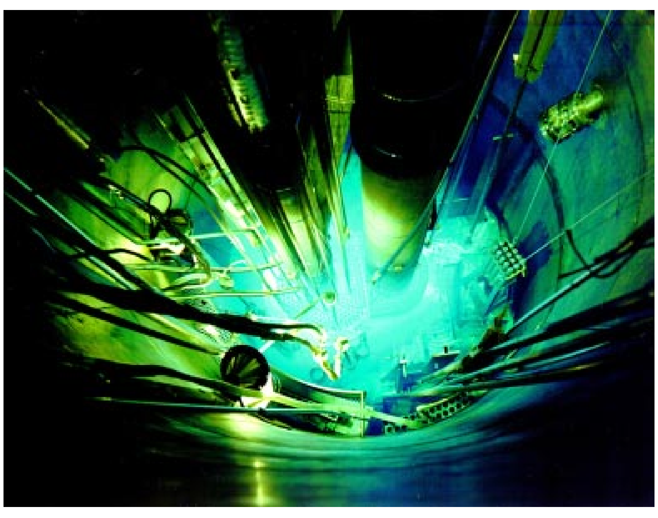
1. Promote the greatest synergism among the national labs, academia, and industry to fulfill the Isotope Program's mission.
2. Acquire a dedicated, single-mision, isotope production and processing facility that would be fully operational by 2010. The facility should include a cyclotron and a reactor both dedicated to isotope production based on off-the-shelf designs.
3. Maintain a stable/enriched isotope inventory for research purposes.
4. Ensure an adequately sized and properly trained work force to meet national isotope needs.
5. Implement a contingency plan to guarantee an uninterrupted radioisotope and stable isotope supply for the country's research needs.

FINAL REPORT

Introduction

Beginning with the Atomic Energy Act of 1954, the Department of Energy (DOE) and its predecessor organizations, the Energy Research and Development Agency (ERDA) and the Atomic Energy Commission (AEC), have actively promoted the use of isotopes by funding (a) production of isotopes at a number of national laboratories with unique nuclear reactors or particle accelerators, (b) nuclear medicine research at the laboratories and in academia, (c) research into beneficial industrial applications of isotopes, and (d) research into isotope production and processing methods. The radiopharmaceutical and radiopharmacy industries have their origin in these DOE-funded programs. Currently, more than 12 million nuclear medicine procedures are performed each year in the United States, and it is estimated that one in every three hospitalized patients has a nuclear medicine procedure performed in the management of his or her illness. Although the funding from various federal agencies has been especially successful in both medical diagnostic and therapeutic arenas, it is now widely conceded that limited availability of specific radionuclides is a constraint on research progress in this exciting area.

The lack of radionuclides significantly inhibits progress in evaluating a host of promising diagnostic and therapeutic drugs in patients with debilitating and fatal diseases, examining fundamental basic science questions, studying human behavior and normal growth and development, and exploring the aging process and the products of transgene expression. This report assesses the current status of radioactive and stable isotope availability for research, medicine, and industry in the United States and makes recommendations to the Department of Energy that will ensure the long-term capabilities of the country to provide this needed resource.



The Annular Core Research Reactor (ACRR) core at Sandia National Laboratory during operation at 2MW.

Use of Isotopes in Research, Medicine, and Industry

Isotopes, including both radioactive and stable isotopes, make important contributions to research, medicine, and industry in the United States and throughout the world. Overall, the biomedical community uses more than 200 radioactive and stable isotopes for research, drug development, and diagnosis and treatment of human diseases. The research leads to the development of completely characterized radiolabeled compounds that permits a physician to target a specific organ or cell type by selecting the appropriate radiopharmaceutical. It is interesting that *80–90% of all drugs that receive Food and Drug Administration (FDA) approval go through a research and development process that uses radioisotopes*. Why?

Because studies in which the proposed new drug is labeled with a radioactive tracer tells us where the drug goes, the rates of transfer, how long it remains in the body, and how, where, and at what rate it is excreted. The radioactive tracer technique measures kinetic functions within the human body without disturbing the normal function one wants to assess. Without the use of these radioactive markers the FDA approval process would take much longer and be more complicated and expensive than it already is.

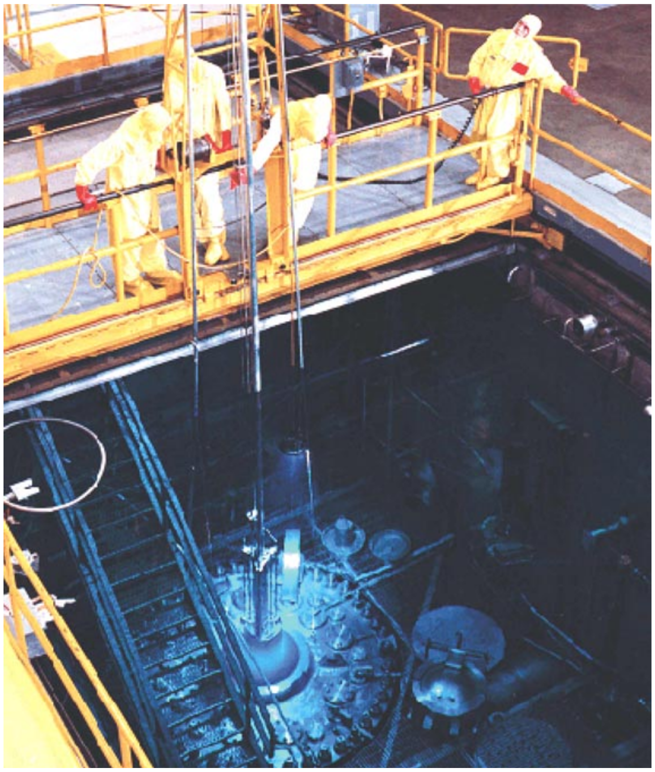
Another category of research is based on the use of stable isotopes. When stable isotopes are separated and enriched, and then introduced into a system under study—whether biological or physical—they can be used to trace accurately the movement of materials or reaction of chemical constituents. Such isotopic tracers give rise to sensitive and nonintrusive measurements in environmental and life sciences, and chemical engineering.

While much less focused on research, isotopes are at work in industry, too. A number of important categories of uses exist: Industrial radiography plays a central role in ensuring public safety by nondestructively examining welds and searching for flaws in pressure vessels, piping, bridges, airplanes, ships, etc. The DOE and a DOE-commercial partnership are two of a half dozen international suppliers of iridium-192 for this type of radiography. Radioisotope instruments have been developed for a number of highly sensitive chemical, elemental, and physical analyses of materials. Radiation processing is widely used to sterilize medical products and food around the world, creating a considerable demand for cobalt-60. Industrial radioisotope gauging comprises a broad set of methods for determining the thickness, concentration, density, or weight of a product undergoing continuous production, like papers and thin films. There are also specialty uses of radioisotopes for unique applications, such as the tritium-powered runway safety lights at airfields and the smoke detectors found in most homes.

The fact that the uses of radioactive materials are ubiquitous in our society, giving rise to enormous economic and health benefits,[1] is generally unappreciated by most Americans. The medical and health uses improve the quality of life and save lives by early diagnosis and treatment of disease. At the same time, the costs of medical care are significantly reduced by the use of radioactive materials. The industrial uses improve public safety and increase the quality while reducing the cost of everyday products. If the widespread uses of radioactive materials are not maintained through research, it will not be possible for this country to sustain, much less expand, our high standard of living and advanced industrial economy.

A technician processing iridium-192 in a hot cell operated by International Isotopes of Idaho, Inc. on the Idaho National Engineering and Environmental Laboratory. This commercial partnership with the government supplies most of the iridium-192 and high activity cobalt-60 used in the U.S. today.

[1] "Economic and Employment Benefits of the Use of Radioactive Materials," Management Information Services, Inc., March 1994.



The 85 MW High Flux Isotope Reactor (HFIR) being readied for a operation at the Oak Ridge National Laboratory.

How Isotopes are Supplied

To understand the supply of radioisotopes, it is helpful to consider the major ways that they are produced, who produces them, and who uses them. It is also important to consider the pricing and costs for isotopes and the policies on federal production. These are discussed in turn below. At the end of this section, the supply of stable isotopes is mentioned briefly.

Reactor and Accelerator Production and Hot Cell Processing of Radioisotopes

The two major means of radioisotope production are with nuclear reactors or particle (typically proton) accelerators. Most radioisotopes can be made via one method or the other, but not generally both. Thus, the nation's supply must have both types of production capabilities. In general, an isotope production reactor should have as high a neutron flux as possible, be designed to offer regions with a choice of high thermal or fast neutron flux, afford easy access of small targets in and out of the reactor, and operate nearly constantly without other demands or program priorities. An accelerator should have a high average beam current of protons of a reasonably high energy (roughly 30–100 MeV), afford flexible arrangements for targets, and operate reliably, that is, without other demands or program priorities.

Both reactor and accelerator production share a common need for chemical processing of the targets after irradiation or bombardment. The processing recovers the desired radioisotope product from the target, separates out the impurities, and brings the radioisotope to the desired chemical state and physical form for use. This typically requires small- to medium-size hot cells located near the production facility, with a substantial infrastructure for chemical processing, radioactive materials handling and shipping, and waste disposal.

A third means of "production" is the separation of desired isotopes from existing stockpiles of transuranic materials or other long-lived radioactive isotopes. An example of this is thorium-228, the parent of bismuth-212, which can be separated from stocks of uranium-232. This type of production requires hot cells, but requires neither a reactor nor an accelerator.

The above requirements are generalizations, and many variations exist. Current producers of radioisotopes in the United States and world today include governments that operate reactors and accelerators at national laboratories or institutes and commercial companies that own and operate accelerators. Most importantly, there are many partnership arrangements where companies lease irradiation space in government reactors or operate processing facilities in coordination with the government.

A few universities also produce radioisotopes, though their small-scale capabilities or operating schedules usually limit the supply.

The ideal of a truly commercial supplier—one whose capital builds the facility and infrastructure and assumes all costs of production, waste disposal, and decommissioning—is currently only realized among the many smaller accelerator-based producers. This is not likely to change in the future. Rather, commercial partnerships with governments are found throughout the world and will continue to be the primary means of production well into the future. Indeed, the commercialization projects that the DOE has recently conducted successfully are all aimed appropriately at building partnerships, not at selling off or shutting down their unique production facilities.

At all DOE production sites, the radioisotope production mission shares the reactor or accelerator with other diverse programs for nuclear science, energy, or defense. In all cases, the other sponsors are much larger than the isotope production and exercise considerable influence on the facility schedules and priorities. This "parasitic production" often yields a lack of priority for radioisotopes, especially for the smallest customers. Many examples of this problem are presented in the Site Visit Reports. In its recommendations, the Subcommittee observes that the only complete solution to the problems of parasitic production is to take steps to provide dedicated, yet modest, facilities for radioisotope production in the future.

Markets and Users of Radioisotopes

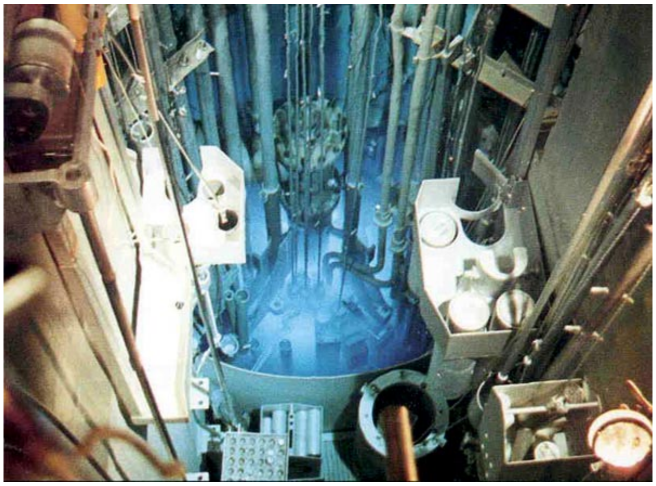
Radioisotope suppliers generally operate in two different markets: Bulk radioisotopes are sold to pharmaceutical manufacturers and distributors (in the case of medical use), or to equipment or sealed-source manufacturers (in the case of industrial use). Bulk radioisotopes are usually not sold directly to the end users. Rather, they become an integral part of the product that the pharmaceutical or equipment manufacturers offer. On the other hand, specialty radioisotope sales to end users, such as researchers preparing for experiments, are typically small quantity orders. The U.S. government conducts both types of business. The bulk radioisotope sales are often referred to as "commercial sales," while the specialty radioisotope sales are often referred to as "research sales." As indicated above, commercial sales can be to either medical or industrial customers. DOE's commercial sales are almost evenly divided between the two. Research sales are much more frequently made to medical researchers, though a few industrial researchers also purchase small quantities of radioisotopes.

The DOE sales of radioisotopes during recent years have been predominately by commercial. By dollar volume, over 95% of the sales were bulk isotopes for medicine

Commercial Sales: Sales of large ("bulk") quantities of radioisotopes to pharmaceutical companies or distributors, or to equipment or sealed-source manufacturers. The DOE prices these orders at full cost-recovery. The DOE produces commercial sales only when there is no U.S. private sector capability or foreign sources are insufficient to meet U.S. needs.

Research Sales: Sales of small quantities of specialty radioisotopes to end users usually engaged in medical research (though there are some physics, chemistry, agriculture, biology, and industry researchers as well.) The DOE prices these orders to produce a reasonable return to the government but not discourage their use.

Full Cost-Recovery: Pricing based on the entire cost of an activity. This includes all the direct labor and nonlabor costs associated with the activity, and indirect costs normally allocated to the direct costs as well. It does not include any profit nor any costs unrelated to the work performed.



The Missouri University Research Reactor (MURR) during operation at 10 MW.

(notably strontium-82, germanium-68, and others) and industry (notably iridium-192, californium-252, and others). Less than 5% were for research sales, though the number of shipments of specialty isotopes greatly outweighs the number of bulk radioisotope shipments, and the kinds of radioisotopes supplied to researchers are much more diverse.

The market changes, of course, to reflect increasing demand for successful new radioisotope products and the decline or replacement of existing products. Only a few of the research isotopes will become successful new market entries, and their applications will grow and eventually shift into commercial use. Accordingly, pricing and supply policies need to reflect the market status of each isotope. The DOE policy is that commercial isotopes are sold on a full cost-recovery basis. Also, the DOE will only produce commercial isotopes when there is no U.S. private sector capability or when foreign sources do not have the capacity to meet U.S. needs reliably. These policies are appropriate. DOE is sometimes reluctant, however, to cease its production of isotopes that the market could reliably furnish. This is because DOE's production of commercial isotopes brings significant revenues to the production sites, which helps to maintain their infrastructure.

At the other end of the market spectrum, research isotopes must be managed carefully. The DOE policy is to provide research isotopes at prices that support a reasonable return to the government but not discourage their use. Also, the DOE attempts to provide all isotopes requested, subject to production capability, inventory, and financial restraints. Again, these policies are appropriate, but difficult to follow because they involve many subjective decisions and tradeoffs. Also, isotopes gradually shift their focus from research to commercial, and sometime even revert their status. A number of the Subcommittee's recommendations deal with more effective means to make equitable decisions with regard to which research isotopes to supply and to assist with evaluations of isotope status and production across the spectrum from research to commercial.

Federal Support for Isotope Production and Processing

Federal appropriations for the DOE's Isotope Program are $20.5 million in FY 2000. Of this, $10.5 million supports operations and production of isotopes. The remainder funds two major initiatives ($8 million for the Isotope Production Facility at Los Alamos National Laboratory and $2 million for the Advanced Nuclear Medicine Initiative). In recent years, sales of isotopes have averaged about $10 million per year, which can be accessed from a revolving fund account and are typically used to fund operations, thereby augmenting the federal appropriations. Thus, the total operations funding is about $20 million per year, which is divided among five DOE sites. At this level of support, the Subcommittee found that the sites have difficulty maintaining their infrastructure and giving support to the production of research isotopes. There needs to be robust support for isotope production because it is a vital contributor to U.S. economic competitiveness and well-being.

D. Allan Bromley, Ph.D., Sterling Professor of Sciences and Dean of Engineering at Yale University, former president of the American Association for the Advancement of Science and former presidential science advisor during the Bush Administration, cited a list of challenging research problems in an editorial in *Science* supporting legislation that would maintain U.S. industrial competitiveness. He went on to state:

> "In all these cases, the role of government should be to uncover ideas that have the possibility of overcoming the technological barriers. Then, as industry nears those barriers, it can pursue the most promising possibilities. It is a symbiotic relationship: industry is attentive to immediate market pressures; the federal government makes riskier investments that assure long-term competitiveness. Industry invests in the present; the government invests in the future."[2]

Many, including David Baltimore, Nobel Prize winner in physiology and medicine and president of Caltech, have pointed out that within the next 50 years a revolution in biotechnology could bring breathtaking advances in health, longevity, food supplies, and even energy supplies. Such developments will depend on robust federal support and an assured supply of radioisotopes.

Congress has acknowledged its responsibility to fund research and to provide policies that stimulate private-sector investment in research and development (cf., H.R. 578 and S. 2217). The House bill was based on principles outlined in the 1998 report, *Unlocking Our Future—Toward a New National Science Policy,*[3] authored by Rep. Vernon Ehlers (R-MI), Vice Chair of the House Science Committee. The Senate bill promoting federal investment in R&D was sponsored by Senators Bill Frist (R-TN), John Rockefeller (D-WV), Pete Domenici (R-NM) and Joseph Lieberman (D-CT), and passed unanimously.

Although there is no consensus about how U.S. science and technology policy should be promoted, the recommendations of the Ehlers' report are noteworthy. Among these are that Congress should give high priority to stable and substantial federal funding for fundamental scientific research, and that the Federal government should invest in fundamental research across a wide spectrum of disciplines in science, mathematics, and engineering. The Subcommittee believes that the DOE long-term goal to have a reliable isotope supply system

Aerial view of the 800 MeV, 1 mA proton linear accelerator at the Los Alamos Neutron Science Center (LANSCV).

U.S. and Russian scientists work together at the Los Alamos National Laboratory Hot Cell Facility on a campaign to make strontium-82 generators.

[2] D. A. Bromley, "Staying Competitive," *Science*, 285:833, August 1999.

[3] Report to Congress by the House Science Committee, www.house.gov/science/science_policy_report.htm, September 24, 1998.

in place that would enable scientists to bring their creative ideas into practical use safely, quickly and efficiently is appropriate, be it basic science research, clinical medicine, or industrial endeavors. The discovery and dissemination of new knowledge should continue to be a core mission, and basic science and the application of basic science to clinical research discoveries to improve the diagnosis and treatment outcomes should be a crucial component of that mission. The Office of Isotope Programs, in providing a federal system for the reliable supply of stable and radioactive isotopes for research, will be an important aspect of fulfilling the federal responsibility to support biomedical research. Substantial justification for all the recommendations is included in the Ehlers' report, which has been strongly endorsed.[4,5]

At the current level of appropriations for isotope production, this Subcommittee makes several recommendations in the spirit of making the best use of limited funds. At the same time, the Subcommittee also makes several strong recommendations that call for vigorous increases in support and changes in the long-term strategy that, if implemented, would strengthen the availability of isotopes well into the 21st century.

Stable Isotopes

The large scale electromagnetic separators (Calutrons) at the Isotope Enrichment Facility (IEF) of Oak Ridge National Laboratory. They are the only large-scale separator of stable isotopes outside of Russia.

The single supplier of stable isotopes for DOE is Oak Ridge National Laboratory. The production of stable isotopes has, during past years, been based on their extensive capability for electromagnetic separation with calutrons, a technology that is now over 50 years old. While this capability was put on standby several years ago and has only operated intermittently since then, the inventory of stable isotopes at Oak Ridge is fairly extensive. In recent years, a foreign supply of stable isotopes from stocks and ongoing operations in the former Soviet Union have emerged. A number of alternative technologies have been proposed within the national laboratories that potentially offer much lower operating costs with an acceptable level of throughput. The Subcommittee recommends that these alternatives be more fully assessed and plan for the support of an appropriate technology choice for resumed supply of stable isotopes in the future.

Problems with Radioisotope Supply

The difficulties experienced by researchers resulting from a lack of isotopes or high costs associated with isotopes in their research are significant and ongoing. Three examples are presented:

Iodine-124, a Long-Lived Isotope for Positron Emission Tomography

The increasing amount of clinically relevant information available from PET, in particular from fluorine-18 labeled fluorodeoxyglucose (FDG), has contributed to the

[4] E. Bloch and C. M. Vest, "Congress and U.S. Research," *Science*, 283:1639, 1999. Vest is President of MIT and also Vice Chairman of the Council on Competitiveness, where Bloch is a Distinguished Fellow.

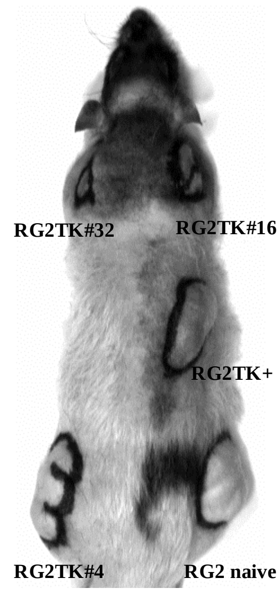
[5] F. D. Raines, "Making the Case for Federal Support of R&D," *Science*, 280:1671, 1998. Mr. Raines was Director of the Office of Management and Budget from September 1996 to May 1998.

expanding interest in additional positron emitting radionuclides for exploration of basic research studies and clinical applications. However, the half-life ($T_{1/2}$) of fluorine-18 is less than 2 hours and limits the period of observation whenever fluorine-18 is used. The spectrum of physiologic processes that could potentially be studied grows as the number of alternative positron-emitting radionuclides increases. In this context, longer-lived radionuclides, such as bromine-76 ($T_{1/2}$ = 16 hr) and iodine-124 ($T_{1/2}$ = 101 hr) provide the opportunity to image for longer times, which has advantages for studying "slow" physiological processes and provides additional time for clearance of nonspecific radioactivity. Iodine-124 was initially identified in a report resulting from a collaborative effort between Brookhaven National Laboratory and the Sloan-Kettering Cancer Institute in the 1950s.

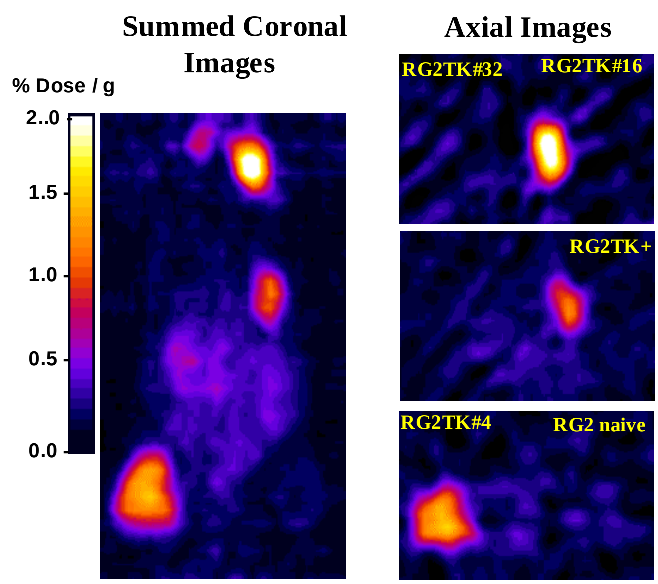
Many research scientists have the opinion that, concurrent with the technical improvements being made on the intrinsic resolution and reconstruction of images obtained with positron emission tomographs, there should be an increased availability of a variety of short-lived, radiolabeled substrates possessing the unique potential to serve as indicators of *in vivo* alteration of biochemical processes. In oncology, the application of PET holds promise through the extension of the metabolic image to pathologic process identification and enhanced nuclide-directed treatments. Many clinical investigators who prefer iodine-124 radiolabeled compounds for their clinical trials appreciated this fact. However, the lack of a reliable source of iodine-124 has hampered progress for nearly a decade.

A recent example of the potential use of iodine-124 is in gene therapy trials to enhance chemotherapy effects in patients with brain tumors. A major step in the management of patients undergoing gene therapy is the determination of the distribution, intensity, and duration of function of the transplanted gene, which usually requires a biopsy to obtain tissue for examination. Repeated biopsy sampling of vital organs or tissues, e.g., brain, heart, is not feasible. Dr. Ronald Blasberg and co-workers at the Memorial Sloan-Kettering Cancer Center have developed an elegant yet simple technique for assessing marker gene transfer and gene expression using noninvasive quantitative nuclear medicine imaging. The best radioactive label for the marker substrate is iodine-124, which has not been available to research groups interested in perfecting the procedure for human use.

Although other isotopes of iodine (such as fission-product iodine-131 and reactor-produced iodine-125) are readily available, the availability of iodine-124 is limited because it is difficult to make. While there have been several reports in the literature over the past decade that indicate iodine-124 can be prepared from low- to



Cancer Research 58: 4333 (1998)



Imaging of gene expression can be achieved by selection of a "marker gene" and "marker substrate" combination. An animal bearing five RG2 tumors is shown at the top: the tumors developed after S.C. injection of four clones derived from the HSV1-tk transduction (RG2TK#16, RG2TK#4, RG2TK#32, and RG2TK+) plus a RG2 wild-type cells (naive). PET imaging was performed 24 hr. after I.V. injection of [124-I]-labeled (FIAU), a substrate that is selectively phosphorylated and trapped in HSV1-tk transduced cells. Highly significant relationships were observed between the magnitude of [124-1]-FIAU accumulation (in-vivo) and the level of HSV1-tk gene expression as determined by two independent measurements. (from Blasberg, RG, et al., Memorial Sloan Kettering Cancer Center).

medium-energy proton cyclotrons using an enriched tellurium target, production of this radioisotope for investigators has not been undertaken. The problem with the supply of this isotope could be overcome by increasing the priority for its production by the Office of Isotope Programs.

Bismuth-212 and -213, Alpha-Emitting Isotopes for Cancer Therapy

Ovarian carcinoma has the highest mortality of any gynecologic cancer. The major reason for this dismal outcome is late detection and the fact that most patients have disease outside the pelvis at diagnosis. Peritoneal spread is an important feature in the natural history; failure to control disease within the peritoneal cavity is a major cause of treatment failure. None of the conventional therapies are of proven value. Radionuclide therapy with chromic phosphate has been used for years, but its effectiveness is still controversial. Similar to x-ray therapy, this form of therapy has been most successful against microscopic disease with 5-year survival rates of 80% being reported for stage I and II disease. However, neither form of radiation has proven effective against diseases that are resistant to chemotherapy.

A health physicist monitors the dose rate at the window of a dedicated glove box at MURR, while a research technician formulates the Sm-153-labeled EDTMP which will be used to treat a dog with bone cancer.

Since 1987, Dr. Jacob Rotmensch and associates at the University of Chicago and Argonne National Laboratory have been investigating alpha-emitting radionuclides, a class of isotopes having radioactive properties that make them attractive for therapy. Unlike conventional forms of radiation such as x-rays and phosphorus-32, these radionuclides have high-linear energy transfer, are densely ionizing, and their effect does not depend on the presence of cellular oxygen.

Early investigations focused on lead-212 ($T_{1/2}$ = 10.6 hr), which was obtained from thorium-228 and its daughter, bismuth-212 ($T_{1/2}$ = 1 hr). These investigators demonstrated *in vitro* that lead-212 was more effective than x-rays against human carcinoma cells grown in monolayers and then showed that alpha-emitting radionuclides have the ability to eradicate microscopic cancer in animals. The studies demonstrated that lead colloids cured animals inoculated with an ascites-producing tumor that simulated ovarian cancer and has real potential for treating microscopic diffuse peritoneal metastasis in patients with ovarian cancer.

Bismuth-212 was also evaluated. This radionuclide is attractive for development for therapy because it has a half-life of only one hour. All the experiments performed with lead-212 were repeated using bismuth-212. Although the Rotmensch group developed a method to produce clinically significant quantities of bismuth-212, further work was required to refine this method before clinical trials could be initiated. However, in 1997 the only supplier of bismuth-212 generators, a DOE facility at Argonne National Laboratory, stopped production.

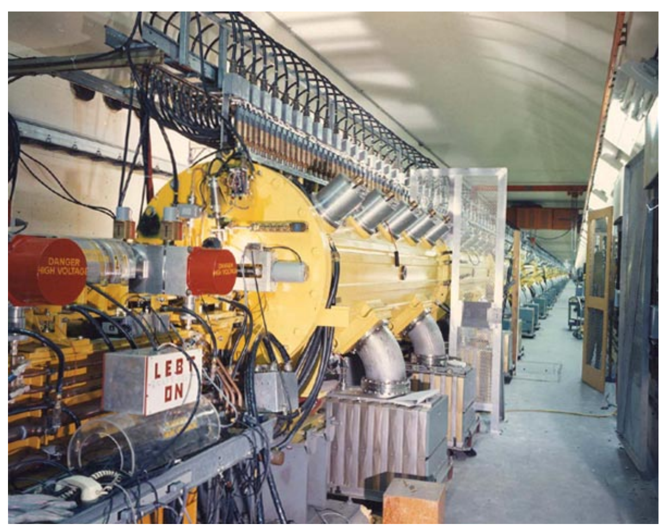
The attraction for using alpha-emitters prompted several groups to explore development of another alpha-emitting radionuclide, bismuth-213. The advantages of this radionuclide are that there is no gamma-ray emission during the decay process, and the half-life is 42 minutes; therefore, there is less radioactivity exposure to personnel.

Radiolabeled monoclonal antibodies are showing increased promise for oncology diagnosis as well as therapy applications. The ideal treatment plan includes a short-lived, radiolabeled monoclonal antibody imaged for clinical staging followed by radiation dosimetry and post-treatment with the monoclonal antibody complexed with a therapeutic radionuclide for management of unresectable, metastatic disease. The goal of radioimmunotherapy is, therefore, the delivery of a large radiation dose to the tumor over a finite time period, while limiting dose-rate effects and radiation damage to normal tissue such as bone marrow. Clinical experiences with several monoclonal antibodies have shown promising results in patients with lymphoma or leukemia, where there is rapid access to malignant cells. An increase in effectiveness of the particular radiolabeled monoclonal antibody could be achieved through the careful matching of the specific radionuclide with consideration for the biological half-life of the monoclonal antibody. Preclinical evaluations of alpha particle-emitting bismuth-213 labeled antibody constructs have demonstrated the specificity and potency of these agents in a variety of cancer systems. The transition of a bismuth-213 radiolabeled antibody from a preclinical construct to a clinical drug represented a difficult task, which involved developing reliable and validated methods to provide multiple activity quantities of a pure immunoreactive agent that met pharmaceutical standards to treat patients.

Although an FDA Phase I clinical trial involving target alpha particles has been initiated by Dr. David Steinberg at Memorial Sloan-Kettering Cancer Center with bismuth-213 chelated to the anti-CD33 monoclonal antibody HuM195 for therapy of myeloid leukemia, the progress and determination of the full potential of this exciting new therapeutic approach has been seriously slowed because of restricted quantities, and frequently a complete lack of availability, of the parent radionuclide, actinium-225.

The supply of bismuth-212 and -213 depends upon expensive handling and chemical separations of parent isotopes from existing stocks of transuranic elements.

Several of Oak Ridge National Laboratory's hot cells are used in the processing and packaging a wide variety of medical and industrial isotopes.



The 200 MeV proton linear accelerator at Brookhaven National Laboratory is used for high energy physics research and isotope production.

The recently refurbished Hot Cell Facility at Sandia National Laboratory has 12 cells which are connected together to accomodate processing of molybdenum-99. Sandia was given the mission to produce a backup supply of this commercial medical isotope in 1996, and began a major upgrade of its facilities. However, the program was halted in 1999 as other commercial supplies were brought online before its completion.

The problem with their supply could be overcome with funding for processing campaigns.

Copper-67, an Isotope for Radiolabeling Monoclonal Antiodies

Dr. Andrew Raubischek of the Radioimmunotherapy Group at the City of Hope National Medical Center has developed a series of antitumor monoclonal antibodies that appear to be most promising for the treatment of both solid tumors and hematopoietic malignancies. In addition, the group has developed novel chelating agents capable of binding copper to a number of antibodies. Drs. Sally and Gerald DeNardo at the University of California Davis have shown favorable clinical responses using the limited copper-67 that had been made available. While the characteristics of this isotope make it an ideal candidate for cancer therapy, the major impediment to clinical trials has been the lack of an adequate supply.

Copper-67 can be made by the accelerators at Los Alamos and Brookhaven, but these facilities only produce isotopes parasitically and are subject to short operating schedules. The problem with the supply of this isotope could be overcome in the short-term by increased funding to lengthen the operating schedules, and in the long-term by the provision of a dedicated cyclotron for copper-67 and other research isotopes.

Recommendations

The Subcommittee has reviewed the recommendations of the 1998 DOE Expert Panel[6] and endorses them.

The Subcommittee makes the following recommendations to address current and future needs for improvements in the supply of isotopes. The recommendations are presented as short-term, which cover the next five years, and long-term, which cover the next ten years. Each recommendation is discussed in turn below.

Discussion of Short-term Recommendations

1. Refocus the Office of Isotope Programs on the supply of radioisotopes and stable enriched isotopes for research within its mission to serve the national need for a reliable supply of isotope products and services for research, medicine, and industry.

The Subcommittee finds that there are insufficient resources and priority for research isotope production. The primary programmatic focus of Isotope Programs should be on the supply of radioisotopes and stable enriched isotopes for research to fulfill the program's mission "to serve the national need for a reliable supply of isotope products and services for medicine, industry, and research." Isotope Programs is in the process of transition from a strict reliance on the revolving fund and focus on revenue-producing isotopes, to yearly appropriations to support a research mission. In the foreseeable future, substantial budgetary limitations for Isotope Programs require that the program focus more on supporting the research community with a consistent, reliable supply of radioisotopes rather than commercial production. In addition, the existing supply of stable enriched isotopes needs to be maintained both for research tools in and of themselves as well as for targets for the production of research quantities of radioisotopes in reactors and accelerators. In the cases of both stable enriched isotopes and radioisotopes, examples have been documented of research suffering because of shortages or interruption in supply. These shortfalls have had a deleterious effect on the progress of nuclear medicine research in particular as well as other areas of science supported by isotopic tools.

2. Limit commercial isotope production to products where the DOE has a unique production capability and where other market supplies are not sufficient to meet U.S. demand.

Commercial isotope production at DOE facilities should be limited to areas where these facilities represent a unique capability and are needed to meet U.S. demand. For isotopes with sufficiently strong suppliers in the market, Isotope Programs should pursue the process of commercialization. To this end, Isotope Programs needs

Short-Term Recommendations (the next five years)

1. Refocus the Office of Isotope Programs on the supply of radioisotopes and stable enriched isotopes for research within its mission to serve the national need for a reliable supply of isotope products and services for research, medicine, and industry.
2. Limit commercial isotope production to products where the DOE has a unique production capability and where other market supplies are not sufficient to meet U.S. demand.
3. Establish an Isotope Review Panel to review and recommend proposals to produce isotopes to the Director of Isotope Programs. The Panel should identify isotopes of interest and preferred sites for production, including alternative supply options, and provide other advice as requested.
4. Consolidate existing radioisotope processing capabilities.
5. Contract with the academic and private sectors to accomplish the primary focus and mission.
6. Expand innovative research in diagnostic and therapeutic nuclear medicine by increasing funding for the Advanced Nuclear Medicine Initiative.
7. Increase the funding for academic training to support the primary focus and mission.
8. Begin conceptual design of a dedicated cyclotron to support the mission to serve the national need for a reliable supply of isotope products and services for research, medicine, and industry.

[6] "Expert Panel, Forecast of Future Demand for Medical Isotopes," http://www.ne.doe.gov/nerac/isotopedemand.pdf, March 1999.

to assess thoroughly the production activities and markets, including the impact on facilities, operations, staff, etc. Isotope Programs should propose realistic approaches to the posed risks to the commercialization entities, and actively match companies with the appropriate skills, staff, and business plans. For each commercialization project, a transition plan should be developed and acted upon to transfer smoothly the production or processing activities and accommodate the transition of the laboratory staff and capabilities into new research directions with appropriate and sufficient funding. Successful transition of the laboratory staff and facilities into new research areas with appropriate and sufficient resources would create valuable motivation and incentive for successful commercialization.

3. Establish an Isotope Review Panel to review and recommend proposals to produce isotopes to the Director of Isotope Programs. The Panel should identify isotopes of interest and preferred sites for production, including alternative supply options, and provide other advice as requested.

The Subcommittee anticipates that an increased emphasis on research isotopes will be difficult to achieve without a means to find a consensus of opinion in the user community on which isotopes are to be produced. The Subcommittee recommends that an Isotope Review Panel be created to make production decisions and act as a resource to review key aspects of Isotope Programs activities.

The Isotope Review Panel should be a standing committee of researchers from academia, government and industry. The Panel should meet as needed and make overall isotope production decisions based on current and anticipated research needs, estimated production capacity and costs, and the overall optimization of facility and resource usage. In addition, the Panel should make key recommendations on isotope commercialization, outsourcing, and collaborative efforts. The Panel should also serve as a resource to Isotope Programs for review of its progress, as well as peer review of research priorities.

4. Consolidate existing radioisotope processing capabilities.

The Subcommittee recommends that processing capabilities at the five existing radioisotope production sites (Brookhaven, Los Alamos, Oak Ridge, Pacific Northwest, and Sandia) be consolidated in order to reduce redundant capabilities and increase the effective use of resources. The site visits conducted by the Subcommittee indicate that there is an excess of processing capabilities, especially hot cells and processing equipment, relative to their system-wide use. In addition, the limited budget of Isotope Programs is insufficient to support continuous operation of the key production facilities. Rather than continuing isotope production as a small-scale operation, subject to the schedules, funding, and priorities of other programs, it is recommended that Isotope Programs work toward a more cost-effective and reliable supply based on as few as two reactor and two accelerator sites. It is recommended that a special panel of experts be convened to evaluate the needed steps to consolidation.

5. Contract with the academic and private sectors to accomplish the primary focus and mission.

As a part of consolidation, the use of production capabilities at universities or other private sector entities should be sought. The site visits to representative facilities determined that they offer cost-effective and flexible irradiation services for reactor- and accelerator-based products. The continuation and possible expansion of collaborative production with sites in other countries also could become an important factor.

The Subcommittee encourages Isotope Programs to avail itself of the cost-effective, established facilities within the private and academic sectors in order to accomplish its mission of providing a reliable supply of isotope products and services. The Subcommittee recognizes that the inclusion of the private sector and academia in its isotope supply system will result in a network of radioisotope providers that will better meet the demand for research isotopes. It must also be anticipated that the impact of outsourcing, technology transfer and commercialization can lead to a reduction of Isotope Programs revenue. A contingency plan within the DOE must be created to allow for reestablishment of credentials and efforts to offset the effect of each successful transfer to the private sector. Also, the contract process should ensure expedited response to DOE proposals and award of contracts.

6. Expand innovative research in diagnostic and therapeutic nuclear medicine as provided by the Advanced Nuclear Medicine Initiative.

The Subcommittee reviewed the Advanced Nuclear Medicine Initiative (ANMI), submitted as part of the FY 2000 budget proposal. The Subcommittee judges this initiative to be of the highest merit to the Isotope Programs and recommends expansion of the ANMI to allow more projects to be added each year. Further, it will be important to establish and maintain communication between the ANMI and programs within the National Institutes of Health and the Food and Drug Administration.

This initiative will employ a peer-reviewed selection process to identify high priority research grant proposals in nuclear medicine science and will seek to make radioisotopes available for research at prices that researchers can afford. The recommendations of the

Isotope Review Panel should play a major role in this process. Nuclear medicine science will include proposals to optimize radioisotope production and processing techniques. The Subcommittee recommends that this initiative focus the program funding on research to apply radioisotopes that would be useful for the treatment of both malignant and important nonmalignant human diseases.

The Advanced Nuclear Medicine Initiative should encourage the training and education of students in nuclear medicine science by supporting scholarships, fellowships, and sponsoring internships at the national laboratories and universities (*vide infra*).

7. Increase the funding for academic training to support the primary focus and mission.

It is increasingly evident that the cadre of personnel with expertise in isotope production and processing is shrinking rapidly, primarily due to retirement. In fact, some believe that the present generation of trained professionals in this field has not reproduced itself sufficiently to sustain isotope production processing at an appropriate level beyond the year 2020.

In a report prepared for the DOE in 1992 by Professor Gregory Choppin, Professor of Chemistry at Florida State University, titled “Status of Graduate Programs in Radiochemistry and Nuclear Chemistry,” Prof. Choppin concluded that radiochemistry and nuclear chemistry graduate programs had declined. Laboratory facilities had deteriorated, and faculty, students, and support for research were insufficient to support most programs. The number of viable radiochemistry programs in 1992 was probably eight. Furthermore, the number of doctoral degrees granted by all programs has averaged fewer than eight annually during the previous three years, with even fewer Master’s degrees during the same period. A *Chemical and Engineering News* report on March 13, 1995, tabulated that there were eight doctoral degrees granted in the previous year. The deteriorating trend reported in the 1989 National Academy of Science / Institute of Medicine report, “Training Requirements for Chemists in Nuclear Medicine, Nuclear Industry and Related Areas,” has been persistent.

The “Education and Training of Isotope Experts Report” (June 1998) for the Subcommittee on Energy and Environment of the House Committee on Science by members of the Senior Scientists and Engineers group of the American Association for the Advancement of Science concluded that too few isotope experts were being prepared to fulfill the functions of government, medicine, industry, technology, and science. If the situation is not reversed, the study predicted these functions would face a national crisis, including slowed progress in medicine and some technologies, an impact on national security, and probable losses in quality health. The Subcommittee observes that previous recommendations to support graduate and postgraduate training have not been addressed, and now a desperate situation exists in the disciplines of nuclear and radiochemistry, where scientists and faculty for isotope fields, including nuclear medicine, radiopharmaceuticals, and radiation safety are educated. Nuclear and radiochemistry are nearly disappearing from research and faculty positions in universities and colleges because experienced graduates are not available to replace those retiring. The major reason for this decline is believed to be the long inattention to alarms about disappearing federal support for these programs.

In view of this critical situation it is imperative that the Department of Energy increase funding for academic training to support the primary focus of Isotope Programs. Such training should be an integral part of the Advanced Nuclear Medicine Initiative (ANMI), the Nuclear Energy Research Initiative (NERI), and the Nuclear Engineering Education and Research Program (NEER). Moreover, all of the isotope production and processing facilities, both present and future, should be adequately funded to incorporate academic training as an important component of their responsibilities. Specific forms of support should include undergraduate scholarships, internships, graduate fellowships, research assistantships, and postdoctoral research assistantships. Efforts should be supported at all facilities to provide on-the-job training for technicians, engineers, and scientists as well as for cross-training to allow for development of expertise in more than one area. By spreading the responsibility for academic training throughout the grant awards structure and isotope production and processing facilities, the nation can be assured of a work force adequately trained and maintained.

8. Begin the conceptual design of a dedicated cyclotron to support the mission to serve the national need for a reliable supply of isotope products and services for research, medicine and industry.

The existing isotope production program relies on multiprogrammatic facilities where isotope production aspects are not the primary mission. Thus, the availability of radioisotopes for the research community is limited by the operating schedule of these facilities. This is especially true for the accelerator-produced radionuclides that rely on the accelerators at Brookhaven and Los Alamos National Laboratories. During 1999, these accelerators were used in a parasitic mode for less than 20 weeks per year. The incremental cost for dedicated radioisotope production at these accelerators, as they are currently configured, is prohibitive. The Subcommittee recommends the purchase of a high current multibeam cyclotron by 2005. The energy of the cyclotron should depend upon other existing accelerator capabilities for these radionuclides at greater than 40 MeV. The Isotope Review Panel should be charged with the task of choosing the specifications for the cyclotron. The siting of the cyclotron should undergo careful consideration with respect to long-term recommendations for combining radioisotope production capabilities at a single site. To meet the time schedule, a conceptual design for the cyclotron should be initiated during FY 2000.

Long-Term Recommendations (the next ten years)

1. Promote the greatest synergism among the national labs, academia, and industry to fulfill the Isotope Program's mission.
2. Acquire a dedicated, single-mision, isotope production and processing facility that would be fully operational by 2010. The facility should include a cyclotron and a reactor both dedicated to isotope production based on off-the-shelf designs.
3. Maintain a stable/enriched isotope inventory for research purposes.
4. Ensure an adequately sized and properly trained work force to meet national isotope needs.
5. Implement a contingency plan to guarantee an uninterrupted radioisotope and stable isotope supply for the country's research needs.

Discussion of Long-Term Recommendations

1. Promote the greatest synergism among the national labs, academia, and industry to fulfill the Isotope Program's mission.

Isotope Programs should adopt a strategy to conduct world-class research and development in support of its mission by promoting the greatest synergism among the national laboratories, academia, and industry. For example, the development of strontium-82 generators for PET imaging leveraged the research and development capabilities of Los Alamos National Laboratory, Baylor University, and Bristol-Myers Squibb Co. Relationships of this type create a network of collaborators in a virtual laboratory of capabilities. The benefits of such a strategy yield significant cumulative effects and a broader research program despite budgetary limitations and limited facilities.

2. Acquire a dedicated, single-mission, isotope production and processing facility that would be fully operational by 2010. The facility should include a cyclotron and a reactor both dedicated to isotope production based on off-the-shelf designs.

Plans for acquiring a dedicated radioisotope production reactor should be initiated so that both the cyclotron and reactor radioisotope production facilities will meet the radioisotope needs of the U.S. research community by 2010. As the most economical solution, the Subcommittee recommends siting the cyclotron and reactor at the same location.

3. Maintain a stable/enriched isotope inventory for research purposes.

Isotope Programs should maintain a stable/enriched isotope inventory for research purposes. The Subcommittee recognizes that commercial entities will pursue a supply of enriched stable isotopes for the production of their products. Several stable and enriched isotope products, e.g., oxygen-18, the target material for producing fluorine-18, for which there is increasing demand because of the increasing number of research and clinical coincidence gamma camera and PET studies being performed, are available primarily from non-U.S. sources. Oxygen-18 is also used in lower enrichment, but in greater quantity, in nutrition studies. In October 1999, a representative of the major Russian supplier of stable isotopes to the U.S. reported a significant number of requests for increasing quantities of oxygen-18 during the past year.[7] There are some researchers who believe that, in addition to oxygen, there will also be a shortage of stable isotopes used for nutritional and biomedical research, e.g., calcium, magnesium, and selenium. This demand will drive a continuing supply of those isotopes. The research community depends on those supplies that are in inventory at ORNL. The Subcommittee is aware of, but did not review in detail, the August 1999 report by A. Weitzberg, "The Future of Stable Isotope Production in the U.S.," prepared for DOE. We believe the technical quality and the various analyses are likely to be proven valid, but offer no position on the specific recommendations in the report. The Subcommittee recommends that Isotope Programs conduct an assessment of the low capacity enrichment capabilities within the national laboratories that can be used to replenish small quantities of those research isotopes that are exhausted. In parallel, the program should investigate alternative sources of those isotopes and use the production channel that will ensure long-term availability of those isotopes. Provided that adequate budgets are available for research, limited funds should be made available for research into enriched stable isotope production using technologies other than electromagnetic separation.

4. Ensure an adequately sized and properly trained work force to meet national needs.

To ensure an adequately sized and properly trained workforce to meet national needs, long-term academic training in isotope production and processing should permeate the entire gamut of funding programs, such as ANMI (Advanced Nuclear Medicine Initiative), NERI (Nuclear Energy Research Initiative), and NEER (Nuclear Engineering, Education and Research Program), as well as continue as an integral component of the mission of isotope production and processing facilities. In addition, the Department of Energy should make a concerted effort to revive radiochemistry and related programs at academic institutions. These programs have been allowed to contract almost into nonexistence. If this trend is not reversed, then no programs will exist to sustain our national needs in this important area.

5. Implement a contingency plan to guarantee an uninterrupted radioisotope and stable isotope supply for the country's research needs.

It is important that contingency planning be performed and implemented by Isotope Programs that act to guarantee isotope supplies in the long term. This must include consideration of facility retirement and/or redirection, potentially major changes in the agreements underlying parasitic production, successful consolidation of processing capabilities, and the timing and uncertainties of bringing new, dedicated facilities online.

[7] "Report on The Supply and Demand of Oxygen-18 Enriched Water," A report of the ad hoc committee of the North American Association for the Study of Obesity, Jan. 21, 1999.

Site Evaluations

Evaluation Procedure and Criteria

The Subcommittee selected four areas of critical concern for evaluation: (1) production of reactor radioisotopes, (2) production of accelerator radioisotopes, (3) current good manufacturing practice (cGMP) capabilities, and (4) education and training. To gather current information and status, seven sites were identified, and site visit teams were formed to gather information and report on each site. The seven sites included the five DOE national laboratories currently engaged in isotope production or research (Brookhaven, Oak Ridge, Los Alamos, Sandia, and Pacific Northwest), as well as two representative nonfederal producers of isotopes. The two nonfederal producers were the Missouri University Research Reactor, the largest university research reactor and most active producer of radioisotopes in academia, and International Isotopes Inc., an emerging entrant into high-energy accelerator operations in the United States and commercial partner for reactor isotope production and processing at the Idaho National Engineering and Environmental Laboratory.

To prepare for each visit, the questions listed in the Charge to the NERAC Subcommittee and additional site evaluation questions (see box) were sent to the manager of each production facility, and written responses were returned. These were reviewed during the visit. Each site team prepared a Site Visit Report, which was shared with the site visit manager. The manager reviewed the report for factual content and possible ambiguity and returned comments to the site-visit chair. The site-visit team then finalized their report. Five Site Visit Reports were subsequently reviewed, discussed, and approved at a first meeting of the full Subcommittee held on June 22–23, 1999. The remaining two reports were reviewed, discussed, and approved at a second meeting of the full Subcommittee held on September 28–29, 1999. During these meetings, the full Subcommittee established the short- and long-term recommendations.

The seven Site Visit Reports, with the written responses to the site evaluation questions, are included as appendices to this Final Report.

The Subcommittee felt a brief summary comparison of the sites would be useful. To accomplish this, criteria were developed within the four areas of critical concern. The criteria are listed in the following table, and the scoring of each production site was discussed by the full Subcommittee to produce the final ratings.

Overall Site Evaluation Criteria

Production of Reactor Radioisotopes	Production of Accelerator Radioisotopes
High thermal neutron flux for attaining high specific activity, and high energy neutron flux for producing (n, p) reactions	High proton energy
A broad flux profile with availability of high neutron energy regions and thermal flux traps	High beam Current
Reactor availability (Percent of time in operation): >98% (excellent), 97-90% (good), 89-80% (fair), <80% (poor), <50% (marginal)	Accelerator availability (percent of time in operation for isotope production): >90 (excellent, 90-80% (good), 80-70% (fair), 70-50% (poor), <50% (marginal)
Easy access to the reactor core, including during reactor operation with a shuttle system	

Processing Capabilities	Education and Training
Current good manufacturing practice (cGMP)	Ability to attract students and operating personnel
Availability and condition of the products	University affilations
Availability and condition of hot cells	Internships
Logistics and personnel	

Site Evaluation Questions

1. How well does the Department's existing five-site production infrastructure serve the current need for commercial and research isotopes?
2. What is the physical condition of the isotope processing facilities and equipment?
3. What capital investments are needed to assure the near term operability of the facilities?
4. If additional resources are needed, are they practical, e.g., technically rational, easily integrated into existing infrastructure, quickly implemented and supportable? Will any portion be sustainable over time by local financial and personnel resources?
5. What is the availability of the primary nuclear facility (accelerator or reactor) over the next five years, e.g., HFIR outage, LANSCE program changes?
6. What understanding exists at each site about the priority of isotope production to serve isotope customers?
7. How much influence does each site manager have in planning the use of multi-purpose facilities?
8. What cost-containment measures are being pursued?
9. What "licensing" issues need to be addressed?
10. What unused or underused capacity, e.g., personnel, facilities, could be mobilized to support growth in isotope demand?
11. Summarize customer inquiries received during the past two years. What percent was filled, referred to other facilities, rejected? Explain unfilled requests.
12. How does each site manager rate customer satisfaction for his site? For the overall program?
13. Kindly detail how you set the price of a mCi of a radioisotope? the detail should show if the cost is fully loaded or incremental, and should include labor, materials and parts, facility rental and amortization costs, listing of all the actual overhead charges, waste disposal (a major cost), and all other costs that are tagged to the cost of producing, marketing, selling, and distributing of the product (e.g., customer service, distribution, ordering).
14. Illustrate the above question for the following radioisotopes: In-111, P-32, I-123, I-125, and several research radioisotopes.
15. What process, mechanism, and organizational structure do you have for the timely distribution of the produced product?
16. What processes, mechanism, organizational structure do you have for customer service?
17. Will you sign contracts that guarantee delivery at the contracted time of delivery and where the contract has penalty clauses for non-timely delivery of the specified product?
18. What should be the long-term role of Government in providing commercial and research isotopes?

Site Assessment Results

A summary of site profile assessments is presented in two tables. The tables overview and compare each site's capabilities. These tables are based on the Subcommittee's site evaluation experiences. Note that the scoring of the factors for sites is based solely on how well the existing in-house capabilities fulfill the mission focus recommended by the Subcommittee, i.e., the supply of research radioisotopes.

The scoring scale is based on a five-point system with five being considered excellent and one being marginal. An excellent rating for a given category means that the site must be able to supply research radioisotopes with superior capabilities related to that category. In the case where no capability exists, it is noted in the table as No Existing Capability (NEC).

The Subcommittee cannot overemphasize that the scoring of the sites focuses on the current and future supply of radioisotopes for research. These assessments do not reflect the enormous contribution that each national laboratory has made in the past and will make in the future to the development of the sciences in the United States.

Each table represents the Subcommittee's assessment relative to the evaluation criteria for the indicated time period. The first table is based on the Subcommittee's assessment of the current data collected by the site visit teams. The second table is the Subcommittee's estimate of the capability of the sites based on their stated budget projections and stated projects in planning for the next five to ten years. Due to the uncertainty in the stated plans of each facility, the second table should be interpreted with caution.

Assessment of Isotope Capabilities in 1999

	Reactor Isotopes	Accelerator Isotopes	cGMP[a] Capabilities	Education & Training
Missouri University Research Reactor	5	NEC	3	5
Los Alamos National Laboratory	NEC	2	5	4
Oak Ridge National Laboratory	4	NEC	3	3
International Isotopes Inc.	3	1	5	NEC
Sandia National Laboratory	2	NEC	3	1
Brookhaven National Laboratory	NEC	1	4	1
Pacific Northwest National Laboratory	NEC	NEC	2	3

Rating Scale: 5 = excellent 4 = good 3 = fair 2 = poor 1 = marginal NEC = no existing capability

Assessment of Isotope Capabilities Estimated in 2005-2008[b]

	Reactor Isotopes	Accelerator Isotopes	cGMP[a] Capabilities	Education & Training
Missouri University Research Reactor	5	NEC	5	5
International Isotopes Inc.	3	4	5	4
Los Alamos National Laboratory	NEC	4	5	4
Oak Ridge National Laboratory	4	NEC	3	3
Sandia National Laboratory	2	NEC	4	3
Brookhaven National Laboratory	NEC	1	4	2
Pacific Northwest National Laboratory	[c]	NEC	[c]	3

a. Current good manufacturing practice.

b. Based on projected budgets and projects currently in planning and development indicated by the sites.

c. The Subcommittee did not rate this category because the Subcommittee does not consider the FFTF to be a viable long-term source of research radioisotopes.

Observations

The Subcommittee makes several observations: first, research isotope supplies outside the national laboratory system offer significant, complementary production capability. Second, DOE sites, as an aggregate, have more than adequate processing capability today. And third, no overall strategy exists regarding the designation of preferred reactor and accelerator sites. This leads to the conclusion that the production capability suffers from funds being shared by too many sites. It is the Subcommittee's opinion that the short-term supply of radioisotopes for research would be adequately served by as few as two reactor and two accelerator production sites.

Comments on the Fast Flux Test Facility For Isotope Production

The FFTF is a research reactor located at Hanford that is proposed for operation at 100 MW. The original mission of the FFTF was to support the U.S. liquid metal reactor technology development program. Although this program ended at about the same time that FFTF commenced in 1982, the reactor continued operation for 10 years as a DOE national facility for production of medical research isotopes, the testing of advanced nuclear fuels and materials, and the development of active and passive reactor safety technologies. The reactor was shut down in December, 1993, but in August, 1999, the Secretary of Energy approved the preparation of a Programmatic Environmental Impact Statement (PEIS) for expanded civilian nuclear R&D and isotope production missions that included the role of the FFTF. A PEIS is now being prepared that includes environmental impact data for future FFTF missions. These missions include isotope production, reactor safety testing, production of plutonium-238 as a power source for deep space exploration missions, testing of reactor fuels and instrumentation, and irradiation services related to materials testing and transmutation of nuclear wastes.

As stated, the role of Isotope Programs in the short and long term should be to maintain a reliable system that produces isotopes for the research community. In limited instances, the DOE possesses unique resources, e.g., the high flux of fast neutrons and large irradiation volume in FFTF, that could be utilized for the production of some research isotopes, but is best suited for commercial interests who might consider its use for isotope production.

A few of the radioisotopes identified in the FFTF documents provided to the Subcommittee fall into this category, notably tungsten-188, the parent of rhenium-188. The team at FFTF and PNNL should be encouraged to pursue commercial production opportunities where they exist. It was apparent to the site visit team that the scope of operations at PNNL will require large amounts of funding, both capital expenditures and operational funds. This funding requirement necessarily requires the isotope production activity to focus on isotopes with large demand and mature markets.

The Subcommittee concludes that the FFTF will not be a viable source of research radioisotopes. Anticipated income from sales likely will not meet expectations thereby curtailing operations and reducing the FFTF's capability to produce research radioisotopes in a timely and cost-efficient manner. In light of these factors, the Subcommittee recommends that the FFTF not be considered as a viable long-term source or research radioisotopes.

The Subcommittee believes that the production needs of neutron-rich isotopes for research purposes can be met by existing reactors. In particular, the operations at the Missouri University research reactor and the High Fluz Isotope reactor are better suited to meeting the demands of users who need small quantities of research isotopes at irregular intervals. Other neutron sources may also be available for research isotope production.

The Subcommittee has reviewed the FFTF business plan and will submit their observations and suggestions for issues to be addressed in the EIS review in a separate document.

NERAC Subcommittee for Isotope Research and Production Planning

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Appendices

Appendix A: Missouri University Research Reactor
Appendix B: International Isotopes, Inc.
Appendix C: Brookhaven National Laboratory
Appendix D: Oak Ridge National Laboratory
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Missouri University Research Reactor (MURR) Site Visit

Site Visited April 28, 1999

1. Introduction

On April 28, 1999 a site visit team including Robert Atcher (LANL), Ralph Bennett (INEEL), and Henry Kramer (consultant) reviewed the operations at MURR. The site visit team heard presentation from Edward Deutsch, MURR director, and had discussions with several other members of the reactor management. They also met with Jack Burns, Vice Provost for Research, at the Columbia campus.

Mission

The mission of the MURR changed when Ed Deutsch became director 18 months ago. Dr. Deutsch has refocused the mission of the MURR on isotope production activities. Prior to his arrival, the primary focus of the reactor was on scattering experiments. The reactor is also used for materials testing, neutron activation analysis, and other research activities.

Facilities

The Missouri University Research Reactor (MURR) provides opportunities for research and graduate education in the neutron-related sciences that are unmatched at any other U.S. university. The central focus of this research center is a 10 megawatt light water moderated reactor that is the highest power university research reactor in this country. The reactor provides extensive capabilities for both neutron beam research as well as irradiation facilities for producing a variety of isotopes and performing activation analysis.

The reactor has been in operation for 29 years (commencing October 13, 1966), and since 1976 has had a 150+ hour per week operating schedule maintained more than 90% of real time. At the end of fiscal year 1995, MURR had a full-time staff of 115 including 25 Ph.D. scientists engaged in research programs. The reactor is a University Research Center, not part of any MU department, and reports to the Vice-Provost for Research.

The operation of the reactor is under the direction of the Reactor Operations Manager and operations group who also handle in-pool and flux-trap sample irradiation procedures. This group has close association with the Facility Operations Manager and group responsible for improvements and maintenance of the reactor and associated instrumentation facilities. This includes a mechanical engineering and design group and complete mechanical and electronics shops.

Development engineering of new electronic instrumentation is provided by the Instrument Development group. Computer software and hardware support, including the facility-wide computer network and instrument control computers, is under the direction of the Computer Applications group. Health physics surveillance and support for the diverse irradiation and laboratory facilities at MURR are provided by a Health Physics Manager and group. Responsibility for all of the operations and support groups is under the leadership of the Associate Director of the Center.

Before any experiment is done or performed at MURR, a Reactor Utilization Request must be filled out and approved. The principle experimenter or assistant fills out a form where they describe the experiment. The experiment is evaluated for radiation safety and reactor safety. The evaluation is reviewed by the reactor manager, health physics manager and the safety subcommittee.

Beamports

There are six beamports, three 4 inch and three 6 inch ports. Beamports “A”, “D” and “F” are 4-inch ports. Beamports “B”, “C” and “E” are 6-inch ports.

Beamports “A” and “F” are located 2 inches below core centerline and have the highest flux. “F” port can penetrate the beryllium but does not. “B” and “E” ports are 7 inches below core centerline. “C” and “D” ports are 14 inches below core centerline and are tangential to the core. This gives the ports good thermal neutrons with less fast neutrons and gammas. “A” port currently has prompt gamma facility. “B” port has SANS and interferometry. “C” port has neutron effect study equipment. “D” port PSD and other material studies. “E” port double and triple axis for material studies. “F” port is neutron beam filter studies.

The pneumatic tube system is used to irradiate samples rapidly and in small quantity. The system has two 1-1/2 concentric pipes which terminate in the graphite reflector. The tubes are operated out of four labs. Two labs assigned to each tube. The p-tubes are used for trace element studies in nutrition, geology, archaeology, chemistry, medicine and veterinary medicine. The tubes are used to make target material to run in the reactor or shipped to another user on or off campus.

The graphite reflector contains 16 irradiating positions which vary from a nominal size of 1 inch to 6 inches. These positions are used to irradiate an assortment of items like silicon, topaz, gold, sulphur, iridium, teeth, sodium, etc.

The center test hole contains the three tube flux traps and is MURR’s highest flux irradiating position and the most valuable real estate in the reactor. The test hole is a 4-inch aluminum tube which goes through the center of the core and is the inner pressure vessel. The restrictions on what can be run are the most strict. The sample placement is critical due to the reactivity effects each sample has which changes with height. These values are measured before full-scale runs are performed. The samples are restricted by weight, size, how it is encapsulated, what effect it has on system components and effect on other samples.

Neutron Fluxes

- Center test hole has an average flux of thermal neutrons of $6.2 \times 10E^{14}$ nv.
- Beam tubes range from $1 \times 10E^{6}$ nv to approximately $5 \times 10E^{8}$ nv.
- Irradiation positions have flux profiles from top to bottom with peaks that range from $8 \times 10E^{13}$ to $1 \times 10E^{10}$ nv.
- Pneumatic tubes have flux rates at $5 \times 10E^{13}$ nv in row one to $1 \times 10E^{11}$ nv in row two.

Products and Services

The Radiation Services Group provides the interface between experimenters and the reactor, and is made up of the Irradiations / Isotope Production, Silicon, Shipping and Gemstones Sections and support staff. The group reviews experiments to ensure that all safety requirements are met, prepares samples for irradiation, processes irradiated materials, and packages and ships materials after irradiation. The group handles the processing of production isotopes, silicon and gemstones that generates the bulk of the Center's revenue for research work. During FY94, Radiation Services performed work for approximately 57 industrial customers, 38 universities and eight government agencies.

Two main regions of the reactor used by this group are the reflector and the flux trap. The flux trap, providing the area of highest flux, is loaded and unloaded once a week during reactor shutdown. Samples can be loaded into the reflector region at any time during the week. Sample size is limited by the diameter of the reflector tubes that hold the samples in the reactor pool. The largest tube can hold a five-inch diameter sample.

MURR ships about 2000 shipments per year. These shipments are divided among commercial customers and research investigators. The material shipped includes some isotopes that undergo processing as well as those that irradiated as a service.

2. Relationship to DOE Programs

DOE Office of Isotope Programs (IP)

At present, there is no formal arrangement with IP. The staff at MURR has submitted a proposal to IP to conduct isotope production activities with funding from IP. This proposal is currently under review.

Other DOE Programs

The MURR is fueled by highly enriched uranium. The reactor is dependent upon DOE to provide the HEU for this fuel. This amounts to $900K per year in support. In light of the fact that HFBR at BNL is in standown, MURR approached DOE about the possibility of moving some of the scattering work done at HFBR to MURR. Their proposal was not accepted. MURR, through its partnership with the Nuclear Engineering program, also has interactions through training programs.

3. Relationship to Academic Programs and Training

Overall, the Missouri University conducts over $380M of sponsored research per year, and is ranked in the top 20 institutions nationwide in terms of research expenditures. The Columbia campus has 13 colleges and professional schools, and features colleges of medicine, veterinary science, engineering, arts and sciences, and agriculture on its campus. A continuing strength in the biomedical and life sciences is seen as the major impetus behind continued operations of MURR. While the University offers a nuclear engineering option with M.S. and Ph.D. students enrolled, there is not a formal Department of Nuclear Engineering. The number of students electing the nuclear engineering option is not expected to grow in the near term.

Radiopharmaceutical Sciences Institute

An interdisciplinary radiopharmaceutical science program has existed on the Columbia campus for over 20 years, involving clinical departments in the School of Medicine, the Departments of Chemistry and Biology, the College of Veterinary Medicine, the Harry S. Truman Memorial Veterans Hospital, and MURR. To build this program, Missouri formally established the Radiopharmaceutical Sciences Institute (RSI) in 1999. This recognition formalized the interdisciplinary program, and underscored its importance with a major financial investment to expand and enhance the RSI with five new tenure track positions to begin in FY 1999 and 2000. There are currently 12 RSI faculty, who in total conduct an average of $1.4M per year of externally sponsored research.

The RSI is an integral part of education and training program in the biomedical and life sciences. RSI faculty hold appointments in Ph.D. granting departments. An average of seven Ph.D. candidates has been supported each year on RSI-generated funds over the last decade. The students meet the Ph.D. requirements in their respective home departments, and participate in RSI seminars, research presentations, discussion groups, etc. They also interact through laboratory rotations within MURR and through the conduct of specific experiments relevant to their research. The RSI faculty is actively involved in training postdoctoral research fellows, averaging five fellows in recent years. Over five undergraduate students are mentored each summer in the RSI as a part of the Research Undergraduate Experience program.

4. Current Isotope Production

Throughput

MURR makes about 2000 shipments per year. These include commercial customers and research investigators. The potential to add Good Manufacturing Practice capability would expand the product line available as MURR could ship radiopharmaceutical grade material. This involves an added cost to the end user, however.

Customers

The customer base includes commercial vendors who sell a product that includes the radioisotope produced at MURR, research investigators who use the product in clinical trials, and research investigators who are conducting preclinical and basic research.

Pricing Policies

Dr. Deutsch emphasized to us that pricing has to be done to recover the costs of operation for the facility. This policy has forced them to narrow the number of isotopes that can be produced on a routine basis. One casualty of this new policy is production of Cu-64. Pricing for larger volume isotopes is done on an individual basis. A price list is expected to be available in June 1999.

Product Development

Product development has been excellent. The staff at the reactor, in collaboration with faculty at MU, has aggressively pursued external funding to develop radionuclides and radiopharmaceuticals. With the support of the RSI, this is expected to continue.

5. Future Capabilities and Resource Requirements

Continued Operation

MURR was originally licensed by the Nuclear Regulatory Commission (NRC) in 1966. Continued operation of MURR beyond 2001 is contingent upon successful re-licensing by the NRC. Costs associated with re-licensing are estimated to be $8.1M, which includes $1.2M for safety analysis and license submittal and the balance, $6.9M, for a variety of upgrades and replacements. The specifications for upgrades and replacements have adopted a long-term view, and their successful implementation will result in a research reactor that can operate for many years into the future.

While there was some experience with nuclear intervenors over a TRU electrochemical separation process at the facility in the early 1990s, the expectation is that the reactor re-licensing will proceed smoothly.

Expanded Operations or Services–Underway

Modification of the center flux trap in the reactor is tentatively scheduled to take place in 1999, although funding is not certain. The redesigned high flux region will be partitioned into smaller regions, several of which will allow insertion and removal of 0.38" diameter irradiation targets during full power operations, rather than during the weekly fuel changeout. This will add a significant capability to MURR for production of high specific activity short-lived radioisotopes. The modification requires NRC approval for a revision to MURR’s Technical Specifications.

Funding is being obtained to build a second high activity general use hot cell. The estimated cost is $200K. Currently, only one high level hot cell exists. There are obvious concerns about operations if this hot cell is not functional for some reason.

As a supplier of high quality radioisotope products, MURR is working toward achieving Good Manufacturing Practices (GMP) status for selected radiopharmaceuticals. This is typically accomplished on a case-by-case basis with the assistance of a pharmaceutical partner. One recent example of this was ^{153}Sm EDTMP.

Expanded Operations or Services–Proposed

To meet expected demand for research radioisotope production, as many as five additional hot cells are proposed for addition over the next three years. The estimated cost is $250K per hot cell.

The availability of space for facilities is a continuing problem for MURR. The MURR facility is fully utilized, and the facility layout does not easily lend itself to expansion. While land is available nearby for additional construction, it cannot be developed until levees are completed to alter the flood plain it occupies. The vision for facility expansion is to construct a $6M building, possibly as a business incubator, to seed the development of products and services based upon the reactor.

A number of studies of power upgrades to the reactor have been performed over the years. These have established the feasibility of upgrading core power to 20 (or even 25) MW, from the current 10 MW level. The studies project a cost ranging from $15–25M to accomplish the upgrade. Funds have not been identified for this purpose.

6. General Issues Related to Isotope Supply

Institutional Support

The operational budget for MURR is approximately $8M per year. This is comprised of roughly $2M from the State of Missouri, $2M from grants and research contracts, and $4M generated from operations. None of these are considered base funding. With MURR's central position in the future of the University's biomedical and life sciences programs, support from the University administration is quite strong. However, the annual operating funds require a considerable effort to maintain or grow because they are derived from different sources, and because none are considered a base commitment of funds.

While it has elected not to submit proposals in recent years, MURR may be able to successfully compete for National Center for Research Resources or Program Project Grants from the National Institutes of Health. These are typically on the order of $1M per year in direct support.

Marketing

MURR makes about 2000 shipments of radioisotopes per year. About 90% are for biomedical / medical / life science applications, and the remaining 10% are for commercial applications. Overall, about 60 different isotopes are available. MURR's customer contracting is quite flexible, ranging from simple purchase orders to long-term supply or partnering agreements. Pricing is set individually for each routinely delivered product or service. MURR's approach to pricing is to consider all costs associated with filling the order.

MURR is aggressively pursuing radioisotopes sales and applications services. This includes marketing at national meetings of prospective customers utilizing an exhibition booth. A campaign has recently begun to increase several of its neutron activation analysis services, a few of which have a fairly strong forecast growth.

Business Practices

In recent years, MURR has been as much as $2M in debt, largely due to spending on R&D at the facility exceeding revenues. The prospects are good that this can be corrected, however, as MURR exits the topaz irradiation business and sells off existing stocks. At this point cash flow is positive. The facility runs on a modified cash flow basis, which allows it some flexibility for the pricing of isotopes. Also, it was noted that MURR has some flexibility in using operating funds for capital equipment purchases.

An important issue for sources of funding for MURR is the University policy on overhead charges for research grants. This currently is set at 46%, which considerably reduces the amount available for operations. An alternative to funding radioisotope production at MURR would be to place a blanket purchase order with MURR for radioisotopes, which would avoid the general overhead charges. Dr. Deutsch noted, however, that this mechanism would require a "pay or take" provision so that he could hire the staff necessary to supply those isotopes.

Waste Management

Waste is handled according to provisions outlined by the State. The cost of radioactive waste handling has escalated which has had an impact on production decisions. These include ceasing Cu-64 production in part because a waste stream of Zn-65 was created. Long-lived radioactive waste is shipped to sites outside of Missouri.

Missouri University Research Reactor (MURR)

Questions and Answers

1. **How well does the Department's existing five-site production infrastructure serve the current need for commercial and research isotopes?**

   In our experience as a back up for MURR it did not serve our needs very well

2. **What is the physical condition of the isotope processing facilities and equipment?**

   The physical condition of facilities and equipment for isotope processing at MURR is adequate for the current level of demand. For any expansion of our current capabilities we'd need capital investment in several dedicated hot cells.

   <u>10 MW Light Water Moderated Reactor:</u> The reactor uses highly enriched uranium, is light water moderated and cooled, and is beryllium reflected. The reactor is pressurized and is centered 25 feet down in a water-filled pool. Eight fuel elements in the fuel zone form the core. Each fuel element is assembled from 24 fuel plates; each plate is a sandwich of uranium aluminide fuel with aluminum cladding, held in place by side plates and end boxes. The core has 6.2 kg of ^{235}U fuel. The active core is 29.77 cm in diameter and 60.96 cm tall, with an active core volume of 33 liters. At the center of the core of the reactor is a neutron flux trap with an unperturbed peak flux of 6 x 10^{14} n/cm^2sec.

   The reactor has a compact core loaded with 93 percent enriched ^{235}U aluminide fuel. The reactor design is derived from the High Flux Isotope Reactor (HFIR) design, but is simplified for lower power operation and ease of maintenance. The fuel is contained in the pressure vessel, through which the cooling and moderating water flows. All moving parts, such as control and regulating blades, are external and visible in the open light water pool. Over the last 20 years, there have been only a few unscheduled shutdowns typically lasting less than one day. The extended history of reliable operation of MURR is a major asset to its users, both scientific and technical.

   <u>Radioisotope Processing Facilities:</u> Four research/processing laboratories (~350 ft^2 each) are dedicated to processing research radioisotopes radioisotopes and radiopharmaceuticals. All of the labs have hoods connected to MURR's ventilation system, which is monitored for radioactive releases. There are six lead shielded gloveboxes for processing up to Curie quantities of some radioisotopes. These can currently be used to process Re-186, Rh-105, Lu-177, Re-188, W-188 and others.

   A small processing hot cell with two manipulators and remotely operated syringe pumps is available for processing holmium target, enabling production of multi-Curies of Ho-166 solution per week. This can be divided and shipped to multiple users. Another lead-lined processing unit with a single manipulator and remotely operated syringe pumps is used for the production of Sm-153 solutions on a weekly basis, enabling the production and supply of up to 40 Curies of Sm-153 solution per week.

   <u>Irradiation Facilities:</u> MURR currently utilizes the flux trap, the graphite reflector region, and the bulk pool facility to irradiate a wide variety of targets to produce radioisotopes and activated samples for testing and analysis. A schematic of the irradiation facilities is included below (Figure 1). The flux trap has a 4.5" annulus and provides a peak flux of 4.5 x 10^{14}n/cm^2/s. With a 30" vertical length, the flux trap has a maximum usable volume of 477 cubic inches. The current flux trap configuration consists of three 1.5" outer diameter (OD) tubes with a total usable volume of 110 cubic inches of 1.13" OD samples.

   Though lower in flux, the graphite reflector region provides a much larger volume for irradiations and also has the advantage of access to targets when the reactor is at full power. The irradiation positions are approximately 30" tall and have diameters and peak fluxes as follows: 1ea @ 1.350" OD (8.0 x 1013 n/cm2/s); 2 ea @ 1.125" OD (5.0 x 10^{13} n/cm^2/s); 5 ea @ 2.350" OD (6.0 x 10^{13} n/cm^2/s); 5 ea @ 3.350" OD (2.5 x 10^{13} n/cm^2/s); 2 ea @ 6.0" OD (1.0 x 10^{12} n/cm^2/s); and 2 ea pneumatically controlled 1.0" OD (5.0 x 10^{13} n/cm^2/s with 4" usable length. The bulk pool facilities allow for larger or especially shielded irradiation positions. Currently there are two 4"-, one 5"- and one 6"-diameter positions 30" in length, and a 1.125"-diameter sample, 10"-long lead shielded position. The peak flux for the bulk pool facility is approximately 6 x 10^{12} n/cm^2/s.

3. **What capital investments are needed to assure the near term operability of the facilities?**

   Relicensing costs and a backup hot cell are required for near term, as well as long term, reliability. Additional hot cells, dedicated to processing radioisotopes for medical applications, are required to increase or radioisotope processing and supply capabilities to meet future demands for clinical grade radioisotopes.

Relicensing of MURR: The State of Missouri and the University of Missouri are making plans now for the relicensing of MURR with the NRC in 2001. Expenses associated with this relicensing are estimated at $8.1 million and serve to illustrate the commitments of the State and the University to MURR.

Backup Hot Cell: Steps to obtain / build a second high activity general use hot cell are currently underway. The estimated cost for such a hot cell is ~$200,000.

Dedicated Processing Hot Cells: To meet the expected increase in demand for research radioisotopes additional hot cells which will allow us to produce clinical grade radioisotopes for medical application are required. We anticipate adding 5 such hot cells over the next 3 years. The estimated cost for each hot cell, including manipulators, is ~$250,000 for a total cost of ~$1,250,000 for five such hot cells.

4. **If additional resources are needed, are they practical, e.g., technically rational, easily integrated into existing infrastructure, quickly implemented and supportable? Will any portion be sustainable over time by local financial and personnel resources?**

The relicensing philosophy will be to request the funds necessary to allow us to provide the reliability to operate ~90% of all available hours for the next 20 years. We will have done a condition assessment of all operating equipment and proposed the replacement and timing of replacement so we can continue our historic availability record. This will involve both capital investment and ongoing operating costs be considered for twenty years of reliable operation.

All additional hot cells and major equipment will be integrated into our maintenance and replacement program to ensure MURR's long term capability and reliability as a supplier of radioisotopes.

5. **What is the availability of the primary nuclear facility (accelerator or reactor) over the next five years, e.g., HFIR outage, LANSCE program changes?**

Projected to be 90% of all hours available as we have achieved since 1977.

History: MURR was commissioned in 1966, beginning its operations at 5 MW. In 1970 the operation schedule was expanded to 100 hours per week, and in 1974 the power was increased to 10 MW, the highest power research reactor on any university campus in the US. In 1977 the operating schedule was increased to more than 150 hours per week. Since then, the reactor has operated more than 90 percent of all the available hours in the year. Its on-line availability is a remarkable level of reliability which is unmatched by any research reactor in the US. The only deviations from that record have been associated with one-week shutdowns required once every eight years for the replacement of the beryllium reflector and one 3-day shutdown for change-out of the pool heat exchangers. The beryllium reflector was last replaced in September 1997, and replacement will not be necessary again until 2005. MURR's reliability is a critical factor in meeting the national needs for short-lived isotopes.

Current Reliability: MURR already serves as a reliable national resource for reactor-produced radioisotopes and the primary source of many research radionuclides used in the US. MURR supplies isotope irradiation and related services to over 300 clients in 45 industries, seven state and federal laboratories, and over 31 universities. In fact, the reactor was designed from the beginning to permit scientists easy access to neutrons for a variety of research applications, including activation analysis, neutron scattering and radioisotope production.

6. **What understanding exists at each site about the priority of isotope production to serve isotope customers?**

We've been serving our radioisotope customers for many years and are now focusing even more attention and more resources to do more and do it better. Recently MURR has shifted its primary service mission to providing medical and research radioisotopes. This focus has become the highest priority behind the safety and maintenance of the reactor.

7. **How much influence does each site manager have in planning the use of multi-purpose facilities?**

The Director has total responsibility and authority for planning the use of MURR facilities. He has the support of the MU Administration to focus MURR efforts into radioisotope and radiopharmaceutical development, because these areas provide significant and unique opportunities for several MU departments, including the Medical School, Veterinary School and Agriculture.

8. What cost-containment measures are being pursued?

Cost containment and cost consciousness have long been ingrained in MURR's operating philosophy out of necessity. We have never been fully base funded, but have had to depend on our inventiveness and resourcefulness in R&D and service to industry to generate a significant part of our annual budget.

Management is keenly aware of the importance of carefully monitoring and controlling costs. MURR's minimal base funding forces management's constant attention on stretching limited resources to maintain reactor reliability and thereby serve our customers which include patients undergoing radiodiagnostic and radiotherapeutic procedures.

9. What "licensing" issues need to be addressed?

MURR Relicensing

MURR was built in the mid-1960s and licensed for operation by the U.S. Nuclear Regulatory Commission (NRC) in 1966. MURR's current NRC license expires in 2001. Efforts are underway to upgrade the facility infrastructure in preparation for the new license application. The relicensing effort will cost $8.1 million and consist primarily of relicensing application costs (e.g., safety analysis report and license submittal) and reactor and facility upgrades. Examples of reactor and facility upgrades include: 1) assessing the condition of the reactor's systems, 2) evaluating the integrity of the pool liner, 3) replacing reactor instrumentation and control components and wiring, 4) evaluating and replacing health physics instrumentation, 5) improving fire protection and detection systems, 6) replacing pool water storage tanks, 7) reconditioning radioactive sumps and drains, 8) replacing the beryllium reflector, 9) updating the pneumatic tube sample irradiation system, and 10) updating security and surveillance systems

10. What unused or underused capacity, e.g., personnel, facilities, could be mobilized to support a growth in isotope demand?

One fully utilized facility that can be modified (expanded) to provide growth in isotope demand is the flux trap. Engineering and design are underway to allow access to flux trap volume more frequently than once / week which is our current access to the high flux volume. We are in the process of increasing our staff and reallocating staff to meet the increase in demand for isotopes we currently see.

<u>Six Barrel Flux Trap:</u> A new flux trap that will containing three additional 0.75" OD tubes is shown in the figure 2 below (cross sectional view). The current flux trap is classified as a secured experiment which can only be removed when the reactor is not operating. Each of the three new tubes is shown as a tube within a tube. The outer small tube is part of the secured flux trap. The inner small tube is sized (0.56" OD will hold 0.38" OD samples) so the reactivity affect of removing or inserting it will be within the American National Standard Institute Standard's definition of a movable experiment. This will allow samples to be safely removed while at full power. This modification will require NRC approval of a revision to the MURR Reactor License Technical Specification before it can be used as a movable experiment. This approval will enable access to the high flux region at any time, giving MURR tremendous flexibility in the scheduling of targets.

Feasibility studies have also been completed which indicate that the reactor could be upgraded in power to 20-25 MW. This would significantly increase our isotope production capabilities by increasing the maximum flux to over 1x1015 n / cm2 / s

11. Summarize customer inquiries received during the past two years. What per cent was filled, referred to other facilities, rejected? Explain unfilled requests.

Many of our customer requests for isotopes are long standing ones (P-32, S-35, P-33). A number of others are for development of radioisotopes used for medical products (Ho-166, Sm-153, Y-90) and others have been requested for various R&D needs. We fill >95% of the requests that we receive. Most of the unfilled requests are for isotopes where we have no existing safety analysis in place and the requestor is not interested or able to assist with the cost of analysis to fulfill their request.

12. How does each site manager rate customer satisfaction for his site? For the overall program?

We don't have a formal customer satisfaction measurement system in place. We look at the number of long term users who regularly request a large fraction of our service and who haven't moved their business to other reactors as a measure of our ability to meet their needs. Our on-line reliability (>90% since 1977 and our access to isotopes on a weekly basis make us a unique supplier to most of our customers.

13. Kindly detail how you set the price of a mCi of a radioisotope? The detail should show if the cost is fully loaded or incremental, and should include labor, materials and parts, facility rental and amortization costs, listing of all the actual

overhead charges, waste disposal (a major costs), and all other costs that are tagged to the cost of producing, marketing, selling, and distributing of the product (e.g.,. customer service, distribution, ordering).

Isotopes provided for commercial use are priced at market value which is presumed to cover fully loaded costs.

14. Illustrate the above question for the following radioisotopes: In-111, P-32, I-123, I-125, and several research radioisotopes.

Most high volume radioisotopes, such as P-32 and S-35, are provided as part of irradiation services for large customers. Those prices are set in accordance with volume purchase plans from the various customers. We are currently in the process of revising the price list for research radioisotopes and plan to have a list available in the first part of June '99.

15. What process, mechanism, and organizational structure do you have for the timely distribution of the produced product?

MURR's Income Generating Operations (IGO) division is dedicated to the processing and delivery of radioisotopes requested by industry and researchers. Within IGO resides a mature and tested shipping group that makes over 2000 radioisotope shipments per year. The variety and quantities of radioisotopes shipped is far beyond the capabilities of any other shipper in the US.

16. What process, mechanism, and organizational structure do you have for customer service?

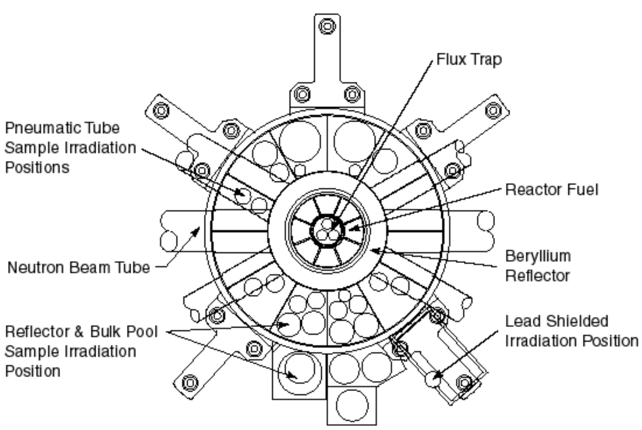
Customer service is provided by customer communications with the section leaders in IGO irradiations, processing and shipping groups.

17. Will you sign contracts that guarantee delivery at the contracted time of delivery and where the contract has penalty clauses for non timely delivery of the specified product?

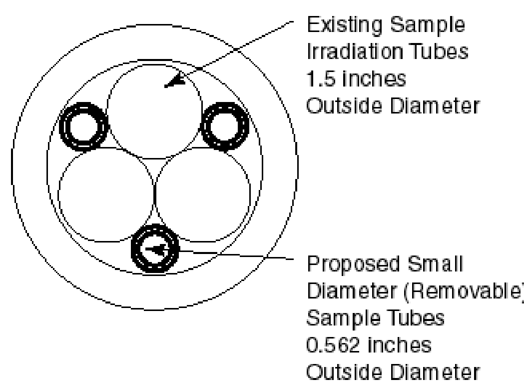
MURR typically has not entered into such contracts, but would seriously entertain them.

18. What should be the long-term role of Government in providing commercial and research isotopes?

The Federal Government should subsidize the production and supply of research (and in some cases commercial) radioisotopes by providing long-term financial commitments to and capital investments in the most cost effective and reliable facilities available in the US. This list should include non-DOE facilities such as MURR.



Research Reactor Center Irradiation Facilities



Proposed 6-Barrel Flux Trap Irradiation Facility

International Isotopes, Inc., Site Visit

Site Visited May 7, 1999

1. Introduction

A site visit was conducted at International Isotopes, Inc., (I3) in Denton, TX on May 7, 1999. Site visitors included Dr. Ron Finn, Memorial-Sloan Kettering Cancer Center, Dr. Tom Ruth, TRIUMF- UBC PET center, and Dr. Robert Atcher, Los Alamos National Laboratory. Mr. Carl Seidel, President of I3 acted as host for the site visit. During the course of the visit, we had a telephone conference with the site manager for International Isotopes operation at the Advanced Test Reactor in Idaho.

Mission

International Isotopes, Inc. is a company that was founded to produce radionuclides and radiopharmaceuticals utilizing accelerators on site as well as reactors outside of Denton. The company also has imaging technology for tomographic imaging and accelerator technology based on the linac which was installed at the Denton site.

Facilities and Services

The company was founded to exploit resources developed in Texas during the construction of the Superconducting Super Collider (SSC). Th SSC facility was partially constructed when DOE canceled the project. I3 bought assets from the SSC facility, including the linac that was built to inject protons into the larger accelerator. This linac underwent modifications to increase the beam current to a level that is sufficient for isotope production. The linac was in the process of testing at an intermediate energy to the proposed final energy of 70 MeV. There are hot cells for target handling in the building above the linac tunnel. In addition, there are labs equipped for radiochemical work. This building is located across town from the main offices and building of I3.

I3, in partnership with the University of North Texas (UNT), moved a CP-42 cyclotron from M.D. Anderson Hospital in Houston to a site adjacent to the main I3 facility. The cyclotron is owned by UNT but is being leased and operated by I3 staff. During the site visit, initial testing of the cyclotron had produced a circulating beam. Since that time, production of Thallium-201 has been undertaken and regulatory approval was obtained for its sale. A hot cell was under construction at the cyclotron at the time of the site visit. The intent is to produce F-18 for local distribution in addition to the longer-lived commercial products.

I3 has production facilities in Idaho at the Idaho National Environmental and Engineering Laboratory. They utilize the Advanced Test Reactor for isotope production. Given the inability to remove targets via a pneumatic system, the production is better suited to isotopes with longer half lives. However a pneumatic “rabbit” system is planned for 2001. This operation is focused on commercial isotope production.

The main facility at I3 has GMP facilities that are designed for radiopharmaceutical synthesis. The company’s Iodine-125 seed manufacturing is conducted there. In addition, they have the capacity for several other production lines. There is more than 40,000 sq. feet of expansion room for additional radiopharmaceutical and medical device production lines in the main facility.

Brief History

The company was founded in 1995 and went public with an Initial Public Offering (IPO) in August 1997. Since then the company has built or purchased 5 buildings with over 150,000 square feet for production of radioisotopes and radiopharmaceuticals as well as manufacturing equipment (total worth over $45M). The 42 MeV cyclotron is operating and I3 has begun to sell Tl-201 made on the machine and processed in the radiochemical labs under their Drug Master File (DMF). I3 plans to make F-18 and I-123 from this machine by the end of the year. They plan to make research radioisotopes on this machine beginning in the year 2000. The 70 MeV LINAC is now operating at 30 MeV and has irradiated some targets in a preliminary production mode as they bring the machine up to full current and test each of the six target stations. Tl-201, In-111, Co-57, Pd-103 and several other radioisotopes are planned for production in large quantities when the LINAC is in full operation next year. They have also begun validation procedures for the production of finished radiopharmaceuticals at their facility and plan to distribute these products beginning next year.

Development programs on new imaging systems and other instruments in collaboration with several Texas institutions have begun and should produce working prototypes in the near future.

2. Relationship to DOE Programs

DOE Office of Isotope Programs (IP)

Currently, there is no programmatic interaction between I3 and DOE. The Idaho facility (I4) has a contract to lease space and facility at the ATR for several more years and they plan to make improvements to the facility that will allow them to produce short-lived radioisotopes which will be shipped to the Denton facility for final radiopharmaceutical manufacturing.

In addition they have signed a contract and made initial payments to the Sandia reactor facility for the production of I-125 for the next three years. Discussions are being held with the facility to produce other radioisotopes.

Other discussion have been held with DOE about using the facilities at other laboratories, providing research isotopes to their customers and acting as a marketing agent for products the DOE labs produce.

Other DOE Programs

I3 bought a company called MacIsotopes. This company privatized the isotope production activity at the Idaho National Engineering Laboratory. This production program centers on the Advanced Test Reactor, a Defense Programs reactor. I3 has had discussions with the IP concerning distribution arrangements. In addition, they have had discussions with production sites within the DOE labs for isotopes of interest.

The site visitors discussed the potential for the IP to purchase irradiation time on the accelerators at I3. This appears to be a viable option until demand increases to the extent that there is no accelerator time available. The likelihood exists, though, that time on the CP-42 could be purchased for short irradiations of limited quantities of research isotopes.

3. Relationship to Academic Programs and Training

I3 has a close working relationship with North Texas University. Interactions are primarily focused on the Department of Physics, which has a program in accelerator physics. The University of Texas Medical School at Dallas is in the early stages of developing a relationship with I3. The exact form of this relationship is not clear at this stage of the interaction. The Physics Department at NTU plans to use one of the beam lines on the CP42 for proton irradiations. There are discussions of beginning a training program in radiopharmacy that would provide a source of students for I3 in its radiopharmacy operation. These discussions are continuing with U. of Texas and in addition they are planning an imaging equipment development center with Southwest Medical center that will include a clinic for patient treatment using PET radioisotopes.

4. Current Isotope Production

At this stage I3 is generating only Thallium-201 from their cyclotron. They are not producing any radioisotopes on the linac yet. They are preparing radioactive seeds from radioisotopes acquired from smaller reactors. They have signed an agreement with Univ. of Missouri Research Reactor for isotope production. They have also agreed to purchase Iodine-125 from Sandia reactor when they begin routine production. They have produced F-18 and I-123 on the cyclotron in preliminary test targets and have sold some Tl-201, produced on the cyclotron and processed under their DMF. The LINAC has irradiated some pre-production Tl-201 targets and will be producing product for sale by the end of the year.

Throughput

The facilities appear to have the capacity to handle a large number of shipments. Their hot cell capacity looked somewhat limited for the number of products being proposed (a total of 4 hot cells with one of these dedicated to receiving from the accelerator). The hot cell area at the cyclotron building was still under construction at the time of the site visit in May 1999. It now has three small hot cells in the cyclotron building for Tl-201 and I-123 production.

Customers

At this point in time they are producing limited quantities of accelerator-produced radioisotopes. They have 3 contracts that have made public. The Imagyn contract is for the marketing of I-125 brachytherapy seeds. The Bracco contract is for the production and distribution of a finished radiopharmaceutical . The Gamma Plus contract is for a joint venture to produce and distribute F-18 FDG for the Dallas Ft. Worth market.

Research and Development (R&D)

Both accelerators require R&D work in the opinion of the site visitors. The CP42 that was acquired from M.D. Anderson in Houston has not been run under the demanding conditions proposed by the I3 team. While other CP42s have run and continue to run as production machines at other sites around the world (MDS-Nordion, Canada and Amersham, UK) this productive capability came at a price in terms of major upgrades. They anticipate that the CP42 will be operating in the 100 to 150 µA. They are now irradiating at the 80-100 µA level.

The Linac is based on the original injection accelerator for the now defunct Super Conducting Super Collider (SSC). The SSC was designed for low beam current operation while the I3 production machine requires high beam current and relatively high duty factor. This total reversal of design criteria has been a challenge for the accelerator engineers and physicists. It is too early to determine if they have been successful with the modifications.

With respect to research associated with the completed facility, they plan to start supplying research radioisotopes to the user community during the second year of operation. This would obviously entail development work. I3 is planning on a target development program as well.

5. Future Capabilities and Resource Requirements

Continued Operation

The physical plant has the capacity to meet the needs of the research community for many years to come. However, whether that comes to pass will depend upon the success of I3 in the commercialization of the proposed products over the next few years.

Expanded Operations or Services—Underway

The whole facility is in process at this point in time. Nothing has really been tested in a production mode (other than their seed production facility which makes use of I-125 purchased from off site). They will be producing I-125 from the Texas A&M reactor next month.

Expanded Operations or Services—Proposed

The facilities in Denton are a recently completed green field facility thus the only expansion in the foreseeable future would be to meet expectations in terms of design criteria and operational reliability.

6. General Issues Related to Isotope Supply

Institutional Support

As a commercial entity they have total autonomy. However, they appear to support from the participating institutions such at University of North Texas and University of Texas Medical Branch.

Marketing

Marketing is still under development as yet since they have such a limited product line. However, they have been quite successful in raising money for the creation of the company so one assumes that they understand the market place. The assembled team certainly has extensive experience in producing and distributing radioisotopes.

Waste Management

Almost all the waste is segregated and held for decay. Other longer lived waste is properly stored for periodic removal to approved waste burial sites.

International Isotopes, Inc.

Questions and Answers

No Q&As were submitted.

Brookhaven National Laboratory (BNL) Site Visit

Site Visited May 11, 1999

1. Introduction

On May 11, 1999, a site visit to Brookhaven National Laboratory (BNL) was conducted by a special Site Team assembled by the DOE Nuclear Energy Research Advisory Committee's (NERAC) Subcommittee on Long-Term Isotope Research and Production Planning. The Team was composed of Sekazi Mtingwa, Ph.D., NERAC Site Team Leader, Wilkins Professor of Physics, Morgan State University; Robert Atcher, Ph.D., Chemical Science and Technology Division, Los Alamos National Laboratory; Ronald Finn, Ph.D., Chief, Cyclotron/Radiochemistry, Medical Imaging Department, Memorial Sloan-Kettering Cancer Center.

The purpose of the site visit was to conduct an in-depth review of BNL's present and future capabilities to meet a substantial portion of the national need for a variety of radioisotopes for medical, research, and commercial applications.

To facilitate the visit, the NERAC Site Team electronically submitted a list of questions prior to the site visit to Leonard Mausner, Ph.D., Director of BNL's Radionuclide Research, Radioisotope Production, and BLIP Operations. Those questions and Mausner's responses are attached.

Mission

The primary mission of BNL's Radioisotope Production and Research Program is to prepare certain commercially unavailable radioisotopes to distribute to the nuclear medicine community and industry, and to perform research to develop new radioisotopes desired by nuclear medicine investigators. In conjunction with this mission, the group also performs service irradiations, sells by-products and explores opportunities for new products and radioisotope applications as needed. [1]

Facilities and Services

BLIP

The only isotope production facility currently operating at BNL under the auspices of the Department of Energy's Isotope Programs (IP) is the Brookhaven LINAC Isotope Producer (BLIP). Until recently, BLIP has used the excess, amounting to 78%, of the proton pulses produced by the 200 MeV LINAC, whose primary mission was the production of protons for injection into the Booster and subsequently into the Alternating Gradient Synchrotron (AGS) for high energy physics experiments. However, the AGS will soon operate as a heavy ion Booster for injection into the new Relativistic Heavy Ion Collider (RHIC), whose goal is to create a quark-gluon plasma - a form of hot, dense matter that has not existed since the Big Bang. With a start-up scheduled for later in 1999, it is anticipated that the RHIC accelerator complex will operate in proton mode for up to 21 weeks in both FY 2000 and FY 2001, and there may be an additional 2-4 weeks per year of proton operations each year supported by DOE Defense Programs. It is during such periods that BLIP should be able to produce radioisotopes. Beyond FY 2001, there will be 6-12 weeks per year of proton beams for RHIC, and BNL is requesting between 15 and 30 weeks per year of AGS proton experiments, concurrent with RHIC operations. Thus, after the first two years of RHIC's operations, it is difficult to predict the number of weeks that the accelerator complex will operate in proton mode. In the past, the BLIP staff has been actively involved in the scheduling meetings where beam time was allocated by the AGS management, and the plan is to continue that input during periods when the AGS will accelerate protons instead of ions.

The radioisotopes produced and distributed by BLIP since FY 97, along with typical applications, are as follows:

Be-7	Berylliosis studies
Cu-67	Radioimmunotherapy
Ge-68	Parent in the generator system for producing the positron-emitting Ga-68; required in calibrating PET tomographs, potential antibody label
Mg-28	Magnesium tracer
Sr-82	Parent in the generator system for producing the positron-emitting Rb-82, a potassium analog
Zn-65	Zn tracer

To date, the primary shipments for FY 99 have been Ge-68 and Sr-82.

HFBR

Last operated as a 30 MW reactor, the High Flux Beam Reactor (HFBR) also has been used for the production of radioisotopes. Unfortunately, the reactor has been in standby mode since December 1996 due to a leak into the soil of tritiated water from the reactor's spent fuel storage pool. Presently, it is unclear if and when the reactor will resume operations. However, once restarted, DOE's Basic Energy Sciences Advisory Committee has recommended that its power be boosted to 60 MW.

The reactor generally operates much of the year in roughly 6-week cycles - 30 days of operation followed by a 12-day shutdown for fuel change and maintenance. The HFBR has/could have the capability of producing the following radioisotopes: Sc-47, Sn-117m, Cu-64, Sm-

153, Re-186, Gd-153, Ho-166, Lu-177, Au-198, and Au-199, with all but the last two being recommended by the DOE Expert Panel.

Typical applications of these isotopes are as follows:

Sc-47	Cancer therapy with radiolabeled monoclonal antibodies
Sn-117m	Treatment without marrow toxicity of pain due to metastatic bone cancer
Cu-64	Diagnosis of cancers by PET imaging
Sm-153	Treatment of pain due to metastatic bone cancer
Re-186	Bone cancer therapy; treatment of rheumatoid arthritis
Gd-153	Source isotope
Ho-166	Cancer therapy and treatment of rheumatoid arthritis
Lu-177	Cancer therapy with radiolabeled monoclonal antibodies
Au-198	Treatment of severe arthritis in knee joints
Au-199	Cancer therapy with radiolabeled monoclonal antibodies.

Other Facilities

Presently, six of seven hot cells are being utilized. During recent upgrades, nine radiochemistry labs were totally renovated, two more hot cells were added, and existing hot cells received shielding enhancements. [See Questions 1 and 9.]

Brief History

In general, the DOE-supported Radionuclide and Radiopharmaceutical Research Program in the Medical Department at BNL has a distinguished history. Over 80% of all clinical imaging procedures carried out worldwide at the present time (approximately 12 million in the U.S. per year) utilize radionuclides and/or radiopharmaceuticals developed at BNL. Examples include the technetium-99m generator and various technetium labeled radiopharmaceuticals, blood cell labeling kits, thallium-201, iodine-123, xenon-127, copper-67, ruthenium-97, and a number of other radionuclides. Today, more than 85% of the nuclear medicine procedures done annually in the U.S. utilize technetium-99m.

BLIP

In 1950, the Brookhaven Graphite Research Reactor was established and produced a variety of radioisotopes for research and development. Subsequently, in 1972, BLIP was commissioned to open new paths in radioisotope R&D, and for the first time, it became possible to produce large quantities of a variety of radioisotopes for medicine, research, and commercial applications. As a result of recent upgrades, the maximum LINAC beam intensity was increased from 65 to 145 mA and provision was made for a variable proton energy option for BLIP.

HFBR

Since it began operating in 1965, HFBR has provided neutron beams for a variety of neutron scattering experiments in physics, materials science, biology, and chemical crystal structure. Moreover, it has the capability of irradiating samples for the production of radioisotopes. It operated from 1965 to 1982 at 40 MW power level. In 1982 the power level was increased to 60 MW, in order to improve research capacity. After a safety assessment in 1989 the power level was decreased to 30 MW. An increase in the power level back to 60 MW has been recommended by the Basic Energy Science Advisory Committee if restart is allowed.

2. Relationship to DOE Programs

DOE Office of Isotope Programs (IP)

Brookhaven's Radioisotope Production and Research Program is located at a DOE laboratory and is operated under the auspices of the Office of Nuclear Energy, Science & Technology. However, parts of the financial support for the program's activities come from other sources, such as DOE's Office of Science. As for the prices of isotopes distributed by the program, DOE's Office of Isotope Programs sets the prices, not BNL. [For more details, see Questions 12 and 13.]

3. Relationship to Academic Programs and Training

The site team was concerned that there have been no postdoctoral associates or graduate students trained by the Radioisotope Production and Research Program over the past three years. While part of the reason may have to do with funding limitations and the need for extensive radiation safety training, there is general agreement that the future of the field is being jeopardized by the low numbers of new personnel being trained in the experimental methods of radiochemistry.

4. Current Isotope Production

Throughput

The Radioisotope Production and Research Program keeps a careful log of all inquiries by potential customers interested in purchasing radioisotopes. This is done regardless of whether the inquiries come into the main distribution office or are made to individual members of the program. Whenever possible, orders are filled; however, typical reasons for not filling orders are as follows:

- BLIP not operating
- Not practical at BLIP
- New isotope, large development required
- Cannot meet minimum order
- HFBR-produced and hence currently unavailable.

Customers

Currently, only the accelerator-produced (BLIP) isotopes enumerated above are being produced at BNL. The customer base is composed of entities, both private and public, who have a need for radioisotopes for medical, research, or commercial applications.

Research & Development (R&D)

The BLIP is a world class radionuclide research and production facility that has continued to serve as a unique national resource for the production of many isotopes which are generally unavailable elsewhere. It has supported research at BNL on diagnostic and therapeutic radiopharmaceuticals and remained a source for distribution of many difficult-to-produce isotopes to industry and other research investigators.

A number of research projects have resulted into successful technology transfer. Examples include (1) A new ^{99m}Tc-RBC Kit presently being marketed by Mallinckrodt Inc., under an exclusive AUI license; (2) FDA-approved isotopes (^{127}Xe, ^{82}Sr, and others) routinely distributed to industry for resale; (3) Use of BNL-developed technology for commercial production of ^{99}Mo / ^{99m}Tc generators, kits, and radiopharmaceuticals, ^{201}Tl, ^{123}I, ^{67}Cu, and ^{127}Xe, etc. Efforts are in progress to transfer two other technologies: ^{117m}Sn-DTPA for bone pain palliation therapy, and new semi-rigid chelating agents for producing stable radioimmunoconjugates for imaging and therapy.

5. Future Capabilities and Resource Requirements

Continued Operation

Currently, the physical facilities at BLIP and related research areas are in varied condition. A problem with the steering magnet that introduces beam into BLIP resulted in a hole being burned in the side of the equipment. As a result, there needs to be a substantial repair in a high radiation region of BLIP in order to continue operations. Due to the upgrades outlined above, the support facilities are in good condition. In FY 97, an upgrade was completed at a cost of $5.82 M that should enable BLIP to improve its production and distribution capabilities. Parts of the upgrade involved increasing the available beam from 65 mA to 145 mA, providing a variable proton energy option for BLIP, adding two rooms to the BLIP work area, and adding two new hot cells to the Target Processing Laboratory (TPL). All laboratory renovations and hot cell construction are nearly complete and are scheduled to be finished before the end of this fiscal year. Moreover, the BLIP beamline repair is scheduled to be completed in September 1999. [For more details, see Questions 1 and 9.]

As for HFBR, its future is uncertain and the current activity revolves around cleaning up the tritium contamination and insuring that the systems would operate without problems should they be recommissioned. A decision on restart is expected from DOE at the end of the calendar year 1999.

Expanded Operations or Service—Underway

With the completion of the recent upgrades and the addition of two new hot cells to the TPL, BLIP and related facilities are positioned to increase their isotope production, distribution, and research activities. However, the BNL staff stated that, aside from the obvious need for LINAC operating funds to extend the running period of BLIP, the biggest single bottleneck to expanded operations is the lack of sufficient personnel. Another problem perceived by the staff is the hefty amount of reporting and documentation that is required for submission to DOE headquarters. Finally, given the commissioning of RHIC, another major concern for BLIP is the uncertain availability of proton beams in the LINAC.

Expanded Operations or Services—Proposed

To insure a reliable year-round supply of radioisotopes for medical, research, and commercial applications, BNL has proposed acquiring and installing a 20-70 MeV cyclotron with a beam current in the range 750-1,000 mA. The proposal involves constructing three beam lines: one for isotope production, one for PET studies, and one for target and isotope R&D. A building to house the facility also is included in the proposal. Early estimates of the total capital cost are in the range $17-25 M.

6. General Issues Related to Isotope Supply

Institutional Support

The BNL management has a history of strongly supporting its radioisotope production, distribution, and R&D activities. Moreover, supporting BLIP has been designated as an official - although secondary - mission of the Collider Accelerator Department, which sometimes provides support to BLIP without charge. [For more details, see Questions 5 and 6.]

Marketing

Users of radioisotopes know of the limited sources from which to obtain both accelerator and reactor-produced isotopes. With BNL housing each of the two types of isotope-producing facilities (BLIP and HFBR), prospective purchasers make inquiries to the BNL Isotope Distribution Office or directly to the staff. As mentioned previously, all such inquiries are tracked from the initial time of contact to the final distribution, or non-distribution, of the requested isotopes. The numbers and amounts of shipments made per year and the reasons for inquiries not leading to shipments are carefully logged into the Distribution Office's records. [For more information, see Questions 10-16.]

Waste Management

Waste management at BNL is currently under tight scrutiny by environmental authorities to insure that it is being conducted in accordance with existing government regulations. There are a number of concerns that are presently being addressed, with perhaps the most publicized concern having to do with the leak into the soil of tritiated water from HFBR's spent fuel storage pool. Another concern is the tritium-contaminated soil south of BLIP. Measures to correct this BLIP problem and others are discussed in Questions 2 and 8.

7. Summary Comments

Brookhaven has been one of the longer-standing radioisotope producers for the Department of Energy; however, it currently is experiencing more limited periods of operation, exacerbated by the HFBR shutdown and the parasitic operation of BLIP impacted by the current high energy physics research scheduled for RHIC. Under the present configuration, the minimal staff of the Medical Department's Radioisotope Distribution Program has restricted input in production schedules. Therefore, the staff is represented in the table of organization in several roles with a major emphasis on research in the areas of therapeutic radioisotope development, radiolabeled monoclonal antibodies and peptides, and pain ablation chelated radionuclides. The campus atmosphere includes the unique laboratory facilities, such as BLIP, HFBR, the Brookhaven Medical Research Reactor (BMRR), two cyclotrons, and high-level radiation processing cells. A note of caution was interjected to the site visitors in that HFBR is presently shutdown and the prognosis for restart by DOE is not available. Also, BLIP is operated parasitically with the BNL High Energy Physics Program, and the direction of that program's Relativistic Heavy Ion Collider research interjects some uncertainty as to the need for protons in the future.

The DOE IP has attempted to form a Virtual Isotope Center through coordination of the operating schedules of accelerators at LANL and TRIUMF with BNL, such that a "year-round" availability of specific radionuclides could be forthcoming. The primary shipments from BLIP are Ge-68 and Sr-82. IP lists BNL and LANL as their primary suppliers of accelerator-produced isotopes with marketing management at Germantown, Maryland. The Department of Energy sets all pricing, and the current isotope production activity is focussed on the two nuclides mentioned above. The time available when BLIP is not in operation for radionuclide production is spent in repairs and upgrades of the BLIP / LINAC facilities, such as the recently completed beam upgrade of available current and research and development efforts relevant to the nuclear medicine field.

It was extremely difficult to anticipate the future developments and capacities of the program due to the indecision on HFBR and the outcome of the high energy physics research program with RHIC. It is therefore difficult to determine the status of the operations at Brookhaven for the current year. The facilities for radionuclide production are present; however, they still require some renovations and overhauling. The present staff is primarily focussed on research and development activities. Should the decision be made to operate BLIP for a more significant portion of the year and / or should the HFBR start-up be authorized, the needs of the facility to expand / maintain operations would include adding technician production staff. The internal programmatic support within Brookhaven National Laboratory has been strong due to its public relations role, which this operation has generated. There is a renewed direction on the site for the environmentally safe handling of radionuclides and wastes generated. This is an important consideration for the public at large, but it is also a significant burden on the research staff in terms of time and effort for completion and documentation. It also presents a potential problem for the isotope production activity at BNL since environmental concerns have interrupted operations in the past.

The BNL production staff appreciates the problems with the parasitic operation necessitated, and therefore, it shared with us the option of installation of a dedicated cyclotron of nominal 70 MeV proton energy, to undertake the production program. Space for siting the instrument, the continued use of existing hot cell processing facilities, and health physics support were addressed appropriately.

If a reliable source of accelerator-produced radioisotopes is to be assured for future medical, research, and commercial applications, the establishment of such a dedicated facility should be given full consideration by DOE. However, it is not clear that the need for such a facility is warranted given the construction of the IPF facility at LANL, the impending start of operations at International Isotopes, Inc., in Denton, Texas, and the success to date of the Virtual Isotope Center.

[1] Excerpted from www.medical.bnl.gov / iso.htm

Brookhaven National Laboratory (BNL)

Questions and Answers

Capability, status, and operation of DOE isotope production infrastructure

1. **What is the physical condition of your isotope processing facilities and equipment?**

In general our facilities are in excellent condition! This represents a big change from five years ago and is the result of several large renovation efforts. In 1994 the lighting throughout the laboratory area was replaced using BNL special maintenance funds. From 1995-1997 the Biomedical Isotope Resource Center project (DOE Office of Energy Research funds) along with Accelerator Improvement Project funds (DOE OER) spent about $8.7M to upgrade the LINAC, the Brookhaven Linac Isotope Producer (BLIP) and selected areas of our Target Processing Laboratory (TPL). This resulted in an increase of the maximum LINAC beam intensity from 65 to 145 mA, provided a variable proton energy option for BLIP, added two rooms to BLIP working area, upgraded the BLIP beam line vacuum, control, cooling and waste systems, added two new hot cells to the TPL and upgraded the hot cell ventilation system. This was followed by the Building 801 Renovation Project ($6.7M from DOE OER) 1996-1999. This ongoing work is making major improvements to the laboratory infrastructure items, such as HVAC, asbestos removal, and bringing waste piping up to code. In addition nine radiochemistry labs were totally renovated, two more hot cells added and existing hot cells got shielding enhancements. A BNL funded project starting soon will upgrade our aqueous radwaste storage tanks. Note that the DOE Office of Isotope Programs provided none of this funding. During your visit you will have ample time to see all these facilities.

2. **What capital investments are needed to assure near term operability?**

The most important short term investment is operating funds for the LINAC to extend the running period of BLIP beyond that of the limited and declining proton physics program (see question #4 below). Depending on the status of the rest of the accelerator complex these costs range from $25,000 - 98,000 per week. It will also be possible to operate intermittently for short periods with the charge by the hour, ranging from $250 / hr (with a $900 set up fee) to $450 / hr (with a $5000 set up fee). Funding permitting, this option would allow us to stretch our production for short lived isotopes beyond the normal period of accelerator use for proton physics. Nevertheless, within five years it is not clear that there will be enough proton operating weeks, in a contiguous block, for BLIP to remain viable. Therefore we are investigating the purchase and installation of a cyclotron, tunable from 20-70 MeV and with at least 750µA of beam intensity. The preliminary concept is for three beam lines; one for regular isotope production, one to support the Chemistry Department PET program, and one for target development and isotope research to be shared by both the Medical and Chemistry Departments. The capital and operating costs would also be shared. Very early estimates of the total capital cost are approximately $17-20M. Existing laboratory facilities would continue to be utilized. This machine and its mission do not completely fulfill the NBTF goals as defined earlier. However, at a much lower cost it would allow a year round supply of about 90% of the isotopes included in the NBTF list.

There are also several facility environmental issues requiring capital investments. These are described in more detail below in question #8. Prime among these is the tritium contaminated soil south of BLIP. In FY 98 DOE Office of Isotope Programs provided approximately $76,000 to upgrade the BLIP downspouts and cap our shield berm to partly address the soil problem. In FY1999-2000 a $600,000 project has been proposed to inject silica grout into the activated zone of soil under BLIP, forming a viscous barrier layer. The Engineering Evaluation Cost Analysis (EECA) has been submitted for review by all the cognizant environmental authorities (EPA, New York State, Suffolk County etc.).

3. **Are the additional resources practical, quickly and easily integrated into existing infrastructure, and sustainable by local financial and personnel resources?**

Additional operating weeks of the Linac will not cause infrastructure burdens. However, isotope production of greater than approximately 6 months per year would require additional personnel to keep up with maintenance, waste disposal etc, while performing isotope irradiations and processing. The BLIP tritium remediation work is to be funded by DOE Office of Environmental Management, Superfund, and BNL general plant funds, and can be scheduled for installation during accelerator downtime. The new cyclotron project is not likely to be complete until 2004, unless the DOE Office of Isotope Programs and Office of Biological and Environmental Research can get Congressional fast track approval.

4. **What is the availability of your primary nuclear facility over the next five years?**

   Our primary facility is the BLIP, with the High Flux Beam Reactor (HFBR) a secondary facility. The BLIP utilizes extra pulses from the 200 MeV Linac. The Linac prime mission is to supply protons for subsequent acceleration in the Booster and Alternating Gradient Synchrotron (AGS) for high energy physics research. The high operating cost of the large Linac has limited BLIP to secondary or parasitic running with the high energy physics program. Parasitic operation is very efficient because only incremental accelerator costs are charged to the isotope program, while the high energy and beam current allow simultaneous production of many isotopes. The principal impediment to better isotope availability from BNL is the declining operational funding of the proton physics program at the AGS. From a high of 34 weeks in 1983 BLIP operations have slowly declined to an average of 18 weeks over the last several years. A major program change at BNL in FY 2000 may reduce this inadequate level even further in the future. In FY 2000 the Relativistic Heavy Ion Collider (RHIC) becomes operational and the accelerator program emphasis will shift from high energy proton physics to heavy ion nuclear physics. Indeed the AGS proton physics program will continue only as an incremental parasitic operation with RHIC. It is expected that there will be 16 weeks of such proton running in FY 2000, perhaps followed by about 5 weeks of polarized proton experiments at RHIC for a total of ~21 weeks for BLIP. Although the overall mission emphasis on protons in later years is expected to decline, an increase in proton operations in some years may occur if RHIC mounts a major proton experiment (colliding proton and gold beams for example). We have no quantitative prediction at this time however. Senior BNL management and the chairman of the Collider Accelerator Department will be present during your visit and may be able to address this question for you.

   The HFBR has been in standby mode since December 1996 due to a leak into the soil of tritium containing water from the spent fuel storage pool. Its restart will be decided by the Secretary of Energy following the completion and public comment on an Environmental Impact Statement. This is expected by the end of 1999. The HFBR could commence operations within 18 months of a positive determination. If the HFBR restarts we will use it for the production of such isotopes as Sc-47, Sn-117m, Re-186, and Sm-153.

5. **What understanding exists at the site about the priority of isotope production to serve isotope customers?**

   This program's visibility and the attention we get from upper management is considerably better than might be expected given our small staff and funding level. In fact, supporting BLIP operations is an official mission of the Collider Accelerator Department, albeit a secondary one. Technical assistance from the Accelerator Department is generally not hard to get and is sometimes gratis. We have also received assistance from the Directorate on several occasions in cutting through red tape and mobilizing non accelerator resources, such as waste disposal and environmental management. As mentioned above, senior management and Accelerator Department personnel will be available to discuss this issue with you.

6. **How much influence do you as site manager have in planning the use of multi-purpose facilities?**

   In general the needs of the Isotope Program do not significantly influence the macro-scheduling and long term planning of the accelerator complex. However, through the 27 years of BLIP's existence and many technical and programmatic changes at the Linac and AGS, the Accelerator Department has maintained the compatibility of our operations with the physics programs, sometimes at additional development cost. For example, it is projected that probably in the Spring of 2000 there will be a polarized proton experiment at RHIC. The polarized beam intensity is several orders of magnitude too low for isotope production, but a pulsed switching magnet will be installed to allow simultaneous high intensity BLIP running. The Isotope Program will not be charged for this device.

   For short term scheduling and planning we do have direct input. Each week there is an accelerator scheduling meeting at which BLIP is always represented and recognized. Our short term scheduling needs are usually met, sometimes even when they conflict with physics. For example, repairing the BLIP beam line due to a vacuum leak requires that the entire accelerator complex be shut down. We generally get this access as soon as safety reviews allow, despite the disruption to the many AGS users.

7. **What cost containment measures are being pursued?**

In an attempt to reduce the BNL overhead rate in the last year many overhead items are now direct charged. For the isotope effort the major items so far have been the space charge, waste disposal charge, and instrumentation calibration service. In order to contain the impact of these new fees we have given up space and consolidated our operations, retired some older radiation detectors, and revised some isotope processes to reduce or eliminate the creation of mixed waste. Also, to reduce radwaste shipping charges we have procured two special use casks for our more radioactive waste forms. We are also in the midst of an effort to build a neutralization and solidification system for our hot cell liquid waste. This will reduce overall volumes needed to be stored and shipped.

8. **What "licensing" issues need to be addressed?**

In the wake of the above mentioned leak of tritium containing water from the HFBR fuel pool, the DOE and the new BNL management have instituted wide ranging reforms. At this time <u>all</u> applicable town, county, state and Federal (DOE, EPA, DOT, OSHA etc.) regulations are being rigorously implemented and enforced. The major items that we need to address which involve substantial labor and/or equipment include:

a) Category III Nuclear Facility exemption to allow production of Xe-127. The radioiodines predicted to be coproduced with Xe-127 put BLIP and the TPL above the radioactive inventory threshold to become a Category III Nuclear Facility. The financial, personnel, regulatory, and liability burdens from such a classification are unsustainable for this program. Indeed the BNL Director's Office has told us that they do not want another such facility onsite. Therefore, we have been working for the last year on obtaining an exemption based on a more realistic release scenario. At this point we have developed a methodology to justify an exemption that has been accepted by the BNL Radiological Control Division and the DOE Area Group, but there are still many details to address.

b) remove, cleanup or isolate activated soil beneath BLIP for compliance with the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA); the various actions taken and planned are described above in #2.

c) install quantitative airborne radioactive emission monitoring in order to bring BLIP, the Target Processing Laboratory (TPL), and all radiochemistry labs into compliance with 40CFR61- Emissions;

d) upgrade TPL access security and install shielding for hot cell HEPA filter bank to bring the TPL into compliance with 10CFR835 - Radiological Control;

e) establish mechanisms and controls to bring all our facilities and operations into compliance with ISO14001 Environmental Management Standards;

f) perform engineering and safety analysis of lead transport casks for onsite movement of BLIP targets to document equivalence with DOT standards or procure new certified casks;

g) implement new DOE Office of Isotope Programs QA Plan directives for compliance with DOE Order 5700.6C-Quality Assurance.

9. **What unused or underused capacity, e.g. facilities, personnel, could be mobilized to support a growth in isotope demand?**

We presently utilize 6 of our 7 hot cells. With two more new ones entering into service shortly we will have 3 underutilized hot cells available. There are also three very large, heavy duty hot cells in a room adjacent to ours, designed for metallurgical analysis of reactor core samples. This program is experiencing funding difficulties, so it is possible that these hot cells may become available for isotope processing in the future. There are also some underutilized target slots in BLIP, primarily in the energy range of 180-120 MeV. The high energy slots (200 MeV) and especially those receiving energies under 120 MeV are used constantly. Our major limitations in supporting growth in isotope demand are processing personnel and beam time.

10. **Summarize customer inquiries received during the past two years.**

Table 1 summarizes the isotope shipments for this period and Table 2 summarizes the customer inquiries that did not culminate in a sale, along with the reason. For example, some requested isotopes are presently producible but are not available year round. Some inquiries request isotopes that are not practical or possible to make at BLIP. Some requests are for isotopes that could be made at BLIP but would require extensive and expensive development effort. We also get requests for isotopes on the current distribution list but for minute quantities that do not justify the substantial cost of the production run. Finally, some inquiries are for information only, with no short term need at all.

11. How do you rate customer satisfaction for your site? For the overall program?

We feel that customers are satisfied with the quality and timely delivery of our products. In FY 1998 we received no complaints, and only one in FY1999. However, there is great dissatisfaction with the overall availability of our isotopes, due to very limited operating periods. We also sense general frustration with the overall DOE program as being unresponsive to the needs of the research community. The Office of Isotope Programs does put its major emphasis on larger volume routine isotope distribution, such as Sr-82 and Ge-68.

12&13. Kindly detail how you set the price of a mCi of a radioisotope? Illustrate with several examples.

The DOE Office of Isotope Programs sets isotope prices, not BNL. They no longer use a full cost recovery strategy, but rather price to market. Nevertheless, each production site does prepare detailed cost studies annually, both as a pricing guide and for budget development. The entire methodology we use, "Activity Based Costing", was mandated by DOE Office of Isotope Programs. The activities are: Target Fabrication, Irradiation, Hot Cell / Lab Maintenance, Chemical Processing, Waste Management, Quality Assurance, ESH and Regulatory Compliance, Production Packaging, Customer Sales & Service, and Program Management. The exact definitions of each were also provided by DOE. Each activity typically includes labor, materials and supplies. Some of the activities also include machine or glass shop costs, plant maintenance costs, computer support, and health physics support. No research or facility development costs are included in isotope production costs. Also, unused capacity is not charged to production activities but put in an unassigned category.

Each isotope requires each of the above activities, but to differing extent. We therefore have allocation formulas to apportion the costs. For example, we apportion the irradiation charge to a product by creating a cost per "slot hour". This is calculated by dividing the total annual cost of operating and maintaining the BLIP by the total anticipated number of operating hours and by the available number of target slots (12 typical). In FY 1999 this worked out to $10.67 per slot hour. The number of slots occupied by the target multiplied by the hours that target is to be irradiated is the irradiation cost for the product. Unassigned target slots are not charged to the product.

Hot cell costs are allocated by dividing the total operating and maintenance costs of the hot cell suite by the number of hot cells available in order to obtain an individual hot cell annual cost. This is then multiplied by the fraction of the hot cell space dedicated to a particular isotope and divided by the anticipated number of runs per year to obtain a per run hot cell cost. Similar strategies are used for all the other activities.

14&15. What process, mechanism, and organizational structure do you have for the timely distribution of your product? For customer service?

The initial contact by telephone, FAX or email for any user is with the Medical Department Isotope Production Office, which is staffed by an administrative secretary. Those radioisotopes with a half life less than one month, e.g. Cu-67, Sr-82, are not inventoried but are shipped as soon as produced. For these situations the irradiation and processing dates are prescheduled by the Program Manager, generally 3-4 months in advance. All known users are informed of the schedule by the group administrative secretary. Any other inquirers to the Isotope Production Office concerning these isotopes are given the schedule. Shipping, license, technical specification data and ordering information are also imparted. All required paperwork is sent to the Isotope Production Office. We then prepare the necessary internal documents for each shipment. Back up administrative staff from within the Medical Department is arranged as required so that we can always respond to customer inquiries or questions within 24 hours. Technical questions beyond the customer liaison staff member's expertise are referred to the Program Manager or in his absence the Staff Radiochemist or Hot Cell Processing Supervisor. The internal isotope order form is sent to the Hot Cell Processing Supervisor, who is responsible for preparing the bottle of radioactive liquid in a shipping pig. The pig is transferred to members of the Isotope and Special Materials Group (housed in the same building but not a part of the Medical Department), who prepare the final shipping package, the required documentation and arrange for pickup (we usually use Federal Express).

We try to maintain longer lived isotopes, e.g. Ge-68, Be-7, Zn-65, in inventory. Therefore, we fill orders for these isotopes as they come in throughout the year. The mechanism for customer contact is the same as for short lived isotopes. Typically, shipment is within 4 days of our receiving the required paperwork.

16. Will you sign contracts that guarantee delivery at the contracted time of delivery and where the contract has penalty clauses for non-timely delivery of specified product?

No. This is not feasible due to the lack of control over many of the required production resources, such as the accelerator and waste disposal schedules. Also, BNL research facilities are constantly being modified to experimental needs. This usually reduces overall reliability. However, the DOE Office of Isotope Programs can and does establish such contracts. There are several such contracts presently in place to deliver Sr-82 and Ge-68. Please note that in order to fulfill these contracts it requires the efforts of accelerators at BNL (BLIP), LANL (IPF), TRIUMF in Vancouver Canada, the National Accelerator Center in South Africa and the Institute of Nuclear Research in Troitsk, Russia. No one or even two institutions can pull it off. Table 3 summarizes the latest multi accelerator production matrix for Sr-82. This type of international effort is not feasible for shorter lived radioisotopes.

17. What should the long term role of government be in providing medical, commercial and research isotopes?

In our opinion the mission of government in providing isotopes and isotope related technology and products should concentrate on supporting and encouraging research. Government (in this case mostly DOE) should provide healthy, stable funding for R&D into new isotopes and isotope applications, and providing such isotopes to researchers. Isotopes whose production is routine should largely be a commercial function. Government can step in if the commercial sector cannot or will not (for example for "orphan" isotopes), or if commercial production capacity is inadequate to meet need. We suggest that the costs of operating and maintaining the very large infrastructure necessary for isotope production should be a government responsibility with core support, with research users bearing incremental, out of pocket production costs for labor, supplies, packaging, waste disposal etc. This is analogous to the model already practiced by DOE and NSF for physics and chemistry research at large accelerator or reactor facilities. Researchers at such facilities are responsible for building and operating their experimental equipment, but do not pay for beam.

Table 1. Production of Radionuclides

	FY 97		FY98		FY 99+	
Radionuclide	No. of Shipments	Amount (mCi)	No. of Shipments	Amount (mCi)	No. of Shipments	Amount (mCi)
Be-7	4	15	2	3	3	4
Cu-67	24	466	13	68	7	89
Ge-68	13	262	16*	1236*	12*	266*
Mg-28	1	.04	0	0	0	0
Sc-47	8	38	0	0	0	0
Sn-117m	0	0	3	145	0	0
Sr-82	4	3950	4	3150	4	4673
Zn-65	0	0	0	0	1	50

* Includes transfer to LANL to fulfill DOE contract
+ To date

Table 2. Inquiries Not resulting in Sale

Isotope	Inquiries	Reason*
Ag-105	1	c
Ag-110	1	b
Ar-39	2	b
As-72	1	d
Au-195	4	c
Au-198	1	b
Au-199	1	b
B-11	1	b
Be-10	1	b
Be-7	7	d(6),e
Ca-47	2	b
Ca-44	1	b
Ca-48	1	b
Ce-144	1	c
Co-55	1	d
Co-57	2	b
Co-58	2	b
Co-60	1	b
Cu-64	8	D(6), a(2)
Cu-67	33	a(18), d(15)
Fe-52	2	e
Fe-55	1	b
Fe-59	1	b
Ga-66	1	d
Gd-153	1	b
Ge-68	19	d(18), a
I-123	1	d
I-124	1	b
I-125	1	b
In-113m	1	b
Kr-85	1	b
Mg-28	7	e(4), d(2), b

Isotope	Inquiries	Reason*
Mn-53	1	b
Mn-54	1	b
Ni-56	2	d, c
O-16-18	1	b
P-32	1	b
Pb-203	2	c
Pb-212	1	b
Pt-193m	2	c
Pt-195m	1	c
Ra-226	1	b
Ru-106	1	b
Sb-124	1	b
Sc-47	1	d
Si-32	1	d
Sm-153	1	b
Sr-82	4	d
Sr-89	1	b
Sr-90	2	b
Tc-94m	1	d
Tc-95m	6	d(4), e(2)
Tc-96	3	e(2), d
Tc-97	2	b
U-235	1	b
V-49	2	b
W-188	1	b
Xe-127	2	c
Y-86	1	c
Y-87	1	c
Y-90	1	b
Zn-65	2	d
Zr-95	1	b

a = BLIP not operating
b = Not practical at BLIP
c = New isotope, large development required
d = Information request only
e = Can't meet minimum order

Table 3. Sr-82 Production Matrix

(4/21/99 rev)

Squibb/Nycomed Delivery Date	Accelerators Operating	BNL (mCi)	LANL (mCi)	INR (mCi)	NAC (mCi)	TRIUMF (mCi)
1/12/99	B,T		400			1200
2/9/99	B,I,T					1600
2/24/99 Nycomed	B,I,N,T		516		500	1100
3/10/99 Nycomed	I,N,T	516				1600
3/17/99 Nycomed	I,N,T	516				1600
3/24/99 Nycomed	I,N,T	516			500	1100
3/9/99	I,N	600		1000		
4/6/99	I,N		200	900	500	
5/4/99	I,N			1150	650	
6/1/99	I,N			1000	650	
6/29/99	N,T					1600
7/27/99	N,T					1600
8/24/99	N,T					1600
9/21/99	I,N,T				1200	400
10/19/99	I,N			1200	500	
11/16/99	I,N,L,?			1200	500	
12/14/99	I,N,L?,T					1700
1/11/00	I,N,T					1700
2/8/00	I,N		1700			
3/7/00	I,N			1200	500	
4/4/00	B,N,I			1200	500	
5/2/00	B,N,I	1700				
5/30/00	B,N,I	1700				
Nycomed 6/29/00	B,N,I	1700				

Oak Ridge National Laboratory (ORNL) Site Visit

Site Visited May 12, 1999

1. Introduction

On May 12, 1999, a site visit to Oak Ridge National Laboratory (ORNL) was conducted. The team was composed of Sekazi Mtingwa, Ph.D., Site Team Leader, Morgan State University; Richard Reba, M.D., Robert Atcher, Ph.D., Los Alamos National Laboratory; and Ralph Bennett, Ph.D., Idaho National Engineering and Environmental Laboratory.

The purpose of the site visit was to conduct an in-depth review of ORNL's present and future capabilities to meet a substantial portion of the national need for a variety of radioisotopes for medical, research, and commercial applications.

To facilitate the visit, the NERAC Site Team electronically submitted a list of questions prior to the site visit to Jerry Klein, Ph.D., Manager of ORNL's Isotope Production and Distribution Program. Those questions and answers are attached.

Mission

The primary mission of ORNL's Isotope Production & Distribution Program is to produce and distribute to vendors a variety of stable and radioactive isotopes for medical, research, and commercial applications. To fulfill its mission, the program utilizes four main facilities: a set of thirty electromagnetic separators called Calutrons (**CAL**ifornia **U**niversity Cyclo**trons**), the High Flux Isotope Reactor (HFIR), the Radioisotope Development Laboratory (RDL) also called the Building 3047 Hot Cell Facility, and the Radiochemical Engineering Development Center (REDC) for the production of californium-252 and other transplutonium isotopes.

Facilities and Services

Calutrons

The Calutrons are located in what is called the Isotope Enrichment Facility (IEF). The Calutrons consist of 30 high-current mass spectrometers housed in individual tanks. However, the first eight tanks, the second eight tanks, the third eight tanks, and the final six tanks operate together and are referred to as segments. Although the Calutrons are presently in standby mode, when operating they are capable of enriching some 225 stable isotopes from approximately 50 multi-isotopic elements. The process of electromagnetic separation used by the Calutrons is applicable to many elements and all isotopes of a multi-isotopic element are enriched simultaneously. The facility is well suited to produce modest quantities of isotopes at high enrichments. In addition to enriching stable isotopes, IEF also provides a myriad of other services for customers, such as using chemical and high vacuum processing techniques to convert inventory materials to custom-order forms (such as metals and oxides) and shapes for direct application by customers.

HFIR

The High Flux Isotope Reactor is an 85 MW reactor, with one of its primary missions being to produce californium-252 and other transplutonium radioisotopes for medical, research, and commercial applications. Reaching the highest thermal-neutron flux (2.3×10^{15} neutrons / cm^2 - sec) in the world, the reactor is well-suited to provide irradiation of a variety of target materials. In addition, HFIR provides fast-neutron irradiation-damage studies and neutrons for neutron scattering experiments to reveal the structure and dynamics of a variety of substances of interest to solid-state physicists, chemists, biologists, and others. Some 200-400 researchers use the facility annually.

Some of the medical radioisotopes produced and distributed by HFIR, along with typical applications, are as follows:

Tungsten-188	Decays to rhenium-188 for treatment of cancer and rheumatoid arthritis
Yttrium-90	To radiolabel various molecules as cancer therapeutic agents
Copper-67	Cancer therapy and to label antibodies for cancer therapy
Iridium-192	Cancer therapy with sealed sources
Dysprosium-166	Decays to Holmium-166 which is used in cancer therapy
Holmium-166	Cancer therapy and to treat rheumatoid arthritis
Lutetium-177	Cancer therapy and to label antibodies for cancer therapy
Rhenium-186	Bone cancer therapeutic agent and to radiolabel various molecules as cancer therapeutic agents; also used to treat rheumatoid arthritis
Tin-117m	Treatment without marrow toxicity of pain due to metastatic bone cancer

In the above isotopes, rhenium-188, yttrium-90, copper-67, holmium-166, lutetium-177, rhenium-186, and tin-117m are all recommended for production by the DOE Expert Panel Report. [1]

Radioisotope Development Laboratory

The Radioisotope Development Laboratory (RDL) in the Chemical Technology Division at ORNL is a hot cell facility located in Building 3047. It houses four b-g hot cells and one a hot cell. In addition, the RDL utilizes a variety of radiochemical analytical tools, including a gamma spectroscopy system, a beta liquid scintillation counter, an a spectrometer system, and a new ion chromatography system.

Radiochemical Engineering Development Center

Working closely with nearby HFIR, the Radiochemical Engineering Development Center (REDC) in the Chemical Technology Division at ORNL is the production, storage, and distribution center for transplutonium elements, such as californium-252, in the United States. It provides selected radioisotopes and related technical services to customers involved in medical, research, and commercial applications of radioisotopes. In addition, the REDC houses the Californium User Facility (CUF) for Neutron Science. californium-252 is an intense neutron source, and thus can substitute for a neutron-emitting reactor when a low neutron flux is adequate for any application. At the CUF, researchers can irradiate their samples with californium-252 neutrons in uncontaminated hot cells.

Brief History

Calutrons

The Calutrons were constructed in the 1940s for the enrichment of uranium-235 and later converted for the separation of stable and actinide isotopes. Presently, they are in standby mode, apparently scheduled to be permanently shutdown. More modern and possibly cost-effective techniques, such as utilizing plasmas for isotope separation, are being considered by the Department of Energy. At present, ORNL has in its inventory up to $300 M of stable isotopes left over from the days of Calutron operations. However, several isotopes, such as Ru-96 and Hg-202, are either in short or zero supply.

HFIR

The status of the transuranium production program was critically reviewed by the U.S. Atomic Energy Commission (AEC) Division of Research at a meeting on January 17, 1958. At that time the AEC decided to embark on a program designed to meet the anticipated needs for transuranium isotopes by undertaking certain irradiations in existing reactors. By late 1958 it became apparent that acceleration of this program was desirable. Following a meeting in Washington, D.C., on November 24, 1958, the AEC recommended that a high-flux reactor be designed, built, and operated at ORNL, with construction to start in FY 1961.

As a result of this decision ORNL submitted a proposal to the AEC in March 1959. Authorization to proceed with the design of a high-flux reactor was received in July 1959. The preliminary conceptual design of the reactor was based on the “flux trap” principle, in which the reactor core consists of an annular region of fuel surrounding an unfueled moderating region or “island.” Such a configuration permits fast neutrons leaking from the fuel to be moderated in the island and thus produces a region of very high thermal-neutron flux at the center of the island. This reservoir of thermalized neutrons is “trapped” within the reactor, making it available for isotope production. The large flux of neutrons in the reflector outside the fuel of such a reactor may be tapped by extending empty “beam” tubes into the reflector, thus allowing neutrons to be beamed into experiments outside the reactor shielding. Finally, a variety of holes in the reflector may be provided in which to irradiate materials for later retrieval.

In June 1961, preliminary construction activity was started at the site. In early 1965, with construction complete, final hydraulic and mechanical testing began. Criticality was achieved on August 25, 1965. The low-power testing program was completed in January 1966, and operation cycles at 20, 50, 75, 90, and 100 MW began.

From the time it attained its design power of 100 MW in September 1966, a little over 5 years from the beginning of its construction, until it was temporarily shut down in late 1986, the HFIR achieved a record of operation time unsurpassed by any other reactor in the United States. By December 1973, it had completed its 100th fuel cycle, approximately 23 days each.

Notable accomplishments resulting from HFIR operation include the production of californium-252, which is used for reactor startup sources, scanners for measuring the fissile content of fuel rods, neutron activation analysis, and fissile isotope safeguards measuring systems. In addition, californium-252 is used as a medical isotope to treat several types of cancer. Also, neutron activation analysis at HFIR has been used by the semiconductor industry, environmental remediation operations, and the Food and Drug Administration.

Radioisotope Development Laboratory

The Radioisotope Development Laboratory was built in 1962 for research and development involving beta and gamma-emitting radioisotopes. Subsequently, the necessity of working with alpha-emitting radioisotopes led to the construction of a water-shielded alpha facility for studying and performing research on transuranic elements.

Radiochemical Engineering Development Center

The REDC and neighboring HFIR began operations in 1966 to produce transplutonium elements for use in research. Since then, the REDC has been the main center of production for transplutonium elements in the United States.

Target rods containing principally curium oxide are remotely fabricated at the REDC, irradiated in the HFIR, and then processed at the REDC for the separation and purification of the heavy actinide elements. All elements from plutonium through fermium are separated and purified. Portions of the americium and curium are refabricated into targets for additional irradiations. The berkelium, californium, einsteinium and fermium are distributed to researchers.

2. Relationship to DOE Programs

DOE Office of Isotope Programs (IP)

ORNL's Isotope Production & Distribution Program is operated under the auspices of DOE's Office of Nuclear Energy, Science & Technology. However, parts of the financial support for the program's activities come from other sources, such as DOE's Office of Science and its Office of Defense Programs. As for the prices of isotopes distributed by the program, DOE's Office of Isotope Programs (IP) sets the prices, not ORNL. For more details see Questions 12 & 13, attached.

3. Relationship to Academic Programs and Training

Although ORNL's Isotope Production & Distribution Program recently hosted a postdoctoral research associate from the University of Tennessee and two graduate students who received their Master's degrees from Rice University, the site team was concerned that insufficient academic training opportunities exist within the program. While part of the reason may have to do with the need for extensive radiation safety training and particularly funding limitations, there is general agreement that the future of the field is being jeopardized by the low numbers of new personnel being trained in the experimental methods of radiochemistry.

4. Current Isotope Production

Since the Calutrons are in standby mode, no stable isotopes currently are being enriched. However, inventory still includes some $300 M of stable isotopes left over from prior Calutron operations. The continued shutdown of the Calutrons and any interruption in the Russian supply from Sverdlovsk could lead to a shortage of targets for radioisotope production at both reactors and accelerators.

The only facility presently available for isotope production at ORNL is the High Flux Isotope Reactor.

Throughput

ORNL's Isotope Production and Research Program keeps a careful log of all inquiries by potential customers interested in purchasing isotopes. This is done regardless of whether the inquiries come into the main distribution office or are made to individual members of the program. Radioisotope orders may not be filled if the order is not large enough to be practical to the customer. However, stable isotope orders always are filled, no matter what the size. Shipments of all isotopes are coordinated through the Lockheed Martin Energy Research Corporation's shipping department.

Customers

The customer base is composed of entities, both private and public, that have a need for stable or radioactive isotopes for medical, research, or commercial applications.

Research & Development (R&D)

Presently, no R&D activities are associated with the Calutrons. As for HFIR, it was designed to produce transplutonium isotopes, including curium-244, berkelium-249, californium-252, einsteinium-253, and fermium-257. Even though only small quantities are produced annually, they have been used to study the chemical and physical properties of transcurium isotopes, as well as to provide target materials for the production of still heavier isotopes in accelerators. Other medical isotopes produced at HFIR are listed above.

Cf-252 has been used extensively for medical, defense, and industrials applications, including the treatment of cervical and uterine cancers, neutron radiography of aircraft for the Air Force, and as the industry standard for a neutron source in the start-up or restart of nuclear reactors. As for cancer therapy, over 2000 patients have been treated with Cf-252 neutron brachytherapy. For cervical and uterine cancer, the overall results are impressive with a 75% 5-year survival rate for otherwise fatal cases of those cancers.

Limited funds have been used to develop radiochemical separation and purification procedures for radioisotopes produced at HFIR. The program at ORNL has been limited in its ability to expand operations by limited funds. For example, Th-229 supplies needed for production of Ac-225 are available in stores of U-233 on site. Limited funds have been made available for separating the Th-229 from the U-233, although this has somewhat limited the amount of Ac-225 that can be produced for existing customers. In addition, customers who need Ra-224 generators also have not been served due to the lack of funds to establish operations.

5. Future Capabilities and Resource Requirements

Continued Operation

A number of improvements to the Calutron facility have been implemented in recent years. The staff believes that, with the improvements and spare parts currently available, the Calutrons could continue to operate for some time to come. As for HFIR, it is in good operating condition.

Expanded Operations or Services—Underway

For the Calutrons, current or just completed upgrades include a new roof, emergency generator, a 13.8 kV switch gear, and a 50 megawatt transformer. [For more details, see Question 1, attached] However, there are no plans to expand the operations, or operate at all, at this time.

At HFIR, the recent addition of 42 new Peripheral Target Positions have dramatically increased its isotope production capabilities.

Expanded Operations or Services—Proposed

The staff needed to operate the Calutrons includes 5 facility and compliance, 4 chemistry, 4 isotope distribution, and 3 IRML staff, for a total of 16 FTEs. Standby costs are $3.6M per year, with the option of operating one segment estimated to require $5.2M, and two segments estimated at $6.2M per year (see detail in Section VI). Sales of existing stocks are currently about $2.4M per year. A Commerce Business Daily (CBD) announcement for expressions of interest in privatization of the Calutrons was released in May, and responses are due in June. DOE has initiated a study by an outside consultant to investigate possible replacement technologies for enriching stable isotopes. Also, DOE has signed an agreement with Theragenics, Inc., for their exclusive use of the existing Plasma Separation Process equipment. Their intent is to use this equipment to produce enriched Pd-102 with subsequent HFIR irradiation to supply Pd-103 for use as brachytherapy sources.

Major upgrades are planned for HFIR during the year 2000, including a beryllium reflector change. The upgrades should increase the availability from the current 64% to 65-70% while maintaining the reliability at the current 100%. The joint venture with Theragenics, Inc., to produce palladium-103 should lead to the establishment of 16 new removable hydraulic target positions. Although the HFIR upgrades will lead to a 6-8 month interruption in isotope production, they should insure the soundness of the facility for isotope production for the next 25-30 years.

6. General Issues

Institutional Support

The ORNL management has a history of strongly supporting its radioisotope production and distribution activities. However, the Site Team has concerns about support for R&D on new research isotopes, since there is not much discretionary funding awarded to this activity at ORNL. While there are some opportunities for Laboratory Directed R&D (LDRD) support, there needs to be R&D support from external sources.

Marketing

Users of radioisotopes know that ORNL is one of the limited sources from which to obtain both stable isotopes and reactor-produced radioactive isotopes. Therefore, prospective purchasers make inquiries to the ORNL Isotope Distribution Office or directly to the staff. As mentioned previously, all such inquiries are tracked from the initial time of contact to the final distribution, or non-distribution, of the requested isotopes. It frequently takes about one month to fill a customer order for radioisotopes due to the unique studies that often are needed to formulate a response. However, an initial reply to the customer's inquiry is made within several days. Moreover, off-the-shelf stable isotopes are shipped to the customer within several days.

Waste Management

Waste management at ORNL is conducted in accordance with existing government regulations. However, costs for waste management are not a major component in ORNL's radioisotope pricing, since the hot cell facility charge for Building 3047 includes a waste collection system that reduces waste costs charged specifically to radioisotope products.

7. Summary Comments

ORNL has two major facilities for producing isotopes: the Calutrons, which are capable of enriching most stable isotopes of Z equal to about 12 and higher; and the High Flux Isotope Reactor, which is designed to produce radioactive transplutonium isotopes. In lieu of permanently shutting down the Calutrons, the ORNL staff estimates that it could operate on a part-time basis for about $4 M per year. Full-time operation of one segment of the Calutrons would cost approximately $5.2 M. This would include the recommissioning of one Calutron segment, or eight isotope enrichment spectrometers. An additional segment could be recommissioned for an extra $1 M. While they enrich stable isotopes, other options of enriching the isotopes, such as the plasma separation technique, could undergo more research and development. As for HFIR, the upgrades to be performed in the year 2000 will increase the thermal core flux to 2.2 to perhaps 3.5×10^{15} neutrons / cm^2 -sec. Finally, the hot cell facility requires about $1.5 M per year to operate and $0.5 M per year for 3 years to upgrade.

ORNL currently is selling about $2.4 M of isotopes annually. There is some indication of a future shortage of stable isotopes that could be used as reactor or accelerator targets for the production of other isotopes. To date, these isotopes have been available from foreign sources. The long-term availability and reliability of these sources is unclear. Current stable isotope inventory at ORNL stands at a net worth of about $300M. It may be wise to investigate whether the physical security of those isotopes needs improvement. However, with the internal organizational controls and the location of the inventory within the Y-12 Exclusion Area, ORNL believes that the physical security of the stable isotope inventory is more than adequate.

The current focus of ORNL's Isotope Production and Distribution Program has been on providing commercial needs with little attention paid to research isotopes. No development for the production of new research isotopes has been performed other than, on occasion, to provide a cost-estimate to DOE Headquarters. The ORNL facility is a deteriorating infrastructure in maintaining a development expertise in isotope production, chemistry, and source fabrication and recovery. The Site Team is concerned about the present and especially future lack of trained personnel in this field. In most instances, staff is only one deep and many of those staff are close to retirement.

A prominent complaint of the ORNL staff is that sufficient resources often are not available to allow ORNL to respond adequately to customer inquiries, especially those that require development activities. They also feel that too much reporting and documentation is required by DOE Headquarters. They estimate that one man-year of effort is required to comply with DOE Headquarters reporting requirements.

The status of stable isotope enrichment in the United States is at a crossroads. The Calutrons could be recommissioned, even at partial capacity, while other enrichment techniques are being studied, or the Calutrons could be shutdown permanently while a new alternative is explored. Since the inventory of certain stable isotopes has become exhausted, vendors have to purchase them from Russia. It is important to note that, even with current inventory, Russian prices are cheaper. Thus, DOE has to come to a decision soon as to the future of stable isotope enrichment in the United States.

[1] Expert Panel: Forecast Future Demand for Medical Isotopes, Appendix D, March 1999. http:/www.NE.doe.gov/nerac/isotopedemand.pdf

Oak Ridge National Laboratory (ORNL)

Question and Answers

How well does DOE's existing five-site production infrastructure serve the current need for medical, commercial and research isotopes?

1. **What is the physical condition of your isotope processing facilities and equipment?**

Isotope production facilities located at ORNL include the electromagnetic separators (calutrons), the High Flux Isotope Reactor (HFIR), the Building 3047 Hot Cell Facility, and the Radiochemical Engineering Development Center (REDC) for the production of Californium-252 and other transplutonium isotopes.

The calutrons are presently scheduled for abandonment, but are currently in good operating condition for a fifty year old facility. Many of the Calutron support systems have been replaced in recent years including: mechanical vacuum pumps, oil diffusion pumps, Z-Oil circulating pumps, demineralized water pumps, Z-Oil reclaiming system, vacuum oil reclaiming system, Z-Oil head tank, cooling tower, and demineralized water heat exchangers. Completed within the last year or currently in progress are: new roof, emergency generator, 13.8 kV switch gear, 50 mega-watt transformer and refurbishment of the Isotope Research Materials Laboratory which includes new ceiling and windows. A more than adequate supply of spare parts has been maintained, but recent decisions by DOE / HQ / NE have resulted in the loss of key operating personnel.

The HFIR is in good operating condition. The HFIR will be temporarily out of operation for about 6 months in the year 2000 for a beryllium reflector change and other modifications which will increase the radioisotope production capabilities and provide the foundation for operation for at least another 30 year period. The recent installation of 42 new Peripheral Target Positions (PTP) have dramatically increased the production capabilities of the HFIR and medical and other radioisotopes - Tungsten-188 / Rhenium-188 being a prime example. Theragenics Inc., as part of a recently announced venture to produce Pd-103 in Oak Ridge, has stated their intention of installing two new Hydraulic Tubes (HT) in the HFIR. These tubes, when not being used for palladium irradiations, will add an additional 16 removable target positions. The HFIR does requires close attention by management with regards to scheduling and maintenance in order to achieve reliable operation. This has not always occurred in the past, but during FY 1999 HFIR has achieved an availability of 64% and a predictability / reliability performance indicator of 1.

The Building 3047 Hot Cell Facility (4 beta / gamma cells, 1 alpha cell) is required for the processing, and packaging for the majority of the radioisotopes produced at ORNL. The facility requires and will continue to require periodic upgrades to maintain its operability. Currently modifications / upgrades are underway on two of the building's 5 hot cells (Cell D and the alpha cell). Cell C and possibly Cell A will need to be upgraded within the next year.

The REDC is in very good operating condition. It is jointly funded by DOE / DP and DOE / SC. DOE / NE only contribution relates to the production of Cf-252.

2. **What capital investments are needed to assure the near term operability of your facilities?**

Based on recent decisions from DOE / HQ continued production of stable isotopes will depend upon the future investment in an alternative facility for their production. The type of facility, necessary capital investment, and realized production output have yet to be determined. No capital investments are required to assure near term operability of the current Calutron facility.

$1 million would purchase and install three or four small hot cells which would be perfect for many HFIR produced research radioisotopes, especially for the beta-emitting and alpha-emitting isotopes, and would have the distinct advantage of minimizing cross contamination.

3. **If additional resources are needed, are they practical, e.g., technically rational, easily integrated into existing infrastructure, quickly implemented and supportable? Will any portion be sustainable over time by local financial and personnel resources?**

The technical rational for acquiring an alternative method for the production of stable isotopes that is flexible (capable of separating a wide range of isotopes), is capable of producing milligram quantities of isotopes annually (as opposed to microgram quantities), and can be acquired and operated at a reasonable cost remains to be determined. The infrastructure, both facilities and personnel, currently exist at ORNL, but are eroding due to a lack of support from the national program. There is no mechanism for providing local financial and personnel resources.

Additional small hot cells for the production of a wide variety of medical radioisotopes are readily obtainable and can easily be incorporated into the existing infrastructure.

4. **What is the availability of your primary nuclear facility (accelerator or reactor) over the next five years, e.g., operational outages and program changes?**

The calutrons are currently in a cold shut down mode with no intention of restarting.

The HFIR will be implementing a major planned upgrade program in the year 2000. This will preclude the production of reactor produced radioisotopes for a 6-8 month period in that year. However, the major upgrades to the HFIR will insure that this resource will be able to operate and fulfill an important role in radioisotope production for at least another 25-30 years.

5. **What understanding exists at your site about the priority of isotope production to serve isotope customers?**

Although it is the stated intention of ORNL management to serve the many and varied isotope customers, the HFIR is operated by DOE/SC and as such its first priority is meeting the needs of the high-energy research community it serves. For the calutrons, the emphasis appears to be, not on isotope production, but on cost recovery.

6. **How much influence do you as site manager have in planning the use of multi-purpose facilities?**

As ORNL Isotope Program site manager, I have little influence in the use of the multi-purpose facilities. For the HFIR, schedules and proposed maintenance items are communicated to the Isotope Office, but we have little control over these items. In a few specific areas, such as use of some of the HFIR target positions, the Isotope Program has considerably more influence. Our design, planning, and installation of the new PTP units is an excellent example of the influence that the Isotope Program can have and how we can work effectively with multi-purpose facilities.

7. **What cost-containment measures are being pursued?**

In the recent past the stable isotope inventory, the Isotope Distribution Office, and the Isotope Research Materials Laboratory were consolidated under one roof at the Calutron facility to achieve a more efficient utilization of personnel and to minimize overhead and administrative costs. In order to contain further costs, the calutrons have been placed in cold shutdown and a number of staff terminated or reassigned to other positions. A number of research projects have been eliminated or scaled back.

8. **What "licensing" issues need to be addressed?**

A number of licensing items have been considered recently. Over the last few years, these have included licensing of Mo-99 / Tc-99m and W-188 / Re-188 concentrators, exclusive rights to pursue In-111 technology, and the transfer of Plasma Separation Technology to a private firm, the privatization of iridium targets (for the production of Ir-192). Stable isotope production, sales and distribution are currently being evaluated for privatization.

9. **What unused or underused capacity, e.g., personnel, facilities, could be mobilized to support a growth in isotope demand?**

ORNL currently has unused or underused capacity in terms of facilities, but not in terms of personnel. The existing calutrons could support a very large increase in the production of stable isotopes if an immediate decision would be made to reverse the recent decisions to shutdown the calutron facility. Personnel are being lost, but for the immediate future the facility remains in an operable condition. The HFIR and Building 3047 hot cells have a considerable amount of remaining capacity. A number of other facilities, including additional hot cells, have been shutdown, but could be resurrected if the need required.

10. **Summarize customer inquiries received during the past two years. What per cent was filled, referred to other facilities, rejected?**

A variety of requests for quotation are received during the fiscal year ranging form off-the-shelf inventory stock to customized fabrications and conversions. For the fiscal years 1997 and 1998, the number of quotations processed were 829 and 734 respectively. For the first six months of fiscal year 1999, there have been 376 quotations processed. These numbers do not include informal phone quotations that are received daily. Of the formally documented quotations, approximately 30% result in orders. Referrals to other DOE facilities are seldom necessary since the Web site and published catalog give the site location and contact point for each product offered. ORNL is currently the only site offering stable and reactor produced isotopes among the DOE facilities.

11. How do you rate customer satisfaction for your site? For the overall program?

No formal mechanism exists for rating customer satisfaction for ORNL's service within the Isotope Program. ORNL has no way of knowing the customer satisfaction rating for the overall program. Anecdotal feedback would indicate that most customers would like lower costs, increased availability, and guaranteed reliability. The quality of ORNL's products has generally been considered of high quality.

12. Kindly detail how you set the price of a mCi of a radioisotope? The detail should show if the cost is fully loaded or incremental, and should include labor, materials and parts, facility rental and amortization costs, listing of all the actual overhead charges, waste disposal (a major cost), and all other costs that are tagged to the cost of producing, marketing, selling, and distributing of the product (e.g., customer service, distribution, ordering).

DOE / IPDP sets radioisotope prices based in part on ORNL price recommendations which are based on an analysis of expected costs incurred to produce the subject radioisotope at the required production level plus an allocation of other necessary business expenses of the program (Isotope Sales Office / DOE Added Factor). The structure for these studies is based on the established DOE / NE IPDP Budget and Reporting Codes for radioisotope production cost reporting. Projected costs are categorized as:

Category	Budget and Reporting Code
Target Fabrication/Purchase	ST0101010
Target Irradiation	ST0101020
Hot Cell Operations	ST0101030
Processing	ST0101040
Waste Management	ST0101050
Quality Assurance	ST0101060
ES&H Regulatory Compliance	ST0101070
Production Packaging	ST0101080
Program Management	ST0101090

Each category is estimated using the current rates for direct labor, site services, and material purchases. Applicable ORNL overhead is shown separately for each cost item.

<u>Target Fabrication / Purchase:</u> The specific cost for purchase of feed material (target) or site fabrication of the required target to produce specified quantity of radioisotope product is included in the product estimate.

<u>Irradiate Targets:</u> ORNL radioisotopes are irradiated in ORNL's High Flux Isotope Reactor (HFIR). Based on the position and number of cycles, irradiation costs are estimated using current pricing list for use of HFIR services.

<u>Hot Cell Operations:</u> The ORNL IPDP is responsible for the facility operation and maintenance costs for Hot Cell Building 3047 which is used for the processing of radioisotopes. In order to allocate the cost of this facility to the radioisotope products produced, the annual operating / maintenance costs is forecast and divided by the expected available hot cell hours yielding a "hot cell rate". The projected cost per hot cell hour is then used for product price studies to estimate the portion of hot cell operations costs to be assigned to the product. Currently, ORNL does not include amortization for any "unassigned" operating / maintenance costs or facility upgrades for Building 3047 in radioisotope price studies.

<u>Processing:</u> The estimated effort needed to process / analyze irradiated material and place into shipping container based on customer request is included in this category.

<u>Waste Management:</u> Costs for waste disposal directly related to the production of the specified radioisotope are included in this category. Generally, waste management costs are not a major component in ORNL radioisotope price studies due to the fact that the hot cell facility charge for Building 3047 includes a waste collection system which reduces waste costs charged specifically to radioisotope products.

<u>Quality Assurance:</u> The estimated effort from QA personnel to meet quality standards is included in this category.

<u>ES&H Regulatory Compliance & Safety:</u> The estimated effort from Health Physics personnel necessary to meet ES&H regulations in included in this category.

<u>Production Packaging:</u> The estimated effort for "custom" packaging per customer request (prior to placing into shipping container) is included in this category. Routine placing of completed product into

shipping container is normally included above as processing effort. Final labeling, packaging and shipping costs are included below in the added factor for packing and shipping.

Program Management: The estimated effort required by the project manager to coordinate and supervise activities throughout the production process is included in this category.

Total of Cost of Production: Total of all direct charged categories which will be recorded as cost of goods manufactured in the accounting system.

Added Factor for Isotope Sales Office: In order to recover the indirect cost of the Isotope Sales Office, a predetermined percentage of total production cost (currently 6.5%) is included in the price study.

Added Factor for DOE Cost Recovery: In order to recover other DOE indirect costs, a predetermined percentage of total production cost (currently 3.0%) is included in the price study.

Addition for Final Packaging and Shipping: In order to recover the cost of final labeling, packaging and shipping, an addition based on the number of shipping containers is included in the price.

13. Where applicable to your facility, please illustrate the above question for the following radioisotopes: In-11, P-32, I-123, I-125, and several research radioisotopes.

Answer combined with the response to Question 12.

14. What process, mechanism, and organizational structure do you have for the timely distribution of your product?

ORNL is a multi-faceted research organization. As such, few employees are dedicated solely to the production and distribution of isotopes. However, the Isotope Distribution Office does maintain four full-time employees to handle all customer quotations, customer contracts, shipping documentation, and customer invoices. In addition, for EM-Stable isotopes, there are personnel assigned in the loading facility, the chemistry laboratory, and in the special conversions and fabrication areas. These employees are generally cross trained for other assumable duties should some personnel be not available. The EM-Stable isotope production and the entire isotope distribution functions are ISO 9000 certified. For radioisotope production, the program does sponsor the building 3047 hot-cells. Production of the different isotopes, however, crosses divisional lines. Shipments of all isotopes products are coordinated through the Lockheed Martin Energy Research Corporation's shipping department.

15. What process, mechanism, and organizational structure do you have for customer service?

With the ISO 9000 certification, a formal customer structure and resolution procedure exists. This procedure is used by the Isotope Distribution Office for both stable and radioactive isotopes.

16. Will you sign contracts that guarantee delivery at the contracted time of delivery and where the contract has penalty clauses for non-timely delivery of the specified product?

As a DOE facility, I do not believe that we are allowed to sign contracts that contain penalty clauses for the non-timely delivery of product. This option, if possible, can only be negotiated with the concurrence of DOE.

17. What should be the long-term role of government in providing medical, commercial and research isotopes?

The long-term role of government (U.S. DOE) should be related to the providing of the necessary infrastructure and support necessary to produce those isotopes (stable and radio) that are required by the medical, commercial, and research communities. For commercial isotopes this role should be limited to the infrastructure that is either impossible or very difficult for industry to provide (i.e. reactors). Other support should only be provided on a full cost recovery basis. For medical isotopes, institutional decisions will need to be made as to whether this support should be full cost recovery (even if the decision means the medical application may be too expensive to provide) or if the support should be subsidized (as should be for research isotopes). The Isotope Program cannot be operated in a true business sense, since the program's requirements and constraints are different than that of a private entity.

Los Alamos National Laboratory (LANL) Site Visit

Site Visited May 17, 1999

1. Introduction

A site visit was conducted at Los Alamos National Laboratory (LANL) on May 17, 1999. Site visitors were Dr. Ralph Bennett, Idaho National Engineering and Environmental Laboratory, Dr. Henry Kramer, consultant, and Dr. Richard Reba, University of Chicago. Mr. Gene Peterson acted as host for the visit.

Mission

The mission of LANL with regard to isotope production is primarily as a source of accelerator-produced radioisotopes for medical research and commercial uses, with a variety of additional roles based on unique capabilities. The mission has primarily been derived from the longstanding capabilities of the high energy linear accelerator at the Los Alamos Neutron Science Center, as well as staff strengths in accelerator and target design, radiochemistry, and more recently, the life and physical sciences.

Facilities

The Los Alamos Neutron Science Center (LANSCE), is the cornerstone of isotope production at LANL. This 800 MeV, 1 mA linear accelerator has been operating for 25 years. It is capable of delivering beams of H^+, H^-, and polarized H^- ions. For many years, isotope production has been based on direct interactions with high-energy protons as well as a spallation reaction capability with up to 9 target stations. It is notable that the first section of the accelerator drives the beam to 100 MeV. The ability to divert a portion of the beam at this point affords the construction of an Isotope Production Facility (IPF) which is discussed below under Expanded Operations—Underway.

The TA-48 Hot Cell Facility is located at the Main Radiochemistry Site, about four miles from LANSCE. Within the facility is Building RC-1, which houses the primary hot cell facility for processing of accelerator targets. The facility consists of two banks of six hot cells, connected at one end by a large multipurpose "dispensary" cell into which materials are received or removed from the facility. Most of the cells are dedicated to various radioisotope production campaigns, with some capacity still available. There are about eight full time staff dedicated to radioisotope production. While other staff and technicians are located in the facility, they would need training to be available to support production. A number of the products are prepared under current good manufacturing practice (cGMP) protocols required by FDA regulation of the products and the facility. Supporting the facility are several radiochemistry laboratories, a machine shop, two analytical chemistry laboratories, a well-equipped counting room, and staff offices. The hot cell facility has recently received upgrades to its air handling system, bringing it to state-of-the-art, and a crane.

The Chemistry Metallurgical Research (CMR) building's Wing-9 hot cells are a complementary facility to the TA-48 hot cells. The Wing-9 hot cells are a Category 2 nuclear facility, available for work that requires such a safety authorization basis. The CMR is the site for high enriched uranium (HEU) target fabrication to support ^{99}Mo production at Sandia, for example. The facility could also process reactor-irradiated targets from the Annular Core Research Reactor (ACRR) facility at Sandia, excluding the ^{99}Mo targets. Currently the isotope program is installing an electromagnetic isotope separator in the CMR to be made available for the separation of radioactive isotopes.

Several important waste treatment and disposal facilities exist within LANL. The TA-50 Radioactive Liquid Waste Treatment Plant treats and disposes liquid effluents from isotope production activities. All such effluents are received by TA-50 via an acid waste line that connects from both TA-48 and CMR. The TA-54 Solid Radioactive Waste Disposal Site is used for storage and permanent disposal of low-level wastes. All wastes except mixed wastes are handled on site at LANL. It is important to note that the isotope production activities at LANL have been extensively engineered to produce no mixed wastes, making the isotope program self-contained from a waste treatment and disposal standpoint.

Products and Services

Overall, LANL produces about 160 shipments of radioisotopes per year. The range of isotopes that can be produced is found in Table 1. The number of these isotopes actually produced in any year is about half of those in the table, however. The isotopes with the largest demand are ^{68}Ge and ^{82}Sr, whose revenues give a considerable stimulus to the overall program at LANL. None of the radioisotopes supplied have very short half-lives, so the shipping time from the laboratory to the Albuquerque airport and on to customer sites has not been a factor.

The largest barrier to increased production is the lack of availability of irradiation time at LANSCE, stemming primarily from the limited time that the facility operates the beamline during the year. Recently the facility has operated only about 5–6 months per year. In an effort to increase radioisotope supply, LANL coordinates a Virtual Isotope Center (VIC) in collaboration with four other accelerator centers (described below under Business Practices). LANL's chief contribution to the VIC is the operation of its FDA-approved processes in the TA-48 hot cells, which affords high-quality processing and finishing of targets irradiated at other facilities in the Center.

Other products and services at LANL include (1) distribution of actinides, (2) unique electromagnetic separations at CMR, (3) fabrication of HEU Cintichem-style targets to support ^{99}Mo production at Sandia, and (4) recycle of ^{82}Sr generators. In recent years, actinide distribution amounts to sales of $240K per year, with the chief product being ^{241}Am. To provide electromagnetic separation of radioactive isotopes, a 1 m radius separator is being installed in a cell at CMR, and is capable of separating about 1 milligram per day. The primary motivation for the investment is the separation of Sr and P isotopes to improve product quality, and to improve specific activity of reactor-produced isotopes. Another use of this unique capability is planned to be separation of several fission product isotopes from the ^{99}Mo operations at Sandia. The limited capacity of the separator is actually well-matched to the required throughput of very small radioactive samples rather than large quantities of non-radioactive elements. Also in conjunction with Sandia is the fabrication of HEU targets for demonstration of the ^{99}Mo process. This involves the application of a thin layer of HEU inside a tubular Cintichem-style target. Recent funding for this activity has been about $800K per year, with plans for doubling this amount to support active production operations at Sandia. Recent decisions by DOE have redirected this activity, however, and the plans are to discontinue this work. A new service developed recently at TA-48 is the recycle of ^{82}Sr from Cardiogen (^{82}Sr / ^{82}Rb) generators that are routinely received in the facility from the generator customers. The service developed on the initiative of the hot cell staff, who recognized the value of the recycling and suggested it to the pharmaceutical manufacturer, who had independently developed the same idea. The recovery process is the subject of a joint patent between the manufacturer and LANL.

Table 1. Radioisotopes Historically Produced by LANSCE Irradiation

Radioisotope	Expert Panel Category	Half-life
^{26}Al	Not identified	720,000 y
^{105}Ag	Not identified	41 d
^{72}As	Not identified	1.1 d
^{73}As	Not identified	80 d
^{74}As	Not identified	18 d
^{7}Be	Not identified	53 d
^{207}Bi	Not identified	32 y
^{109}Cd	Not identified	1.3 y
^{77}Br	Not identified	2.4 d
^{67}Cu	3	2.6 d
^{146}Gd	Not identified	48 d
^{148}Gd	Not identified	75 y
^{68}Ge	3	270 d
^{172}Hf	Not identified	1.9 y
^{194}Hg	Not identified	520 y
^{163}Ho	Not identified	33 y
^{172}Lu	Not identified	6.7 d
^{173}Lu	Not identified	1.4 y
^{52}Mn	Not identified	5.6 d
^{22}Na	Not identified	2.6 y
^{83}Rb	Not identified	83 d
^{86}Rb	Not identified	19 d
^{44}Sc	Not identified	2.4 d
^{46}Sc	Not identified	84 d
^{72}Se	Not identified	8.4 d
^{75}Se	Not identified	120 d
^{32}Si	Not identified	104 y
^{145}Sm	Not identified	340 d
^{82}Sr	Not identified	26 d
^{179}Ta	Not identified	1.8 y
^{95m}Tc	Not identified	61 d
^{44}Ti	Not identified	44 y
^{48}V	Not identified	16 d
^{49}V	Not identified	330 d
^{127}Xe	2	36 d
^{88}Y	Not identified	110 d
^{65}Zn	Not identified	240 d
^{88}Zr	Not identified	83 d

2. Relationship to DOE Programs

DOE Office of Isotope Programs (IP)

Funding in recent years by the IP for activities at LANL have averaged between $4–5M per year. A projected breakdown is found in Table 2. The TA-48 hot cells are the only base funded facility. Activities at CMR are funded only on an incremental basis by IP since the facility is base funded by Defense Programs (DP). Also, there is a three-way sharing of operations costs at LANSCE, with isotope production being a very minor contributor in relation to the funds provided by DP and the Office of Science Programs (SC) in DOE. LANSCE operations require about $35M per year overall, of which isotope production contributes only a very small amount to cover facility charges and some incremental costs—the major contributor to LANSCE operations is DP, owing primarily to the very steady needs of the Stockpile Stewardship programs.

Table 2. FY-1999/2000 Funding Levels for LANL

Ta-48 Operations and Upgrades	$2.20M
LANSCE Irradiations	$0.8M
Process Development and Program Management	$0.75M
CMR ^{99}Mo Target Fabrication	$0.80M
Total	$4.55M

As stated above, there is a considerable influence of DP and SC on the management and funding of operations at LANSCE and influence of DP at CMR. In addition to normal operations at LANSCE, there is regular interaction between these programs and isotope production when accessing resources (especially during outages, when maintenance and upgrades need to be performed). To formalize these interactions as well as agreements that need to be reached on the construction, operation and equitable allocation of operational costs for the new Isotope Production Facility (IPF), a Memorandum of Understanding (MOU) between DP / SC / NE has been drafted and is expected to be finalized this summer.

3. Relationship to Academic Programs and Training

Isotope production activities at LANL enjoy a relatively close relationship with the School of Pharmacy at the University of New Mexico. Three members of the LANL staff are adjunct professors in Pharmacy. Also, LANL has close relations with several of the universities within the University of California, the management and operations contractor for LANL, including UC Santa Barbara and UC Davis. There are typically between one and three graduate students conducting research in this area at LANL, with occasional recruitment of summer interns. There are also several postdoctoral fellows on the staff with funding from the Office of Biological and Environmental Research (OBER). Unfortunately, the intense scrutiny on security practices at LANL in recent months has given rise to some concern about whether these levels of participation can continue, since it is expected that expansion of these programs will lead to strong interest in participation by foreign nationals.

4. Current Isotope Production

Throughput

In a typical year LANL will supply approximately 15 to 20 individual isotopes. Four of these isotopes (^{82}Sr, ^{68}Ge, ^{22}Na and ^{241}Am) provide the majority of the revenue, while the other 10 to 15 products are of interest to various research constituencies. As an example, in FY 1998 LANL provided 20 isotopes and generated $2.0 M from their sale.

Customers

Overall, LANL serves about 100 customers with 160 shipments of radioisotopes per year. Of these customers, about 70 are for research needs, and about 30 are commercial needs.

Pricing Policies

Pricing policies have been established and are reviewed yearly with IPDP staff. The new MOU for LANSCE management will consider the future allocation of costs for the IPF, and will have a considerable impact on the basis for cost recovery of isotopes. The current production of isotopes in the LANSCE beam dump is not burdened with any beamline operations costs, since the beam entering the dump is considered to be a by-product of operations. On the other hand, the future production of isotopes in the IPF is considered to use a direct fraction of the beamline, since its extraction reduces the beamline directly.

Product Development

The staff has recognized several dozen new research isotopes. They feel that the most immediate emerging need is for ^{127}Xe, as well as several isotopes of Pt and As. As a general rule, one can expect the development of targetry and processing for a new research isotope to require an effort of about six months.

5. Future Capabilities and Resource Requirements

Continued Operation

The stated goal of the LANSCE facility is to achieve eight months operation in each calendar year over the next five years. Much of the future outlook for radioisotope production at LANSCE depends upon the completion of the IPF, which is described in the next section. With regard to the existing target irradiation station, it is currently operational but needs to have additional H^+ users to share the cost of beam delivery. Recently, the largest user of H^+ ions was the Accelerator Production of Tritium (APT) program. APT offset much of the operational costs during the last three years, but has recently been set aside as the major option for tritium production by the DOE. The next major user of H^+ ions is likely to be the Accelerator Transmutation of Waste (ATW) program, although it is currently a much smaller program than APT and their plans are not yet formalized. Also, the existing target stations do not favor the production of short-lived isotopes, with the minimum irradiation time being seven days per target. This has been better addressed in the design of the IPF.

Expanded Operations or Services—Underway

A major new expansion of operations at LANSCE is underway with the design and construction of the Isotope Production Facility (IPF). The IPF is a 100 MeV, 250 mA irradiation facility that extracts 30 pulses per second from the main beamline with a kicker magnet. The extraction point is just after the first stage acceleration of the main beamline to 100 MeV. The IPF has a set of target irradiation stations and associated equipment for unloading and preparing targets for shipment to TA-48. The total cost of the IPF is projected to be $15.5M, to be funded by IP. The facility is nearing 50% design completion, and is expected to be online in FY-2001. There are felt to be no serious design or construction issues, although the available space in the existing beamline for the kicker magnet is quite limited.

When completed, the 100 MeV IPF will be capable of producing about 85% of the individual isotopes currently produced in the 800 MeV beam dump facility today. However, with the better match of energy for target reactions with a 100 MeV beam, the throughput of those isotopes is expected to increase by as much as 50%.

Expanded Operations or Services—Proposed

The most immediate interest in expanded services is the proposed use of one or more electromagnetic isotope separators within TA-48. Two mass spectrometers are available, both of which are base funded by NN programs and which have considerable excess availability. Both would be appropriate only for non-radioactive separations, unlike the unit being installed in the CMR. The small unit has a 1 m radius, and is capable of separating approximately 1 milligram per day. A larger unit, currently occupied by a physics experiment, has a 1.5 m radius and similar separation capacity. Base funding of the small building they are both located within requires only about $160K per year; the cost of separation campaigns would require additional funding. It was noted that after the initial setup, the machines may run largely unattended. A large campaign for separating Nd isotopes to supply a European stockpile of reference material (not associated with isotope production) is planned, which will occupy the smaller machine for several months.

Several other ideas for expansion of services were also identified. First, there has been some interest in the acquisition of a lower energy accelerator to be dedicated to the production of research isotopes, but plans are not firm. This concept was first developed as part of the Los Alamos response to the call for National Biomedical Tracer Facility (NBTF) proposals. Second, with excess capacity in the TA-48 hot cells and the CMR hot cells, there is some potential for teaming with reactor irradiation facilities and having targets sent to LANL for processing. Again, there are no firm commitments or plans, although discussions with Sandia are ongoing. Finally, there continues to be occasional interest in various partnership or commercialization agreements primarily focused on either the separation of light isotopes in the diffusion columns at LANL, or possibly in the development of accelerator technology and/or applications.

6. General Issues Related to Isotope Supply

Institutional Support

LANL management support for isotope production is very strong and is based on an appreciation of the value of having both isotope production and basic and applied research requiring isotopes at the laboratory. A major Outstanding Accomplishment Award by the laboratory management recognized the efforts to establish the Virtual Isotope Center last year, for example. Also, isotope production has been able to receive General Plant Projects funds on the order of $1M per year on a fairly regular basis, although this is not guaranteed from year to year. There are occasional awards of LDRD funds to projects developing radioisotope applications, although only a portion of the $100–300K funding per project benefits isotope production directly. An effort to define a major $1M support for radiochemistry from discretionary LANL funds is underway, and is expected to begin next fiscal year.

Marketing

LANL operates a modest marketing and sales organization responsible for the 160 orders shipped each year. The organization has two full time staff. While not highly computer automated, their operations are quite adequate to meet their needs. There is a considerable effort by the staff to solicit customer feedback and comments. There is also a plan in place, endorsed by DOE IP, to consolidate the sales and marketing functions for accelerator-isotopes at LANL. Transfer of these functions from Brookhaven National Laboratory (BNL) to LANL and communications to customers will be implemented by FY-2000. Also LANL will provide these functions for Sandia National Laboratory when they begin production operations using the ACRR.

Business Practices

The most important development of recent years in LANL's business practices is the formation of the Virtual Isotope Center (VIC). In concept, the VIC is a collaboration of a number of major accelerator facilities worldwide to collectively produce and process radioisotopes. In practice, radioisotopes that have been produced by the VIC are those needed by researchers in larger quantities and very steady supply—typically for clinical studies or early commercialization efforts.

Interest in the VIC began in the mid-1990s. With a shortage in the supply of ^{82}Sr looming in 1998, plans were finalized in 1997 and collaborative efforts successfully overcame the shortage. Today, the VIC includes the 800 MeV LANSCE at LANL, the 500 MeV main cyclotron at the Tri-University Meson Facility (TRIUMF) in Canada, the 400 MeV linear accelerator at the Institute for Nuclear Research (INR) in Russia, the 200 MeV accelerator at BNL in the U.S., and the 200 MeV cyclotron at the National Accelerator Center (NAC) in South Africa, as well as smaller accelerators and a variety of hot cells at these facilities. These institutions operate with a Memorandum of Agreement to coordinate their irradiation schedules as well as to choose locations for processing campaigns based on the availability of facilities and/or their regulatory approvals and capabilities. The VIC also encountered and solved a number of startup problems dealing with transportation, customs and regulatory issues.

The initial ^{82}Sr campaign culminated in 1998 with the manufacture of the first CardioGen® generators in the U.S. from Russian-irradiated Rb targets processed at LANL. At this time there are about a half-dozen current and planned campaigns for other radioisotopes, with most involving irradiation in Canada, South Africa or Russia followed by processing at LANL or BNL.

Waste Management

With the re-engineering of processes to eliminate the generation of mixed hazardous wastes, and the availability of the facilities to treat and dispose of liquid and solid wastes, the waste management operations at LANL are self-contained and unlikely to be affected by any interruptions or problems at other laboratories.

Los Alamos National Laboratory (LANL)

Questions and Answers

1. **How well does the Department's existing five site production infrastructure serve the current need for commercial and research isotopes?**

   The Los Alamos National Laboratory is one of four sites that produce and distribute stable and radioactive isotopes for the Department of Energy's Office of Isotope Programs in the Office of Nuclear Energy, Science, and Technology. At Los Alamos a variety of products and services are available. These include accelerator-produced isotopes utilizing the Los Alamos Neutron Science Center and the TA-48 main Radiochemistry Site hot cell facilities; chemical processing of reactor-irradiated targets utilizing the CMR wing 9 hot cell facilities; the isotopic separation of stable and radioactive elements using electromagnetic isotope separation techniques; and the distribution of inventories of americium-241 and other actinides. Products and services available from the Los Alamos Isotope Program fill an important niche in the overall worldwide market for isotopes, because they are typically not available elsewhere, or if they are available, they are not available in sufficient quantity to satisfy market demands. Also many of the products are in the earliest stages of research or development, and thus the user community cannot afford to pay the full production costs.

2. **What is the physical condition of the isotope processing facilities and equipment?**

   The Los Alamos Isotope Program currently uses the following facilities.

   The Los Alamos Neutron Science Center is the cornerstone of Los Alamos isotope production. Currently, targets are irradiated at the beam stop at LANSCE in a 25 year old irradiation facility. A new construction project funded by NE is building a new beam line and target irradiation facility that will be dedicated to isotope production. When this facility is operational in FY 2001, the isotope program will have access to 250 amps of 100 MeV protons for target irradiation. It is envisioned that the H+ beam will be available for isotope production any time the facility is operating in the H- mode (for neutron scattering). Also because the beam is only being accelerated to 100 MeV we could consider operation of the front end of the facility in a dedicated mode for isotope production if the isotope availability need required the operation.

   The TA-48 Hot Cell facility at the Main Radiochemistry Site, Building RC-1 is the primary hot cell facility for accelerator isotope production. It consists of two banks of 6 chemical processing cells connected at one end by a large multipurpose "dispensary" cell, where all materials are received into and which all materials leave from the facility. Supporting facilities including several radiochemistry laboratories, a machine shop, two analytical laboratories, an extensive counting room facility, and offices for personnel surrounds the hot cell facility.

   The CMR wing-9 hot cell facility is a complementary hot cell facility to the TA-48 hot cells. The wing-9 hot cells are located in a category 2 nuclear facility, and are available for work that requires a nuclear facility safety authorization basis. Currently the isotope program is installing an electromagnetic isotope separator in this facility for the separation of radioactive samples. The facility is also available for the chemical processing of reactor irradiated targets and will be used in conjunction with the ACRR reactor at Sandia to expand the Isotope Program portfolio of reactor products.

   The TA-50 Radioactive Liquid Waste Treatment Plant is used to treat and dispose of liquid effluents from isotope production activities. All such effluents are received by TA-50 from an acid waste line that connect both TA-48 and CMR to the facility.

   The TA-54 Solid Radioactive Waste Disposal Site is use for the storage and permanent disposal of low-level high activity waste and low-level low activity wastes. All wastes, except mixed wastes are handled on-site. Currently the isotope production activities generate no mixed waste, so the isotope program is totally self-contained at the Los Alamos site and is not dependent on off-site facilities for operations.

   In general these facilities are in good condition, and adequate for the isotope production and distribution function. However, funding for upgrades and preventative maintenance are in short supply, so the previous statement may not continue to be true in a five year time horizon.

3. **What capital investments are needed to insure the near term operability of the facilities?**

   DOE is currently funding the major capital investment required to continue isotope production at Los Alamos, the 100 MeV Isotope Production Facility at LANSCE. The TA-48 hot cell facility has recently undergone several upgrades funded by institutional funds, including a new state-of-the-art air handling system and a crane upgrade. Other upgrades required include an upgrade of the facility electrical systems and the facility hydraulic systems. The CMR hot cell facility is in the midst of significant upgrades funded by Defense Programs.

4. **If additional resources are needed, are they practical, e.g., technically rational, easily integrated into existing infrastructure, quickly implemented and supportable? Will any portion be sustainable over time by local financial and personnel resources.**

   The near term resources required are practical given the extensive infrastructure for isotope production that is currently in place. They are technically feasible at reasonable cost, and can be accomplished quickly if the resources are available. We have been very successful in the past at gaining institutional funds for infrastructure upgrades, but as with all things, these funds are becoming scarce and more difficult to justify.

   One area that could be profitably developed with additional resources over and above the investments that the DOE Isotope Program is already making at Los Alamos is in the area of stable isotope enrichment. DOE is already investing in the development of a radioactive sample isotope separator based on technology developed at Los Alamos for national security programs. Existing isotope separators at Los Alamos already have the capability to separate milligram quantities of stable isotopes that could be used for research purposes. With modernization (computer control and other improvements) and with sufficient operating funds the Los Alamos electromagnetic isotope separators could fill an important need for research quantities of important stable isotope products. This possibility is currently being evaluated by the DOE Isotope Program.

5. **What is the availability of the primary nuclear facility (accelerator or reactor) over the next five years?**

   LANSCE management's stated goal is eight months of operation in each calendar year over the next five years. Defense Programs support baseline operations of the facility. As mentioned previously, the new isotope production facility can run anytime that the facility is operating for other purposes. With respect to the existing target irradiation station, it can be operated currently, but requires additional H+ users to minimize the cost of beam delivery. The last large H+ user was the Accelerator Production of Tritium program. Operations over the past three years have been covered out of APT budgets. The next user will probably be the Accelerator Transmutation of Waste program, but their plans are not yet formalized. Therefore there is currently no high-energy H+ beam scheduled through FY 2000. However, LANSCE management is interested in maintaining the high-energy H+ beam delivery capability and is working with the Isotope Program to attempt to find ways to deliver beam at a reasonable cost to the Isotope Program.

6. **What understanding exists at each site about the priority of isotope production to serve isotope customers?**

   Currently, the Isotope Program enjoys the best relationship with LANSCE management that has existed since the inception of the program. We are actively involved by LANSCE management in all planning activities, we are members of the LANSCE Program Planning Group (LPPG), and we are a voting member of the LANSCE Facility Management Steering Council. The current formal documentation that governs the relationship between LANSCE and the Isotope Program is the Laboratory's landlord-tenant agreement. With all of that, the relationship is still more collegial than formal. However, this collegiality has actually worked well in serving our customers needs. It unfortunately has not led to improvements in availability of short-lived research isotopes because of operational difficulties with the existing target irradiation facility. We are, however, taking steps to change that with the new target irradiation facility. The new facility will lead to the ready availability of research isotopes for at least the baseline eight months per year. We currently have a Memorandum of Understanding (MOU) that will be the framework for future operations and relationship. This will become the foundation for our priority at the facility.

7. **How much influence does each site manager have in planning the use of multi-purpose facilities?**

   As mentioned above the Los Alamos Site Manager is actively involved in program planning with LANSCE Management and other users. His influence is no more or no less than any other user. However, it is also true that the Isotope Program is not as large a customer as Defense Programs, and the larger customers do tend to have more influence when there are programmatic conflicts. As another example the Los Alamos Site Manager has a great deal of influence at the TA-48 hot cell facility because he is resident in the organization that is responsible for the facility. He has less influence at the CMR building because a different line organization is the landlord of the facility. However, he gains influence by having excellent relations with the people who are residents of the facility and responsible for the operations.

8. **What cost-containment measures are being pursued?**

Cost containment is a high priority for the Los Alamos Isotope Program. Numerous examples exist. For example, the program has been at the forefront of the Laboratory's waste minimization activities. In 1996 there was a moratorium on generation of mixed waste at the Laboratory that did not impact a single delivery of isotope products, because the program had already eliminated all EPA listed hazardous materials from the chemical processes. Also the fact that we do not generate mixed waste saves the program money because mixed waste is very expensive to dispose. The program is the first at the Laboratory to have developed a successful "Green is Clean" program. We essentially segregate our waste at generation into suspect contaminated and suspect non-contaminated. We verify the fact that the waste boxes are not contaminated by counting them in a sensitive radiation detector developed for this use, and then they are sent to the county landfill, instead of TA-54. We have eliminated approximately 80% of our low-level low-activity waste by this approach. With disposal costs increasing to over $200 per box in FY 2000, this saves the program a significant amount of money. Other examples of cost containment in the areas of packaging and transportation and chemical processing can also be discussed during the site visit.

9. **What "licensing" issues need to be addressed?**

All current isotope production and distribution activities are properly permitted and licensed. These include all environmental, safety, and transportation activities. The only outstanding "licensing" issue for the program is the licensing of the new transportation container that we are going to be using. The existing shield that we use to transport targets from LANSCE to TA-48 is not DOT approved, and cannot be because it is a one-of-a-kind container. We deal with this by closing the roads when we transport targets. The Laboratory does this routinely for many packages that they must transport from site to site for which there are not suitable containers. The DOE is currently reviewing the new container that we are planning to purchase from Croft Inc., and we expect the DOE to issue a Certificate for this container before it is required for the new facility.

10. **What unused or underused capacity, e.g., personnel, facilities, could be mobilized to support a growth in isotope demand?**

The under used capacity available at Los Alamos is all in the area of hot cells. Both the TA-48 hot cells and the CMR hot cells are both underused at the present time. In the CMR we only pay for what we use so it does not impact cost to the Isotope Program. Since the Isotope Program is the only user of the TA-48 hot cells, the program covers all of the "open door" costs for this facility. We actively market this capability to other projects, but because of the nature of the Isotope Program work (e.g., FDA regulation of products), rarely is the new work compatible with the existing Isotope Program work.

11. **Summarize customer inquiries received during the past two years. What per cent were filled, referred to other facilities, rejected? Explain unfilled requests.**

A list of written inquiries is attached to this document. The majority of written inquiries come as a result of the DOE catalog or the information available on the DOE and Los Alamos Isotope Program home pages. We respond directly to each written inquiry. In most instances we can fill the orders when they concern existing products. For Cu-67 inquiries we refer customer to Brookhaven, since we have not produced it since 1996. Normally unfilled requests are for products that can't be made with our accelerator. In those cases we direct the customer to the appropriate DOE production site, or help them identify other non-DOE sources of material. We also receive telephone inquiries that are kept in a telephone log. We respond to and follow up on each telephone inquiry until it results in a sale or we are told that the customer is no longer interested. All other aspects of telephone inquiries are handled in a fashion similar to written inquiries.

12. **How does each site manager rate customer satisfaction for his site? For the overall program.**

Customer service is rated by individual interactions with customers, both by telephone contacts on a routine basis and with customer visits when appropriate. We also find the various professional meetings and trade shows where DOE exhibits to be important for customer interactions. The Los Alamos Site Manager has at least two personal interactions per year with each major customer. We also keep a complete customer complaint/compliment file. It details each complaint or compliment and is tracked until resolution. The resolution is documented in the complaint file.

13. **Kindly detail how you set prices of a mCi of an isotope? The detail should show if the cost is fully loaded or incremental, and should include labor, materials and parts, facility rental and amortization costs, listing of the actual overhead charges, waste disposal (a major cost), and all other costs that are tagged to the cost of producing,**

marketing selling, and distributing a product (e.g., customer service, distribution, ordering).

The final decision on pricing is made by the DOE. Each summer each site does a cost-price study. It is developed using activity-based costing. A work breakdown structure is used by each site to estimate and collect cost by activities. Each activity is resource loaded based on the estimated work scope for the year. The resource loading determines the number of FTE hours (staff, tech, other) that are required per task, and fully loaded FTE rates are used to determine the estimated activity cost. After the activity costs are developed, the costs are allocated to each isotope that will be manufactured as defined by the estimated work scope. Some costs are allocated directly, as in the example of chemical processing costs. Other costs, such as hot cell operations and waste management costs, are allocated on the basis of campaigns (batches) that are required to meet the production commitments in the estimated work scope. Other costs, such as sales, marketing, distribution, are estimated as well, and allocated to the products in the portfolio. The amount to be produced is estimated, and this is then used to develop the unit cost to produce the isotope. We also estimate the amount that will be sold from each campaign (batch) so that we can estimate the unit cost of goods sold. We provide this information to DOE who then determines prices.

14. Illustrate the above question for the following radioisotopes: In-111, P-32, I-123, I-125, and several research radioisotopes.

Los Alamos does not produce any of the products listed above. Also most of our research isotopes are actually by-product and are thus priced to the marketplace. We do not do cost-price studies on by-products. There are numerous examples of cost-price studies for isotopes that are produced at Los Alamos (the so-called “driver” isotopes), and we will be happy to share this business sensitive information with the committee during the site visit.

15. What process, mechanism, and organizational structure do you have for the timely distribution of produced products?

The production, sales, and distribution functions are all managed as an organizational unit and are tightly coupled. The sales and distribution people are in routine contact with the production people by being physically collocated. There is a stand up meeting every Monday morning in the hot cell facility to determine the deliveries scheduled for the week, the production schedule for the week, and any problems that are anticipated with the deliveries. All activities are boarded at the hot cell facility and tracked during the week by the hot cell team leader. Of course, when Los Alamos becomes responsible for the sales and marketing of Brookhaven and Sandia products, then new mechanisms will have to be put in place. We have already developed procedures for providing these services for the accelerator products from Brookhaven and we can discuss them during the site visit.

16. What process, mechanism, and organizational structure do you have in place for customer service?

Our sales office is the point of contact for customer service. It is staffed with 2 full time sales and customer service representatives, so that there is full coverage during business hours. We can afford this redundancy because of sales/customer service personnel are also our radioactive material shippers. Thus, we have control of our own shipments and do not have to depend on another Laboratory organization for timely deliveries. Our sales/customer service representatives deal with all issues associated with customer service and satisfaction. With regard to technical support, our customer service people route the customer to our technical staff who are very active in providing technical support to our customers. As stated previously we track customer satisfaction through our complaint/compliment process. All of our customers are complimentary about the service and relationships they have with our customer service specialists. I would encourage the committee to contact some of the customers on our customer list to gauge their level of satisfaction.

17. Will you sign contracts that guarantee delivery at the contracted time of delivery and where the contract has penalty clauses for non timely delivery of the specified product?

Yes we will sign contracts that guarantee delivery at a contracted time, but DOE Isotope Program policy prohibits us from accepting penalty clauses in these contracts.

18. What should be the long-term role of Government in providing commercial and research isotopes?

Clearly, the Government’s long-term role in providing isotopes for research and commercial applications has been the topic of many studies by learned committees, by study groups with particular biases, and by private enterprises with extensive market knowledge and experience. All of these various studies agree that there is a role for the Government to play, but there is little agreement as to what that role should be. There is also little agreement about how future markets will develop.

If you are a proponent of an existing reactor or accelerator or a future facility that is trying to appear as a multi-user facility, the Government should be funding that facility to produce isotopes. The concept of whether it makes technical or economic sense is usually lost on the proponents. On the other end of the spectrum are the various user communities that stand to benefit from the isotopes that are produced. Usually these communities have requirements that can be readily defined, but the course to make the isotopes available is usually less clear, especially when the question of where the resources will come from is considered. The users want the isotopes at a reasonable cost, which is usually difficult if the producer is required to recover costs (the private sector or the revolving fund that was established by Public Law 101-101). On the other hand the producer can't understand why the research grant that is funding the research cannot fund the cost of the isotope. If there is one area of agreement among users and producers, whether we are speaking about commercial products or research isotopes, it is that this dilemma must be solved by the Government. If this is true we have a beginning to the understanding of what the Government role should be.

The solution to availability of research isotopes has to be the responsibility of Government, since no other entity has motivation to insure adequate isotope availability at a reasonable cost. The problem that Government faces is that the requirements of various research constituencies cannot be met within the constraints placed by the resources available. Thus prioritization is essential. This prioritization can be rancorous within any one research constituency, and can be impossible when the Government attempts to balance the needs of multiple research constituencies. The clear solution is to obtain more resources for the Government program, and progress in accomplishing this is evident. However, it is slow and not always assured. The DOE is working diligently on this problem, and we should recognize those efforts. Two activities at Los Alamos are examples. The construction of the new 100 MeV IPF at LANSCE is an obvious attempt by DOE to increase the availability of research isotopes. When it is completed DOE and Los Alamos expect that it will operate 8 months per year, and that short-lived research isotopes can be available for 12 months per year, if Los Alamos and Brookhaven schedules can be coordinated. The second activity that is exemplary is DOE's encouragement and support of the "Virtual Isotope Center" concept. Currently, the Virtual Center includes target irradiation at the TRIUMF facility in Canada, the INR facility in Troitsk Russia, and the NAC facility in South Africa followed by shipment to Los Alamos and processing in Los Alamos facilities. This concept has demonstrated our ability to insure the 12 month availability of intermediate and long half-life materials. It has also helped us to support clinical trials of Cu-67 by a combination of TRIUMF and Los Alamos facilities but the logistics are much more difficult.

The Government's role in the availability of commercial isotopes should also be clear. Normally, DOE recovers costs from isotopes that were developed in DOE laboratories, have found application in a commercial products, and there is no current private sector interest in the production. DOE has a responsibility to continue to make these isotopes available to support the commercial products until private sector interest develops. Examples of accelerator isotopes that are in this category are Sr-82 and Ge-68. They generate significant revenue for DOE, offset costs of operating facilities at Los Alamos and Brookhaven, and could become the interest of a private sector entity. If this were to happen then the amount of appropriation required for isotope production activities at these site would increase. It is an interesting dilemma. DOE has an active program in privatization of products that are interesting to the private sector, and it has been very successful. However, if the private sector produces Sr-82 and Ge-68 then DOE has achieved the privatization goal, but the consequence would be that more money would be required from the appropriation to fund isotope production, and less money would be available for isotope research. This is a dilemma for which there is not a clear solution.

In summary, there is a clear role for the Government to play in the availability of research isotopes and the development of isotopes for which production technologies do not currently exist. There is also a role for the Government to play in the availability of commercial "niche" isotopes that were developed by DOE or others, but for which no private sector producer exists. How the DOE balances the needs to minimize appropriations with the requirement to privatize isotope production technology of interest to the private sector is not evident at this time.

Sandia National Laboratories (SNL) Site Visit

Site Visited May 18, 1999

1. Introduction

A site visit was conducted at Sandia National Laboratories (SNL) on may 18, 1999. Site visitors included Dr. Ralph Bennett, Idaho National Engineering and Environmental Laboratory, Dr. Robert Atcher, Los Alamos National Laboratory, and Dr. Henry Kramer, consultant. Dr. Richard Coats acted as host for the site visit.

Mission

The mission of SNL with regard to isotope production has been focused on providing a backup supply of ^{99}Mo for commercial medical use. The mission formally began on September 11, 1996 with a Record of Decision (ROD) by the Department of Energy (DOE) to, "develop the capability to produce ^{99}Mo as a means of establishing a backup source until a more reliable commercial source is available." Initial funding of this work began in 1994.

The mission to provide a backup supply is accomplished by delivering ^{99}Mo to the major manufacturers of ^{99}Mo / ^{99m}Tc generators. This requires the irradiation of high enriched uranium (HEU) targets in the Annular Core Research Reactor (ACRR) and separation of valuable fission products from wastes in the Hot Cell Facility (HCF). These facilities and the upgrades being undertaken to prepare them are described next.

Facilities

The ACRR is an open pool reactor which has been upgraded to 4 MW steady state operation and outfitted with a flooded central region available for Cintichem-type targets. The new configuration has been tested and a new Safety Analysis Report has been prepared and is expected to be approved this fiscal year. There are a variety of options for loading Cintichem-type targets into the central region, with the primary options being either 19 or 37 target elements. With sufficient loading, the ACRR is capable of producing the entire U.S. demand for ^{99}Mo, currently known to require about 3000 6-day Ci per week. The core also has many grid positions available within and outside of the fueled region for other irradiations. The total neutron flux in the central region is 1.0×10^{14} n / cm^2-sec at 4 MW core power, with a thermal component of 0.6×10^{14} n / cm^2-sec. The Cintichem-type targets will be fabricated with high enriched uranium (HEU) in the Chemistry Metallurgical Research (CMR) facility at Los Alamos National Laboratory (LANL).

The HCF is a large hot cell that has been upgraded with a number of clean process boxes that are laid out to accommodate the ^{99}Mo process flow. The HCF is and will remain a Category 2 nuclear facility capable of handling many kCi of activity. The upgraded HCF will accommodate the processing of up to 6–12 fission targets per day. Most facility modifications will be completed by the end of this fiscal year. A new Safety Analysis Report has been prepared and is expected to be approved this year. The Operational Readiness Review and much of the hot cell equipment, however, has been deferred beyond this fiscal year (this is discussed in Section 2 below). All of the facilities are located a few miles from the Albuquerque airport which enhances their ability to deliver products.

Products and Services

The primary product is envisioned to be finished sodium molybdate for distribution to major radiopharmaceutical manufacturers of ^{99}Mo / ^{99m}Tc generators. A demonstration of the capability was held in late 1996 with the irradiation and processing of four targets in the HCF prior to its upgrade. The demonstration resulted in the successful loading and test of several generators by a major radiopharmaceutical manufacturer.

Given the primary mission for a backup supply, the potential exists to separate and supply related commercial or research fission product isotopes as an add-on to the ^{99}Mo operations. The principal commercial fission product isotopes are ^{131}I and ^{133}Xe. A more limited potential exists to supply ^{89}Sr and ^{153}Sm: While these radioisotopes are in commercial demand, their separation from fission products would require an electromagnetic separation to obtain the desired radioisotopes on a routine basis. It has not been evaluated whether these could be produced at or below their market prices.

The principal research fission product isotope is ^{90}Y, which is already available from the commercialized process at Pacific Northwest National Laboratory (PNNL). It was noted that a variety of fission products not identified as important in the Expert Panel Report are produced. Quantities of all the above are listed in Table 1. Of course, these supplies are available only when the backup supply actually operates.

Table 1. Selected Activities Present After a 24 Hour Cooling Period in a Typical ACRR Fission Target Irradiated for 7 Days at 20 kW

Radioisotope	Expert Panel Category	Half-Life	Activity (Ci)
^{99}Mo	1	66 h	670
^{90}Sr/^{90}Y	1	29 y/2.7 d	0.4
^{131}I	2	8.0 d	200
^{133}Xe	Not Identified	5.2 d	600
^{89}Sr	2	51 d	70
^{153}Sm	2	1.9 d	20
^{140}Ba/^{140}La	Not Identified	13 d/1.7 d	320/260
^{141}Ce	Not Identified	33 d	140
^{144}Ce	Not Identified	285 d	15
^{147}Nd	Not Identified	11 d	130
^{95}Zr/^{95}Nb	Not Identified	64 d/35 d	78/7
^{103}Ru/^{103m}Rh	Not Identified	39 d/56 m	60/54
^{105}Rh	Not Identified	36 h	110
^{91}Y	Not Identified	59 d	76

A number of non-fission radioisotopes could also be produced from steady state irradiations in the ACRR. Targetry would be based on the standard techniques of neutron activation reactions, since the reactor produces fluxes typical of a moderate-size research reactor.

2. Relationship to DOE Programs

DOE Office of Isotope Programs (IP)

In order to dedicate the ACRR and HCF facilities to the backup mission, a Management Agreement was executed between Defense Programs (DP) and Nuclear Energy (NE) on June 23, 1997. The Management Agreement decidedly prioritized the use of these facilities to the medical isotope mission and set forth the understanding that NE would assume most responsibilities and base funding indefinitely. The Agreement has no discussion of what happens in the event that no backup supply is developed.

The funding outlook for the program at SNL has changed recently. Prior planning for FY-2000 (shown in Table 2) included completion of the backup supply, and provided a total of $9.87M for the program. This plan was revised by DOE to reflect a halt in the preparations to develop a backup supply. The current FY-2000 budget now focuses on ACRR facility operations and provides funding of $3.5M including $2.8M ACRR base funding for operations, $0.3M to bring the HCF into a standdown condition, and $0.4M for program management and exploration of research isotope products based on the ACRR. The Senate appropriation for FY-2000 includes an additional $2.5 million for this program. At this time, the House has not passed the appropriations bill for the DOE.

Table 2. Prior Funding Plan for FY-2000

ACRR Operations	$2.87M
HCF Operations	$2.58M
ACRR Modifications	$0.28M
HCF Completion	$0.51M
HCF Operational Readiness Review	$0.30M
FDA Validation	$0.67M
LANL Target Production Line and Production	$1.64M
Program/Project Management and Research	$0.90M
Isotope Programs Support	$0.12M
Total	$9.87M

Approximately $40-50M has been spent to date on the mission at SNL, with the prior FY-1999 / 2000 budgets planned to be the amount needed to bring the backup supply online. Since the current FY-1999 / 2000 budgets will not complete the supply, many alternatives have been proposed and are presented below in the discussion of Continued Operations.

Other DOE Programs

Despite the clear priority for medical production in the Management Agreement, DP will have priority in the use of the ACRR in pulsed operation to support national needs in stockpile stewardship. Recent amendments to the Management Agreement provide for a period of time for pulse operations for the DP test program in FY-2000, for example. The use of the ACRR by DP involves reconfiguring the central core cavity from a flooded zone with Cintichem-style targets, to a dry zone for experiments. The reconfiguration requires from several weeks to approximately two months. Subsequent reconfigurations should require approximately two weeks. The optimal configuration for ^{99}Mo is obviously to have the central cavity flooded and loaded with as many HEU fission targets as possible. This precludes pulsed operation, however. The optimal (in fact, required) configuration for pulsed testing is to have the central cavity dry and available for experiment packages. This does not preclude steady state operation in the same day, however, since the control mechanisms can be switched from pulsed to steady state in a few hours. This does severely limit the available target positions for ^{99}Mo production since it precludes the use of the central cavity volume. The only positions available would be on the periphery of the core where the flux is lower by a factor of two to three, but still feasible for limited production.

DOE Nonproliferation and National Security (NN) Programs is funding some limited studies of the potential for fission product ^{99}Mo based on low enriched uranium (LEU) targets. This is support of the Department of State initiatives to reduce the dependence of developing nations on HEU and thereby alleviate proliferation concerns.

3. Relationship to Academic Programs and Training

Sandia's isotope production activity has some involvement with the University of New Mexico's Department of Nuclear Engineering. There is occasional participation on studies by summer interns and graduate students from the department. The level of Laboratory Directed Research and Development (LDRD) at SNL spent on isotope production is quite small, however, with $50K spent recently on a study of ^{125}I production capacity by standard techniques. Sandia has had some contact with the School of Pharmacy, but has not involved any students to date. A fairly substantial amount of SNL funding (approximately $2M) was made available prior to the ROD to decontaminate hot cell spaces in support of isotope mission development.

4. Current Isotope Production

Throughput

SNL is not currently producing radioisotopes.

Customers

SNL does not have any firm customer contracts for radioisotope deliveries.

Pricing Policies

Pricing policies have not been developed.

Product Development

The primary interest in product development (aside from fission products) is for ^{125}I production through standard methods with an enriched ^{124}Xe target loop in a low flux region. There has been other interest expressed by SNL in irradiating semiconductor devices, producing low specific activity ^{192}Ir, and possibly offering radiography services with the ACRR.

5. Future Capabilities and Resource Requirements

Continued Operation

As stated above, redirection of the SNL isotope production activities was given by NE early in FY-1999. With the approaching completion of the two Maple reactors in Canada, the redirection stipulated that there was to be no further HCF development. Accordingly, funding to complete the HCF was reduced in FY-1999 and eliminated in FY-2000, and thereafter. The funding available for the HCF in FY-2000 is only to bring the facility to a standdown condition, although the facility has made considerable progress toward a ^{99}Mo capability. The consequence of not completing the upgrade now would be to increase the cost of completing it at a later time, if needed, since resources and momentum will be directed elsewhere at the laboratories. A further issue with operations is the need to purchase fuel for the ACRR within several years after startup of full production. While SNL has the option to purchase a higher performance ZrH fuel than the BeO fuel needed for pulsed operation, the product pricing will need to yield the funds for its purchase and modification of the safety basis.

The prospects for continued operation need to consider the various production options and their costs. The options are presented against the ^{99}Mo backup or steady production scenarios, which are presented in Table 3.

Table 3. Options for ^{99}Mo Supply at SNL

	Establish capability only [a]	Emergency production only[b]	Subsidized supply	Breakeven supply	Full U.S. supply
Funds to establish the capability[c]	$0.7M	$8.2M	$8.6M	$10.4M	$12.7M
Funds for yearly operations	$7.5M	$8.1M	$8.6M	$12.3M	$17.0M

a Several qualification runs per year, without any sales to U.S. manufacturers.
b Production of 10-25% of U.S. demand during an emergency of 1-2 months.
c Assumes FY-2000 funding is assured without delay. Invalid if funding lapse occurs.

Several headings in Table 3 require further explanation. The term, “Funds to establish capability,” means the one-time expenditures on facility modifications, equipment, qualification runs, documentation and staff development in order to establish a capability with the stated throughput. These funds are based on the assumption that there is no gap in funding after FY-1999, and that these amounts are available in FY-2000 to complete the capability. “Funds for yearly operation” includes all base funding to maintain operations at ACRR and HCF, as well as at supporting operations at Los Alamos. “Subsidized supply” means that annual federal funding (up to these amounts) is required regardless of whether any privatization goes forward and is able to offset these funds. “Breakeven supply” means that privatization is extremely successful and captures 40% of the U.S. market share at current prices, allowing the supply to recoup the full amount of yearly operations shown. “Full U.S. supply” means that the supply has a throughput equal to 100% of the U.S. market, although this is not intended to suggest that the market could actually be captured.

If the SNL facility is to be used for isotope production other than ^{99}Mo, the current plan is to ship the irradiated targets to LANL for processing in their hot cells. There are discussions underway on what isotopes should be produced if the ^{99}Mo production activity is not developed.

Expanded Operations or Services–Proposed

Some discussion was held regarding the possibility of only establishing the capability to send “green solution” (i.e., first-cut separated ^{99}Mo) to Nordion for purification and finishing. It was estimated that the funds required to establish this capability would be $0.6M. This option may not effectively backup the U.S. supply, for example, in the event of a site-wide strike in Canada.

6. General Issues Related to Isotope Supply

Institutional Support

The Sandia management continues its strong support for completing the project, even in a limited capacity.

Marketing

The medical isotope initiative at SNL has no established marketing or sales organization. LANL will provide these functions for SNL when they begin production operations using the ACRR. Distribution is proposed to be handled by the existing shipping and transportation organization for radioactive sources and wastes at Sandia.

Business Practices

There has been a strong interest on the part of the Office of Management and Budget in the potential for privatization of significant portions of the backup supply. Most recently, the Conference Report for Energy and Water Development for fiscal year 1999 requested a plan from NE for privatization of its ^{99}Mo production. The report from NE was completed in January 1999, and specified that a source evaluation board (SEB) would be formed and be responsible for several cycles of requests and proposals, resulting in an award of privatized efforts by September 30, 1999.

The efforts to execute the privatization plan were not successful. At the Expression of Interest stage, a total of eight responses were received. A subsequent request was issued for concept papers which could guide the final Request for Proposal (RFP) provisions. Only one response was received, and it was considered unresponsive because it would not guarantee that government funding would not be required to complete the backup capability before they began operations. This set of events has effectively stopped the privatization process.

Waste Management

The proposed waste management plan envisions neutralization and grouting of the fission product wastes. This would adequately prepare them to meet the waste acceptance criteria for shipment to the Nevada Test Site. It is important to note that the current facility has no space to accomplish this process, however. The current plan is limited to storing barrels of waste in a vault next to the hot cells. The shipment of waste requires the construction of an additional building to handle the outgoing shipments.

Sandia National Laboratories (SNL) Questions and Answers

How well does the Department's existing five-site production infrastructure serve the current need for commercial and research isotopes?

1. What is the physical condition of the isotope processing facilities and equipment?

The SNL Annular Core Research Reactor (ACRR) was recently modified to give an accessible large volume internal flux trap for target irradiation. Likewise, modifications to the SNL Hot Cell Facility (HCF) to give the ability to extract ^{99}Mo or other select fission products (^{131}I, ^{133}Xe, ^{153}Sm, —) from a fission product stream are near completion. However some equipment essential to processing and waste management remain to be procured and installed. Facility functional check-out remains to be accomplished.

2. What capital investments are needed to assure the near term operability of the facilities?

With the exception of an improvement to the ACRR pool cooling system for improved performance and reliability, the no significant capital investment needs for the ACRR are foreseen.

An investment of approximately $2 M is required to achieve full HCF capacity for both near and out-year scenarios.

3. If additional resources are needed, are they practical, e.g., technically rational, easily integrated into existing infrastructure, quickly implemented and supportable? Will any portion be sustainable over time by local financial and personnel resources?

Capital investments discussed in #2 are practical and were included in initial planning. Hence, they are already integrated into existing infrastructure. Some portion may implemented and sustained through other funding sources.

Although no plan has been formalized, it is anticipated that trained adjunct staff will complement a small core of dedicated staff. The adjunct staff, normally working in other areas, will be called upon as need arises to meet changes in demand. Agreements will be in place to establish priorities and to permit rapid implementation of those staff.

4. What is the availability of the primary nuclear facility (accelerator or reactor) over the next five years, e.g., HFIR outage, LANSCE program changes?

With the exception of some near term tests, no major outages or program changes are anticipated over the next five years.

5. What understanding exists at each site about the priority of isotope production to serve isotope customers?

It is understood that the priority for the ACRR and HCF at SNL is isotope production and research. DOE/IP funds both facilities.

6. How much influence does each site manager have in planning the use of multi-purpose facilities?

Baseline funding for the ACRR and HCF operation is provided by DOE/IP and hence, the production site manager has considerable influence in use planning.

7. What cost-containment measures are being pursued?

Assuming that this question applies to production costs, The question is premature for current SNL activities.

8. What "licensing" issues need to be addressed?

NRC licensing is appropriate for transportation casks. Validation as a supplier requires FDA approval in some cases.

9. What unused or underused capacity, e.g., personnel, facilities, could be mobilized to support a growth in isotope demand?

Considerable resources could be mobilized to support a growth in isotope demand. The ACRR and HCF capacity is much greater than current demand.

10. Summarize customer inquiries received during the past two years. What per cent was filled, referred to other facilities, rejected? Explain unfilled requests.

The question is premature for current SNL activities.

11. How does each site manager rate customer satisfaction for his site? For the overall program?

The question is premature for current SNL activities.

12. **Kindly detail how you set the price of a mCi of a radioisotope? The detail should show if the cost is fully loaded or incremental, and should include labor, materials and parts, facility rental and amortization costs, listing of all the actual overhead charges, waste disposal (a major costs), and all other costs that are tagged to the cost of producing, marketing, selling, and distributing of the product (e.g. customer service, distribution, ordering).**

    The question is premature for current SNL activities. Price setting is under study.

13. **Illustrate the above question for the following radioisotopes: In-111, P-32, I-123, I-125, and several research radioisotopes.**

    The question is premature for current SNL activities. Price setting is under study.

14. **What process, mechanism, and organizational structure do you have for the timely distribution of the produced product?**

    The question is premature for current SNL activities.

15. **What process, mechanism, and organizational structure do you have for customer service?**

    The question is premature for current SNL activities.

16. **Will you sign contracts that guarantee delivery at the contracted time of delivery and where the contract has penalty clauses for non timely delivery of the specified product?**

    Although the policy has not yet been established, it is anticipated that some such guarantee will be provided to the customer.

17. **What should be the long-term role of Government in providing commercial and research isotopes?**

Pacific Northwest National Laboratory (PNNL) Site Visit

Site Visited July 23, 1999

1. Introduction

On July 23rd, 1999 representatives of the subcommittee on Long-Term Isotope Research and Production Plan of the Nuclear Energy Research Advisory Committee (NERAC) participated in a site visit of the radioisotope production facilities of Pacific Northwest National Laboratory (PNNL) in Richland, Washington. The NERAC representatives included Drs. Robert Atcher (LANL), Ralph Bennett (INEEL), Henry Kramer (consultant) and Thomas Ruth (TRIUMF), chair. Dr. Thomas Tenforde served as host for PNNL. The agenda for the visit along with the participants is attached.

Prior to the site visit a series of questions that had been prepared by the *Subcommittee* for all site visits was provided to the PNNL team to address. The answers to these questions were provided in report PNNL-12249, which has been excerpted and attached to this site visit report. Supplemental material related to the isotope production program at PNNL was provided in report PNNL-12228.[1] The site visit team was also provided with the *Scoping Plan* submitted to NERAC on the case for restarting the Fast Flux Test Reactor (FFTF).[2]

At the site visit Dr. Walter Apley presented a brief overview of the FFTF *Scoping Plan*. Dr. Tenforde made a presentation covering much of the material provided in the above reports. Topics of discussion included:

- Radioisotopes program at Hanford
- FFTF capabilities
- FFTF medical isotope production
- Operational costs and isotope revenues, and
- Staffing and facilities.

[1] "Isotope Production at the Hanford Site in Richland, Washington," PNNL-12228, Pacific Northwest National Laboratory, Richland Washington, June 1999> (Available on the Web at http://www.pnl.gov/isotopes.)

[2] "Program Scoping Plan for the Fast Flux Test Facility: A Nuclear Science and Irradiation Services User Facility," PNNL-12245, Pacific Northwest National Laboratory, Richland Washington, July 1999.

Mission

The FFTF *Scoping Plan* outlines the plans for restarting the Fast Flux Test Facility at 100 megawatts with four major missions:

- Medical and industrial isotope production
- Plutonium-238 production
- Non-proliferation programs
- Materials testing

As indicated below the medical isotope production program is projected to become a major source of revenues when fully implemented.

Facilities

It is important to note that the FFTF has not operated since 1992, and is not operating at the present. In May 1999 a *Scoping Plan* was requested by DOE for its decision-making regarding restart. This *Scoping Plan* was submitted to DOE in August, 1999. The timetable presented in this document calls for operation to resume in 2004.

The FFTF reactor facilities are described in PNNL-12228 and PNNL12245. The reactor is a liquid sodium cooled nuclear reactor. It was originally designed to operate at 400 MW for testing to support fast reactor development. The planned restart would reduce the operating power to 100 MW. This would reduce fuel consumption and extend the life of the reactor.

Irradiation Facilities

The irradiation facilities include one gaseous isotope production location in the core, 3 to 5 proposed rapid radioisotope retrieval locations in the core and 3 to 12 irradiation vehicles for long-term radioisotope production in the core. In addition, there are other locations both in the core and outside the core for other purposes such as ^{60}Co and ^{238}Pu production.

The target assemblies in the core are exposed to the liquid sodium metal coolant and thus need to be cleaned before transferring to the chemistry processing facilities. The turn-around for removing a target bundle from the reactor and getting it to the lab for processing is approximately 24 hours. Thus the shortest half-life radioisotope that can reasonably be expected to be produced at the FFTF would be approximately 2.5 days.

Neutron Fluxes

The FFTF has a fast reactor neutron energy flux profile (spectrum) range with a peak energy of the neutrons at 300500 keV. The average fluxes at a power level of 100 MW are in the range of 10^{14} to 10^{15} neutrons/cm^2/second. This is a much higher average energy than found in thermal reactors operating in the U.S. The fast spectrum allows significant production via (n,p) and (n,n') reaction channels. In order to thermalize the flux for (n,g) reactions, special energy moderating elements would be required.

None of the other reactors in the world that have medical radioisotope production capability has a similar neutron energy flux profile. To produce radioisotopes of a purity needed for medical applications, it appears that the FFTF would sometimes be required to irradiate enriched stable isotope targets to reduce the production of unwanted radioisotopes that are concurrently produced during the irradiation primarily because of the FFTF's fast neutron flux profile.

Laboratories

The radiochemical processing facilities are located approximately 8 miles from the reactor facility. The Radiochemical Processing Laboratories include 143,700 ft^2 of which general chemistry laboratories occupy 44,500 ft^2. There are two areas that contain heavily shielded facilities for receiving the irradiated targets and the initial processing. There is other lab space that can be renovated to perform radioisotope processing suitable for medical products. Such renovations are estimated to cost $16M. The *Scoping Plan* anticipates getting the bulk of the financial support from outside users.

The other lab spaces include reagent preparation, analytical counting rooms and final product testing.

Personnel

The personnel requirements were also discussed. The staff would have to be increased for the full steady-state isotope production program from the present 12 FTEs to 74 FTEs. The bulk of these would be in target fabrication and testing (34) and in radiochemical processing (21). The remainder would be involved in target handling at the reactor, product packaging and shipping and in customer services, marketing and sales. There is an expectation that a commercial partner(s) would provide some percentage of these positions.

Products and Services

The FFTF has the capability of producing a wide range of radioisotopes in large quantities, a number of which are higher quality than can be produced with thermal reactors. However, the isotope production team has identified ten candidate isotopes to focus on for their business plan. Table 1 lists these isotopes and the corresponding category from the Expert Panel. [3]

[3] "Expert Panel: Forecast future Demand for Medical Isotopes," Arlington, VA, September 25-26, 1998. (Available of the Web at http://www.ne.doe.gov/nerac/isotpedemand.pdf)

Table 1. Radioisotopes proposed for production at the FFTF Identified in the Expert Panel Report.

Radioisotopes	Expert Panel Category
^{131}I	1
^{186}Re	1
^{103}Pd	2
^{117m}Sn	2
^{125}I	2
^{32}P	2
^{153}Gd	3
^{89}Sr	3
^{67}Cu	3
^{188}W	3

Since the FFTF would not be operational for five years, the supply of these isotopes would not be enhanced until that time. The proposed production of these isotopes at FFTF includes a significant percentage (up to 10%) of the total projected U.S. market at the time of re-start.

2. Relationship to DOE Programs

DOE Office of Isotope Programs (IP)

Research into technologies for preparing a-emitting radioisotopes has been supported by DOE Office of Nuclear Energy. The presentations did not specifically address the supply of research isotopes other than these. However, both at the site visit and following the site visit assurances were made that the production of research quantities of radioisotopes could be accommodated. Following the site visit Mr. Bruce Klos responded to the hypothetical question of what would be required to produce a generic radioisotope that had not been produced in the FFTF previously. The lead-time would vary depending on the state of knowledge of the target material and required processing. For small targets that are compatible with other ongoing irradiation programs and for which behavior at the operating temperature is expected to be acceptable, the lead-time could be less than two weeks. For new, one-of-a-kind target assemblies (e.g., a significantly changed driver fuel assembly), the lead-time for design, fabrication, review and approval would be approximately 6 months. For the case of a large number of core assemblies containing a new target with strong reactivity properties and marginal stability, the time required to qualify the targets for full-scale irradiation could be as much as several years.

Other DOE Programs

If the FFTF were to re-start the other programs envisioned for the facility would interact with a number of DOE programs and other government agencies. For example

Material Testing would be sponsored by the Office of Science in DOE, and the Office of Nuclear Energy through the Transmutation Research and Nuclear Energy Research Initiatives. The plutonium-238 production would be sponsored by the Office of Nuclear Energy and the National Aeronautics and Space Administration. The Non-Proliferation Technical Programs would be sponsored by the DOE-Materials Disposition and the Office of Nuclear Energy as well as international organizations such as the International Atomic Energy Agency.

3. Relationship to Academic Programs and Training

During the last few years 12 undergraduates have spent periods ranging from 3 to 24 months on various research projects. These students were associated with a number of different colleges and universities. There has been one graduate student at the doctoral level in Nuclear Engineering. The support for the students came from various sources including the DOE, the Associated Western University scholarship funds and Laboratory-Directed Research and Development funds.

Several research projects that relate to the medical isotope program were cited. They are carried out with researchers from the colleges and universities in the Northwest as well as a couple of Institutes in Russia. These projects range from dosimetry calculations to labeling techniques for various heavy metal alpha-emitters. Support for the various projects comes from DOE, the National Cancer Institute and a private corporation. The total funding level is about $300K / year.

4. Current Isotope Production

Until FY-1998 the primary medical isotope produced and sold by PNNL was ^{90}Y, recovered from stocks of ^{90}Sr. However that technology and a large stock of ^{90}Sr has been transferred to New England Nuclear in Billerica, MA where this isotope is now produced and sold commercially.

During the last 3 years the primary effort has been in the area of developing separation and purification techniques for ^{229}Th, ^{225}Ac, ^{223}Ra and ^{213}Bi, also obtained from parent stocks.

5. Future Capabilities and Resource Requirements

The business plan for recovery and re-start of FFTF and operational costs of the facility was presented. This information was in the provided documents. The restart effort would require approximately 5 years to complete. During that time modifications to the target handling capability and the lab space would be undertaken. The cost for these modifications has been estimated to be $30M. Of this $23M (FY99 dollars) is principally for modifications to the FFTF for rapid sample changing. These costs are included in the estimated $229M for the restart of the FFTF, with annual operating costs estimated to be $55M. The current budget for standby operational status is $40M per year.

Throughput

The projected production quantities and schedule are detailed in the attached questions and answers.

Customers

The *Scoping Plan* included letters of support for the FFTF from a variety of sources including commercial suppliers of radioisotopes, professional societies, regional academic centers and special interest groups. No commitments to purchase radioisotopes or services have been made at this point in the process.

Pricing Policies

Direct discussions between the DOE and the PNNL Project Manager are used to arrive at the sale price for isotopes based on an activity-based costing and isotope pricing policy. It was assumed that there would be no major change to market conditions five years out and that the entry of a new major isotope supplier would not change the market.

Product Development

Most of the proposed products listed in Table 1 have not been prepared in the estimated quantities at the FFTF before (an exception being ^{153}Gd that was produced and sold in large quantities). The Radioisotope processing team plans to utilize the start-up period to prepare the targets and chemical processes.

6. General Issues Related to Isotope Supply

Institutional Support

The production of medically useful radioisotopes is one of the four major functions presented in the *Program Scoping Plan*. This aspect of the program would account for 27% of the projected revenues during the initial five years of operation, growing to 56% of the gross revenues during the period beyond 2010. However, it was not clear what priority this aspect had within the entire PNNL program, given that the other programs will all be DOE sponsored.

Marketing & Business Practices

A whole new infrastructure will have to be rebuilt since most of these activities ceased following the transfer of the ^{90}Y project to NEN.

Waste Management

According to the background documents “various waste streams from the proposed activities are and would continue to be managed in accordance with the applicable Federal and State regulations. In addition, a *Waste Management and Minimization Plan* will be prepared with the states of Oregon and Washington to ensure that any FFTF waste issues do not negatively impact Hanford site cleanup." [4]

7. Summary Comments

Use of enriched stable isotope targets requires the following two key issues to be addressed: 1) cost of procuring the enriched material and 2) the availability of the required isotopes.

Enriched stable isotopes are costly. The cost analysis of the business plan incorporated the cost of target materials into the total cost of target preparation, and did not show a line item that represents the costs of enriched stable isotopes. For realistic operating cost the business plan must include the costs for the enriched stable isotopes per large target for each of the proposed radioisotopes.

The U.S. Department of Energy has a limited inventory of enriched stable isotopes and no longer produces them. Russia is currently the major supplier of some enriched stable isotopes. Thus the supply for the enriched stable isotopes, in a form that can be irradiated in the FFTF, must be determined. If an assured supplier is not presently available then a U.S. government supported program would have to be implemented and maintained to ensure a supply for the FFTF with enriched stable isotopes.

The irradiation environment at 100 MW and 400 MW operation is approximately 725° and 900° F, respectively, for the large target assemblies that are directly cooled by circulating liquid sodium. Higher steady-state temperatures of 1500° F or above may be reached in small metal target materials placed in capsules within rapid radioisotope retrieval systems that are not directly cooled by the liquid sodium. This high temperature may significantly limit the chemical forms (e.g. oxides, metals) of the irradiated target to eliminate target degassing (release of a gas in the sealed irradiation capsule will result in an internal pressure build-up). Exposure of the small targets to such high temperature for significant time periods will most likely alter the chemical structure of the target, making it a challenge to chemists attempting to put the irradiated target into a medically useful chemical form. Some of the points of clarification included that a 20 to 30 day down period between the 100 day operating cycles is required. Most of the production yield measurements have been made on very small quantities of irradiated targets that have not been processed to a completed product. Some key chemical experiments need to be performed utilizing the proposed small FFTF targets exposed to 1500° F for periods of 10 to 25 days. These experiments would be designed to demonstrate what type of research program (if any) is needed to develop post irradiation cost-effective quantitative chemical processes for the production of medically useful radioisotopes in an appropriate useful chemical form. For large target assemblies in which more than 40 types of radioisotopes were produced during the 10 years that FFTF was operational, it was demonstrated that thermal effects of prolonged exposure to 900° F on the physical form and chemical stability of the target materials did not cause problems with post-irradiation chemical processing of the product isotopes.

The site visit team is not in a position to ascertain the viability of the business plan that was compiled to demonstrate the economics of restarting the FFTF with a major mission of supplying radioisotopes for the biomedical community. Nevertheless it should be pointed out that the product line proposed by the PNNL team includes radioisotopes that are presently commercially available. The projected revenues are based on the assumption of breaking into the existing market with a significant share of the existing and projected growth in the demand for these products. The supply of research radioisotopes was not a major consideration in the business plan. The FFTF is more ideally suited to producing large quantities using large volume targets rather the production of small quantities on an irregular schedule. Thus, the ability of FFTF to meet research needs in a cost-effective manner is significantly in question.

[4] Ibid., PNNL-12245, pp. 4-7.

Pacific Northwest National Laboratory (PNNL)

Questions and Answers

How well does the Department's existing five-site production infrastructure serve the need for commercial and research isotopes?

1. **What is the physical condition of the isotope processing facilities and equipment?**

The primary isotope production facilities at the Hanford Site are the Radiochemical Processing Laboratory (RPL) (Building 325 in the 300 Area of the Hanford Site) and the Fast Flux Test Facility (FFTF) reactor (in the 400 Area of the Hanford Site). In addition, there are several other laboratory facilities that are suitable for various aspects of target preparation and radiochemical processing of isotopes. These facilities are discussed briefly in this document, with reference to a PNNL report for additional details. [1]

RPL

The RPL is a 143,700 ft^2 building that contains laboratories and specialized facilities designed for work with nonradioactive materials, microgram-to-kilogram quantities of fissionable materials, and up to megacurie quantities of other radionuclides. The total space occupied by general chemistry laboratories is 44,300 ft^2, of which 6,950 ft^2 (15.6%) is presently unoccupied. All of the occupied, and nearly all of the unoccupied laboratories are functional and fully equipped with standard utilities. Several of the laboratories, especially those used for radioanalytical work, have been renovated during the past few years. The upgrading and modernization of equipment within the chemistry laboratories has been given a high priority during the past two years.

During a recent space utilization survey of the RPL, an assessment was made of the number of fume hoods and shielded glove boxes (including small hot cells) that are available for additional programmatic work. Of the 79 functional fume hoods and 23 shielded glove boxes, 50 and 15, respectively, are available for additional work.

A special feature of the RPL is the existence of two heavily shielded facilities located in annexes on the East and West sides of the building. These shielded facilities are the High-Level Radiochemistry Facility (HLRF) and the Shielded Analytical Laboratory (SAL). These two hot cell complexes, which are heavily utilized at the present time, provide capabilities for conducting bench-scale to pilot-scale work with a wide variety of highly radioactive materials. Capabilities include those required to conduct radiochemical separation and purification procedures, irradiated fuel or target sectioning and processing, metallography, physical properties testing of activated metals, thermal processing (including waste vitrification), and radioanalytical and preparatory chemistry operations.

The HLRF contains three large, interconnected hot cells designated as A-Cell, B-Cell, and C-Cell. The three cells are each 15 ft high and 7 ft deep; the A-Cell is 15 ft wide and the B-Cell and C-Cell are each 6 ft wide. In-cell operations are performed using medium-duty electromechanical manipulators, and the work is viewed through leaded-glass, oil-filled windows. The hot cells are equipped with television cameras, VCRs, overhead bridges, hoists, and standard utilities. They have shielded service penetrations at the front wall for insertion of special instrumentation.

The SAL contains six interconnecting hot cells, each of which is 5.5 ft wide, 5.5 ft deep, and 9.5 ft high. Each hot cell is equipped with a pair of medium-duty manipulators. Turntables built into the rear walls of the hot cells provide rapid transfers of radioactive samples into and out of the cells. The SAL hot cells are equipped to perform a wide variety of analytical chemistry operations with highly radioactive samples.

Additional information on the RPL, and its laboratory facilities that could be devoted to new isotope production missions in the future, is contained in Section 2.5.1 of Reference 1.

FFTF

The FFTF's original mission was to support liquid-metal reactor technology development and reactor safety by providing fuels and materials irradiation services. Although the U.S. liquid-metal reactor program ended at about the same time that the FFTF commenced operation in 1982, the reactor continued operation for 10 years as a national research facility to test advanced nuclear fuels and materials, nuclear power plant operating procedures, and active and passive reactor safety technologies. The facility was also used to produce more than 40 different radioisotopes for use in research, medicine, and industry. In addition, FFTF generated tritium for the U.S. fusion research program and supported cooperative, international nuclear research activities.

[1] "Isotope Production at the Hanford Site in Richland, Washington," PNNL-12228, Pacific Northwest National Laboratory, Richland Washington, June 1999. (Available on the Web at http://www.pnl.gov/isotopes.)

The reactor was shut down in December 1993, and since that time has been in a standby operational condition, pending a decision by DOE on its future use. In May 1999, the Secretary of Energy announced that a special 90-day study led by the Director of the Pacific Northwest National Laboratory, Dr. William Madia, would be conducted to establish whether the FFTF should be considered for future missions related to national and international nuclear technology needs. The nuclear science and irradiation services provided by FFTF will focus on a core federal role of meeting multiple 21st Century needs, including:

1. Providing a large and reliable supply of radioisotopes for research, medical, and industrial applications
2. Promoting safer nuclear technology through reactor safety testing and the development of proliferation resistant nuclear fuels
3. Producing power sources for deep-space exploration through the production of plutonium for radioisotope thermoelectric generators, and for research on compact space reactor technology
4. Sustaining the nuclear option for power production through testing of fuels, components, and reactor instrumentation
5. Conducting advanced research and providing services related to the testing of materials for fusion reactors, hardening and testing of materials such as semiconductors, and research on transmutation of nuclear waste materials.

These future missions, and the business plan for FFTF's proposed future operations, are described in a document that will be submitted to NERAC on July 20, 1999 for review before submission to the Secretary of Energy on August 2, 1999. This document is referred to in this report as the *Scoping Plan*.[1]

The FFTF consists of the reactor, which is capable of steady-state operation at a rated power level of 400 MW, and several support buildings and equipment arranged around the central reactor containment building. Heat is removed from the reactor by liquid sodium that is circulated through three primary loops, which include the pumps, piping, and intermediate heat exchangers. During a total loss of power, the FFTF is designed to shut down automatically and the reactor will continue to be cooled by natural circulation of the sodium. An emergency power source consisting of batteries will provide essential plant monitoring capabilities in the event of a shutdown. The reactor also has safety features that can maintain cooling if a leak occurs in the liquid sodium heat transport system.

Other major systems located in the FFTF reactor containment building are:

- The Closed Loop Ex-Vessel Handling Machine that is used to install fuel and target assemblies in the reactor and to remove them at the end of the irradiation cycle
- The Interim Examination and Maintenance (IEM) Cell, in which an irradiated assembly is washed and dried to remove residual sodium before disassembly; the target pins are then removed from irradiated assemblies with manipulators and placed in containers for removal from the IEM cell
- A Bottom-Loading Transfer Cask, which is used to transfer the pin container from the reactor containment building to a cask loading station in the Reactor Service Building.

Detailed descriptions and photographs of the FFTF containment building and the special facilities described above are contained in Section 2.5.2 of Reference 1.

Other Available Facilities

In planning for a proposed future FFTF isotope production mission, several facilities at the Hanford Site have been examined as possible locations for target preparation and the processing of isotope products. In all cases, these facilities have desirable physical features and equipment that could make them useful if an expansion of facilities is required later to meet a growth in the demand for FFTF isotope products. Three candidate facilities are:

1. Building 306E. Located in the 300 Area of the Hanford Site, this facility has been used in the past to fabricate a variety of reactor components, fuel assemblies, and radioisotope target assemblies. Some of the target fabrication equipment and non-destructive examination equipment still exist in the building and are available for use.
2. Postirradiation Testing Laboratory. Located in the 300 Area at the Hanford Site, this facility contains 13 hot cells and support laboratories for the physical and metallurgical examination of irradiated fuels, fission products, and irradiated structural materials. Decontamination of the hot cell facilities has

been underway for two years, and is expected to be completed within the next two years. Only a small amount of programmatic work is currently being conducted, and a study on the long-range utilization of this facility is underway, including use by commercial companies under lease agreements. This alternative may be attractive for establishing long-term business relationships with companies interested in the preparation and processing of targets irradiated at FFTF.

3. Maintenance and Storage Facility. Located in the 400 Area of the Hanford Site about 500 ft north of FFTF, this facility is a multi-purpose service center that supports the specialized maintenance and storage requirements of the FFTF. A special feature of this facility is a large shielded enclosure that contains two shielded decontamination rooms that can be used for both remote and hands-on cleaning of equipment and tools. This facility, including the shielded enclosures, was not fully utilized during the ten years of full-scale FFTF operation, and consideration has been given to its possible use for the fabrication and disassembly of FFTF targets.

Additional details on each of these facilities are contained in Section 2.5.3 of Reference 1.

2&3. What capital investments are needed to ensure the near-term operability of the facilities? If additional resources are needed, are they practical (e.g., technically rational, easily integrated into existing infrastructure, quickly implemented and supportable)? Will any portion be sustainable over time by local financial and personnel resources?

As part of the planning activities for a future FFTF nuclear science and irradiation services mission, an estimate has been prepared of the costs associated with restarting the reactor for steady-state operations at a 100-MW power level. This estimate, expressed in FY 1999 dollars, is $229M. The capital expenditures are distributed over a four-year period from 2001 – 2004, and include funds for (1) recovering systems that were shut down before the standby decision in late 1993, (2) equipment and instrumentation upgrades, (3) fabrication of rapid radioisotope retrieval (R3) vehicles for removal of short-lived isotope targets while the reactor is at power, (4) modification of hot cells and support laboratories for target processing operations, and (5) staff increases and training. Once restarted, the estimated annual cost of FFTF operations is $55M. A more detailed description of the schedule and costs for FFTF restart is provided in the *Scoping Plan*.

A business model has been developed as part of the *Scoping Plan* that incorporates plans for recovering approximately $100M of the restart costs over the projected 35-year operating life of the reactor. This business model was developed using the guidelines provided in DOE Order 2110.1A, "Pricing of Department Materials and Services and DOE Implementing Guidance on Federal Administrative Charges." The model is comparable to those currently in use at other DOE reactor facilities, and has been reviewed and accepted by the DOE Chief Financial Officer in meetings held during June 1999. The FFTF business model provides adequate resources to ensure both the near-term and sustained future operability of the reactor.

In this business model, the funding in FY 1999 dollars required during the reactor restart phase includes both the $229M discussed above and $55M in operating funds to maintain the FFTF's standby mode of operation during the period 2000-2001. During the projected 35-year operating lifetime of the reactor (2004-2038), a "value recovery charge" of ~4% will be applied to all private-sector irradiation services. The funds recovered through this charge will be placed in an investment fund that is expected to grow at an annual rate estimated to be ~5% above inflation, and thereby generate ~$100M to offset a portion of the restart costs.

The staffing infrastructure to support both the reactor operations and radiochemical processing of irradiated targets are in place and adaptable to rapid growth of the nuclear science and irradiation services components of the FFTF mission. As described in detail in the two referenced reports, the operations staff at the FFTF will increase from the current level of 260 full-time equivalent (FTE) to 410 FTE at the time of restart. This increase will accommodate the full set of operational services required for target insertion, irradiation, and retrieval in the isotope production program. Target preparation is expected to be carried out by a subcontractor working in facilities at the Hanford Site.

Radiochemical processing of the isotope targets will be carried out by members of the PNNL Radiochemical Processing Group (RPG), which consists of 75 technical and administrative staff that occupy the RPL. Section 2.4.1 of Reference 1. The isotope production team within the RPG currently has 12 staff members, of which 5 perform radiochemical processing operations. It is expected that the number of scientists and technicians performing radiochemical operations will increase to 21 FTE at the time FFTF commences full operation. This expansion will be achieved by reassignment of radiochemists and technical support staff within the RPG, and by new hires. In addition to the staff involved in radiochemical processing operations, it is expected that the number of staff involved in packaging and shipping will increase from 0.5 FTE to 7.5 FTE, and that the marketing, sales and administrative staff will increase from 1.5 FTE to 5.5 FTE.

Although the *Scoping Plan* does not explicitly include privatization of the reactor operations or the isotope production mission, discussions have been initiated with private-sector companies that may have an interest in commercializing various components of these operations (e.g., the marketing, sales, and distribution of isotope products). These discussions are expected to continue over the coming five-year period (i.e., during the preparation of the FFTF Environmental Impact Statement and the reactor restart activities), with a reasonable probability of success in establishing partnership agreements between DOE and commercial organizations.

4. **What is the availability of the primary nuclear facility (accelerator or reactor) over the next five years (e.g., HFIR outage, LANSCE program changes)?**

If the current plans to initiate preparation of an Environmental Impact Statement in October, 1999 are met, then it is expected that FFTF will be restarted by July 2004. Details of the restart schedule are given in the *Scoping Plan*. In addition, all of the target preparation and processing facilities such as the RPL are expected to remain available for work in support of the FFTF isotope production mission.

5. **What understanding exists at each site about the priority of isotope production to serve isotope customers?**

Because many of the isotopes produced at the Hanford Site are shipped to customers at medical centers for the treatment of critically ill cancer patients, the isotope production program receives a very high priority. For example, the staff performing the radioanalytical work and on-site transportation services in support of the isotopes program give this work the highest priority among their multiple tasks. A complete radionuclide analysis and Inductively Coupled Plasma (ICP) analysis of the chemical purity of the isotopes sent to customers are performed within 24 hours of the completion of isotope production. These data are then sent immediately to the customer for review before use of the isotope.

Another example of the high priority given to the medical isotopes program occurred five years ago when the RPL was shut down temporarily for safety upgrades. By direct order of the Manager of the DOE Richland Operations Office, Mr. John Wagoner, the production of yttrium-90 for medical customers was allowed to continue uninterrupted during the entire shutdown period, which lasted about one year.

6. **How much influence does each site manager have in planning the use of multi-purpose facilities?**

The Manager of the Hanford Radioisotopes Program, Dr. Thomas Tenforde, also serves as the lead scientist for the isotope production team within the RPG. The organizational structure and primary areas of research are described in Section 2.4.1 of Reference 1. In his capacity as head of the isotope production team within the RPG, the manager of the Hanford Radioisotopes Program has line management responsibilities for the staff and facilities involved in the radiochemical processing of isotopes for commercial, medical, and research applications. These staff, together with a matrixed team of nuclear physicists, engineers, radiochemists, and nuclear safety specialists from PNNL and other Hanford contractor organizations, have functioned since 1997 as a support group for planning the proposed future FFTF isotope production mission. An important part of this planning has been the identification of laboratory facilities that will be given a high priority for future use in support of the FFTF isotope production mission.

7. **What cost-containment measures are being pursued?**

Cost-containment efforts in the isotopes program are centered around the use of activity-based costing procedures for all isotope products. Following the costing procedures adopted by the DOE Office of Isotope Programs (NE-70), an annual cost / price analysis is performed on each isotope product using a four-level Work Breakdown Structure. Examples of this type of cost analysis are given in Section 2.6.1 of Reference 1.

In all aspects of isotope production, efforts are made to streamline the radiochemical laboratory procedures and to use the most economical services available from various contractor organizations at the Hanford Site. For example, ICP analyses of the chemical purity of isotope products are performed at the 222S Building under a subcontract with the Fluor Daniel Hanford Company, which is a less expensive option (by nearly a factor of 2) than performing these analyses in the RPL operated by PNNL.

8. What licensing issues need to be addressed?

If a decision is made to restart the FFTF, it will be subject to all DOE requirements for the operation of a nuclear facility, as described under DOE Order 425.1A ("Startup and Restart of Nuclear Facilities," 1995). Licensing of the FFTF under the regulations for commercial reactors will not be a regulatory requirement. However, it is expected that DOE will request the Nuclear Regulatory Commission to conduct a detailed technical review of the safety aspects of operating the facility, similar to the procedure that was followed prior to initial startup of the reactor in the early 1980s. In addition, the International Atomic Energy Agency (IAEA) may be requested to verify the inventory and characteristics of nuclear materials at the FFTF. The IAEA has declared its willingness to help facilitate FFTF's use by the international nuclear science community.

It is the goal of the Hanford Radioisotopes Program to transfer technology for the production and applications of medical isotopes to the private sector through appropriate licensing agreements. A recent example is the licensing agreement signed by NEN Life Science Products, Inc., on October 12, 1998, to use PNNL's patented process for extracting yttrium-90 from a strontium-90 generator in a highly purified form. Under this license agreement, the management contractor organization for PNNL — the Battelle Memorial Institute — receives an initial fee of $75K and subsequent royalties based on a percentage of the net sales value of yttrium-90 sold by NEN. The estimated value of this agreement for Battelle is approximately $500K over a five-year license period. This licensing agreement was part of a broader commercialization effort in which NEN took over from PNNL all aspects of the production, marketing, sales, and distribution of yttrium-90 (described in more detail in Section 2.2.2 of Reference 1.

Based on the success of the yttrium-90 privatization activity, PNNL is currently involved in efforts to commercialize other technology that has been developed for the medical application of radioisotopes. For example, negotiations are underway with a private company for use of PNNL's radioactive composite polymer delivery system for treating prostate tumors and other forms of cancer.

In addition to technology licensing agreements, consideration has been given to establishing facility lease agreements under which commercial companies could perform work in DOE facilities at the Hanford Site. For example, a study is underway on the feasibility and opportunities for privatizing part or all of the Postirradiation Testing Laboratory described above in the response to Question A.1. This facility, as well as other laboratories in the 300 Area of the Hanford Site, will be considered for use by private-sector companies in future work related to the preparation and processing of targets for FFTF isotope production.

9. What unused or underused capacity, e.g., personnel, facilities, could be mobilized to support a growth in isotope demand?

As discussed above in the response to Question 1, a recent survey of space utilization in the RPL indicated that ~7000 ft^2 of functional laboratory space is currently available for radiochemical work in new projects. It is anticipated that reassignment of laboratory space within the RPL will be made in the future to accommodate the full set of requirements for the radiochemical processing of multiple FFTF isotope targets. In addition, as also discussed above in the response to Question 2, there are extensive support facilities available for isotope target preparation and processing in Building 306E and in the Postirradiation Testing Laboratory at the Hanford Site.

With regard to the availability of trained staff who could be mobilized in support of a growth in isotope demand, there are currently about five scientists and technicians within the 75-member RPG that could be utilized in that capacity (in addition to the staff that are members of the isotope production team). The overall workload and availability for new assignments of radiochemistry staff in the RPG is driven primarily by funding for work in support of the Hanford nuclear waste cleanup mission and the processing and disposal of nuclear fuels. As the time approaches for restart of the FFTF reactor in mid-2004, an assessment will be made of staff assignments to support the isotope production mission. It appears likely at this time that recruitment and hiring of new staff will be required during the year preceding restart of the FFTF. However, as indicated above in the response to Question 2, ongoing discussions with private-sector companies could lead to privatization of various components of the FFTF isotope production program. The commercialization of various elements of work involved in the preparation, irradiation, and processing of isotope targets, as well as the marketing, sales, and distribution of the final isotope products, could have a significant impact on the staffing requirements that must be met by PNNL and other contractor organizations at the Hanford Site involved in the FFTF isotope production mission.

10. **Summarize customer inquiries received during the past two years. What percent was filled, referred to other facilities, or rejected? Explain unfilled requests.**

During the past two years the primary isotope product supplied by the Hanford Site has been yttrium-90. Weekly shipments of this medical isotope have been supplied to more than 40 customers who are using yttrium-90 primarily for cancer radioimmunotherapy. As described in Section 2.6.2 of Reference 2, PNNL provided more than 1200 consecutive on-time shipments of yttrium-90 to DOE customers during the two-year period preceding the commercialization of this program. No orders were rejected and there were no unfilled requests for yttrium-90 over the past two years.

Responses are also made to customer inquiries regarding isotopes that are not produced at the Hanford Site. These inquiries are answered within one work day by referring the customers to other DOE Isotope Production Sites or commercial suppliers.

11. **How does each site manager rate customer satisfaction for his site? For the overall program?**

The level of satisfaction expressed by customers for isotope products supplied by the Hanford Radioisotopes Program has consistently been very high. Our dedication to customer service, as exemplified by the 100% on-time record for more than 1200 shipments of yttrium-90 over the past two years, has earned a number of compliments in letters sent by satisfied customers (summarized in Section 2.6.2 of Reference 1. In addition to the timeliness of isotope shipments, the staff involved in isotope production have received a number of compliments for the consistently high quality of isotope products produced at the Hanford Site.

With regard to the overall DOE isotope program, it is our perception that customers are satisfied with the quality of the isotope products that are provided for medical, industrial, and research applications. However, improvements could be made in the availability and timely supply of isotopes that are in demand for therapeutic medical applications and research (e.g., copper-67 and bismuth-212 for early-stage cancer therapy trials and laboratory animal research).

[2] "Program Scoping Plan for the Fast Flux Test Facility: A Nuclear Science and Irradiation Services User Facility," PNNL-12245, Pacific Northwest National Laboratory, Richland Washington, July 1999.

12. **What should be the long-term role of Government in providing commercial and research isotopes?**

It is our firm belief that the supply of isotopes provided by DOE for medical, industrial, and research applications must be strengthened in the near future. This opinion is reinforced by the conclusions of a recent DOE Expert Panel Report on the future need for medical isotopes. Many of the radioisotopes currently used for medical diagnosis and therapy of cancer and other diseases are imported from Canada, Europe, and Asia. This situation places the control of isotope availability, quality, and pricing in the hands of non-U.S. suppliers. It is our opinion that the needs of the U.S. customers for isotopes and isotope products are not being adequately served, and that the DOE infrastructure and facilities devoted to the supply of these products must be improved. The need for greater U.S. capabilities to supply isotopes for medicine and research is one of the fundamental bases for our proposal to restart the FFTF as a national DOE resource.

Additional Questions and Answers

13. **How many undergraduate, graduate and postdoctoral students have been in the PNNL program during the past three years? What was the source of funding for these students?**

Twelve undergraduate students have worked in the PNNL isotopes program for periods ranging from 3 to 24 months during the past three years. The colleges and universities attended by these students include Brigham Young University (1 student), Columbia Basin College (1), Gonzaga (2), Oregon State University (1), Reed (1), Washington State University (4), and Vanderbilt (1).

One graduate student, who is working on his PhD in Nuclear Engineering at the University of Maryland, is performing thesis research on neutron cross-section calculations under the guidance of a member of the PNNL isotopes program.

Sources of support for the undergraduate students have included direct DOE project work (2 students), Associated Western University scholarship funds (2), DOE summer internship funds (5), Laboratory-Directed Research and Development (LDRD) project funds (3).

The PhD candidate's funding is obtained from a DOE Nuclear Engineering Fellowship, which began in January, 1999.

14. **What academic institutions are affiliated with the isotope production program? Please describe this interaction.**

Members of the PNNL isotopes program are involved in several national and international scientific collaborations with academic institutions. Eleven examples of university collaborations in research related to medical isotopes over the past three years are the following:

1) University of Idaho: Synthesis and testing of chelating agents for the alpha emitters radium-223 and actinium-225

2) University of Washington: Covalent linking of chelated alpha emitters to monoclonal antibodies for cancer therapy; also, collaborative research on the development of an automated bismuth-213 generator

3) University of California at Los Angeles: Testing of affinity, avidity, and biodistribution of chelated alpha emitters linked to monoclonal antibodies for cancer therapy

4) Fred Hutchinson Cancer Research Center: Dosimetry and pharmacokinetic modeling of monoclonal antibodies labeled with yttrium-90 and iodine-131 (used for cancer therapy)

5) Stanford University: Dosimetry of radiolabeled monoclonal antibodies for cancer therapy

6) Syracuse University: Synthesis and testing of chelating agents for the alpha emitters radium-223 and actinium-225

7) Oregon State University: Research on applications of small university reactors for production of medical radioisotopes

8) Reed College: Research on applications of small university reactors for production of medical radioisotopes

9) Washington State University: Development of a graduate-level radiopharmacy program

10) Klopin Radium Institute (St. Petersburg, Russia): Development of a medical isotopes program

11) Russian Research Institute of Chemical Technology (Moscow, Russia): Development of a medical isotopes program

15. What other peer-reviewed, external funding is received by those scientists working in the isotope production program? What research does this support?

The staff members in the PNNL isotopes program have several sources of external support provided by commercial clients and government agencies other than the DOE/NE Isotopes Program Office. Much of the research that does not involve medical isotopes relates to the characterization and containment of radioactive waste materials at DOE sites.

The following are examples of peer-reviewed projects funded by government sources during the past three years:

12) DOE Office of Environmental Management (DOE/EM-50): "Caustic Leaching of Hanford Tank Sludges" (project led by PNNL staff, with ORNL and LANL collaborators); funding levels of $650K in FY 1997 and $900K in FY 1998.

13) DOE/EM-50 programs: "Technetium Flow Studies and Chromium Speciation" (two projects involving PNNL staff); funding levels of $230K in FY 1997 and $150K in FY 1998.

14) DOE Office of Science's Environmental Management Science Program (DOE/EMSP): "Architectural Design Criteria for Metal Sequestering Agents" (project led by PNNL staff, with collaborators from the University of California at Berkeley, Texas Tech University, the University of New Mexico, and the University of Alabama); funding levels of $600K in FY 1997, $600K in FY 1998, and $600K in FY 1999.

15) DOE/EMSP programs in "Aqueous Electrochemical Oxidation Mechanisms and Technetium Species in Hanford Nuclear Wastes" (two projects led by LANL investigators, with PNNL collaborators); funding levels of $86K in both FY 1998 and FY 1999.

16) DOE Office of Science (Office of Biological and Environmental Research): "Development and Testing of Injectable Radionuclide Polymer Composites for Cancer Therapy" (project involving PNNL staff); funding levels of $42K in FY 1998 and $58K in FY 1999.

17) Fred Hutchinson Cancer Research Center, National Cancer Institute Grant (Seattle, WA): "Dosimetry Support for Therapy of Leukemia and Lymphoma with Radiolabeled Monoclonal Antibodies" (collaboration involving PNNL staff); PNNL funding levels of $22K in FY 1997, $23K in FY 1998, and $24K in FY 1999.

18) NeoRx Corporation, National Cancer Institute Grant (Seattle, WA): "Internal Dosimetry and Assistance in the Development of Radiolabeled Monoclonal Antibodies" (collaboration involving PNNL staff); PNNL funding levels of $51K in FY 1997, $53K in FY 1998, and $26K in FY 1999.

19) DOE/U.S. Industry Coalition Program: "High Performance Sealed Source Phantoms for Nuclear Medicine" (project involving PNNL staff); funding levels of $47K in FY 1997, $64K in FY 1998, and $37K in FY 1999.

20) DOE/NN Initiatives for Proliferation Prevention: "Medical Isotope Production in Russian Nuclear Facilities" (two projects led by PNNL staff, with collaborators from the Khlopin Radium Institute and the Russian Research Institute of Chemical Technology); funding level of $100K in FY 1997.

In addition to peer-reviewed projects funded by government agencies, staff in the PNNL isotopes program also receive funding from contracts with private companies. The following are examples of funding support from these sources during the past three years.

1) British Nuclear Fuels, Ltd., Tank Waste Privatization Work: "Ion Exchange Testing" (project involving PNNL staff); funding level of $100K in FY 1999.

2) Private contractor (confidential): "Composite Pipe Coating Using Strontium-90" (project involving PNNL staff); funding level of $250K in FY 1998.

3) International Isotopes of Idaho, Inc. (Idaho Fall, ID): "Calculation of Reactor-Generated Isotope Production Rates" (project involving PNNL staff); funding levels of $20K in FY 1998 and $10K in FY 1999.