Expert Panel:
Forecast Future Demand for Medical Isotopes

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CHARGE TO THE EXPERT PANEL

The Department of Energy, through the Office of Nuclear Energy, Science and

Technology, is responsible to assure a reliable supply of research isotopes not available in the marketplace and a supply of commercial isotopes that can only be produced in unique Department of Energy facilities. To meet its obligations, it is essential for the Department to be aware of current and future isotope demands. With the exciting recent clinical results for new treatments and diagnostic agents in nuclear medicine, the future demand for radiopharmaceuticals is likely to change both in quantity and in types of isotopes. The Department of Energy must examine the capabilities of existing facilities and recommend the need for new production capacity for the U.S. market.

The radiopharmaceutical industry generally focuses on the near term market demand and has been a reliable supplier of medical isotopes for the nuclear medicine and health care community. A number of studies have been conducted during the past several years that attempt to predict the potential market for promising new medical isotopes for cancer therapy, pain control, brachytherapy, encapsulated implants and for more accurate diagnostic applications. These studies do not necessarily agree with one another about the potential demand for isotopes for nuclear medicine.

The Expert Panel is charged to review available reports and studies along with their own knowledge and experience in the field and, based on their collective judgments, develop a consensus prediction of future isotope demand through the year 2020. Where possible, the panel should name isotopes and identify quantities. Among the many factors in its deliberations, the panel may wish to consider the following issues:

- Past attempts to predict the future of nuclear medicine and the consequent isotope demand have been less than successful. The Expert Panel should reflect on how nuclear medicine has grown and how new clinical successes will change the market mix and demand. What factors that were not considered in the past predictions should be considered in predicting the nuclear medicine marketplace between now and the year 2020?

- What competing diagnostic and therapeutic modalities will influence future of nuclear medicine? What external considerations, such as regulation and waste management, will impact nuclear medicine and how? Will these issues influence the selection of isotopes to be used in nuclear medicine. Will they constrain the use of nuclear medicine and force the use of non-radioisotope techniques?

- How will health care cost, payment, and facility use issues influence nuclear medicine and the consequent isotope demand?

- What is the infrastructure needed to assure that isotopes are available to support nuclear medicine between now and 2020 and can the private sector provide this infrastructure?

To best assist the Department of Energy to anticipate the needs of the nuclear medicine community in its long-term planning efforts, the conclusions of the Expert Panel should be distributed by the end of 1998.

Executive Summary

The Expert Panel has concluded that the Department of Energy and National Institutes of Health must develop the capability to produce a diverse supply of radioisotopes for medical use in quantities sufficient to support research and clinical activities. Such a capability would prevent shortages of isotopes, reduce American dependence on foreign radionuclide sources and stimulate biomedical research. The expert panel recommends that the U.S. government build this capability around either a reactor, an accelerator or a combination of both technologies as long as isotopes for clinical and research applications can be supplied reliably, with diversity in adequate quantity and quality.

It has been demonstrated that the use of myocardial perfusion imaging in emergency department chest pain centers can reduce duration of stay (12 hours vs. 1.9 days) and reduce charges ($1832 per patient) compared to conventional evaluation (J Nucl Med 1997:38;131p). ^{18}F-FDG PET has been studied for detecting and staging recurrent ovarian cancer. Potential savings were estimated at $8500 per patient with PET (J Nucl Med 1998:39;249p). Non-Small-Cell-Lung Cancer (NSCLC) can be staged with whole-body FDG PET "resulting in fewer invasive procedures and a savings-to-cost ratio of more than 2:1" (J Nucl Med 1998:39;80p). These examples illustrate that a lack of knowledge is very expensive. Nuclear medicine can offer improved patient care at reduced cost over conventional treatments. Though the cost of providing a reliable and diverse supply of isotopes for medical use may seem expensive, it will surely pay for itself in reduced patient care costs, improved treatment and improved quality of life for the millions patients that will take advantage of this technology.

Introduction

The medical community has a single goal: to provide the best possible health care to the public. What do we do when a time-tested branch of medicine feels its ability to provide the best possible care may be compromised? This is not a story that affects one patient in a million, but one of four hospital patients. This is a story of thirteen million nuclear medicine procedures, 100 million lab tests each year. This is a story of cancer therapy, basic research and drug development. This is a story that extends far beyond the scope of bio-medical science. This is the story of nuclear medicine and how its future and the future of patient care require action today to meet the future health care needs of our citizens.

Nuclear medicine as a scientific and clinical discipline is about fifty years old. Much of the early growth and success in nuclear medicine was due to the support by the Atomic Energy Commission followed by its successor the Department of Energy. The Department of Energy has been responsible for radionuclide production in the United States since the early development of nuclear technologies. Radionuclides or radioisotopes are the basic tools employed by nuclear medicine practitioners. These materials have been historically produced in accelerators and reactors run by the DOE and several commercial entities.

Many of the facilities operated by the DOE are no longer operating, or are being operated at greatly reduced levels. Commercial producers of radionuclides have been willing to produce some of the more profitable materials. Because of the high capital costs of constructing and operating these facilities there has been a great reluctance to expand their production capabilities, resulting in shortages of some isotopes. Foreign suppliers have become invaluable in providing for our domestic isotope needs, but concerns do arise that if a particular radionuclide's popularity should increase rapidly so that demand exceeds supply, these foreign production facilities will not meet U.S. needs first. If this scenario should occur, patient treatment could be placed in jeopardy and there will be a public outcry on the lack of vision by the government in dealing with its health care needs.

Without modern, reliable radionuclide production facilities, the practice of nuclear medicine, and the patients that require these services will surely suffer. Nuclear medicine is being crippled by the fact that the present infrastructure for radioisotope production is crumbling, due to aging facilities and their high cost of maintenance. Research radionuclides and radionuclides for promising new nuclear medicine products are frequently unavailable or very expensive. Clinical trials, which are the kernels of promising and exciting new therapies, often need large quantities of radionuclides that are not always readily available. This can lead to the abandonment of research, or at least significant delays in clinical trials.

Nuclear medicine is a well established part of *functional imaging*, which is now a major focus of NIH research.

Imaging is the creation of a visual representation of the measurable property, object or phenomenon. Imaging systems can create a visual map of what the eye and mind can see or they can serve as transducers converting what the eye and mind cannot see into a visual representation that the eye and mind can see.

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In many ways nuclear medicine is similar to x-ray, CT, Ultrasound or MRI. All of these techniques paint an internal picture of the structure of the body that is indispensable for diagnosis. CT, or Computed Tomographic scans use x-rays to build images of soft and hard tissue within the body. MRI, magnetic resonance imaging applies nuclear magnetic resonance (a radio frequency phenomena) to image soft tissue. Ultrasound makes use of high frequency sound waves to make images of soft tissue. But nuclear medicine is different. Unlike these other modalities, nuclear medicine provides functional information. In other words, it allows a physician not only to see the disease, but also to see how it is behaving and changing in real time. The acceptance of PET imaging (positron emission tomography) procedures for reimbursement by the managed care community indicates the clinical value and cost savings of this technique.

In addition to diagnostic imaging, nuclear medicine provides a therapeutic tool. As of 1997 four radiopharmaceutical based therapeutic applications were commercialized in the United States. In addition, over ninety nuclear therapy research trials were under way.

Nuclear therapy will improve patient care by reducing pain, improving the quality of life, reducing costs and shortening treatment times. Without the ability to produce the necessary variety and quantities of radionuclides, many patients may be forced to accept less effective treatments, or be denied treatment altogether. Such a scenario would be unacceptable and unnecessary.

Rationale

The expert panel has been asked to provide their analysis of the current and future radioisotope demands. The analysis will allow the Department of Energy to evaluate its existing facilities as well as provide recommendations for new production capabilities within the United States.

As part of the 'Charge to the Expert Panel' the Department Of Energy contends that although "a number of studies have been conducted during the past several years that attempt to predict the potential market in promising new medical isotopes these studies do not necessarily agree with one another about the potential demand for isotopes for nuclear medicine". The Expert Panel believes that there is only a debate with some differences of opinion about specific isotopes or the rate of growth of medical isotope usage. The panel recognizes that these reports all identify the same trends: growth in isotope use, expected shortages of some major isotopes, lack of a reliable supply of research isotopes produced at a reasonable cost, crumbling Department of Energy infrastructure, over-dependence on foreign radionuclide production, and lack of support for the basic science that drives the application of radiotracers in biomedical research and clinical practice.

"Isotope demand is evolving owing to the development of new applications on one side and to the progressive phase out of some uses on the other side… Inadequate supply of major isotopes produced with reactors, such as molybdenum-99 and iridium-192, would have detrimental impacts in medical and industrial sectors. Although usually they are supplied on a commercial basis, it is important that governments keep interest in monitoring the supply of such important isotopes. It is essential to promote basic research in medical, physical and life sciences that requires small quantities of diverse isotopes.

Some isotopes useful in medical care are produced with high neutron flux reactors and/or special processing facilities, which are very limited all over the world today. Governmental policies are instrumental in maintaining adequate production capabilities for the isotopes used in those fields… Recognizing the great potential of isotopes and their beneficial uses for medical, industrial and scientific applications, governments should consider policy measures for ensuring adequate supply of isotopes adaptable to existing and foreseeable demand."

Beneficial Uses and Production of Isotopes
AEN/NEA Report, 22 May 1998
Page 2, Executive Summary

"It is recommended that governments consider adequate policy measures to guarantee continued supply of isotopes that are essential in medical and industrial applications such as molybdenum-99 and iridium-192. Although the production of those isotopes generally is ensured by the private sector, the consequences of supply shortages would have drastic consequences that call for governments' attention.

To obtain some isotopes especially useful in medical care, high neutron flux reactors and/or special facilities are needed. It is recommended to maintain in operation the few existing reactors and facilities that can be used for this purpose and to plan for their replacement at the end of their lifetime.

Small quantities of diverse isotopes are needed in basic medical, physical and life science research that is essential for progress. It is important to make sure that adequate supply of such isotopes continues to be ensured.

The demand for stable isotopes is increasing, as they are essential for some applications. Although the production of most stable isotopes is likely to be ensured as long as industrial enrichment plants using gaseous centrifuge technology will continue to operate, it is recommended that countries, in particular OECD countries, pursue the development of new technologies or plants for separating stable isotopes that cannot be obtained from the centrifuge technology.

Beneficial Uses and Production of Isotopes
AEN/NEA Report, 22 May 1998
Pages 34-35, Finding, Conclusions and Recommendations

"This research concludes that the nuclear medicine market is likely to enter a phase of strong growth in the twenty first century, both in the United States and around the world. However, the U.S. supply of isotopes is not expected to keep up with rise in demand.

The U.S. nuclear medicine industry relies largely on foreign sources for medical isotopes. In addition to the isotopes MDS Nordion supplies from Canada, overseas reactors such as those in South Africa and the former Soviet Union, are commercializing medical isotopes. Frost & Sullivan estimates that approximately 90% of the medical isotopes used in the United States comes from non-U.S. sources… the dependence on foreign isotope sources concerns all the participants interview by Frost & Sullivan… Shortages of radioisotopes have been well documented in several reports, as well as in hearings before Congress.

The DOE is only producing approximately 10% of the reactor-produced isotopes demanded by U.S. nuclear medicine. Most of the DOE reactors have been shut down, are being shut down, or their primary mission has been refocused. This is a consequence of a change in national and scientific priorities, which reduced funds for isotope production. The remaining reactors can no longer support rising demand for medical radioisotopes.

The reduction in the supply of medical isotopes has led to reduction in research activities in the United States. Radioisotope-based therapy has suffered greatly from a lack of a comprehensive radioisotope policy at the DOE. Most of the nuclear therapy clinical trials conducted in the United States need specific isotopes to measure the efficacy of new technologies. Without an adequate supply of high-quality exotic radioisotopes, nuclear medicine therapy cannot develop.

Frost & Sullivan forecasts that medical isotope demand will increase considerably in the near future. Not only is nuclear therapy expected to become a dynamic new medical field, but nuclear diagnostics is poised for considerable expansion as well."

FFTF Medical Isotopes Market Study (2001-2020)

Frost & Sullivan, 20 November 1997

Pages 5-1 to 5-5, FFTF Opportunity Analysis

"The revolutionary applications of radionuclides for the diagnosis and treatment of a multitude of cancers and illnesses are causing a rapid expansion of the nuclear medicine field. Industrial uses of radionuclides, although not expanding as quickly, also require large amounts of radionuclides. A reliable future supply of radionuclides are essential. Currently, the major production sources of radionuclides are either aging or abroad, or both, and thus cannot be depended upon for radionuclide supplies in the future. Some of these facilities are the major suppliers of research nuclides; their shutdown will effect the future position of the U.S. in the nuclear medicine field. Even at facilities in current operation, many nuclides are

not produced at all or only in a discontinuous fashion because their production is not economically feasible given the design and energy constraints of the producing facilities."

Evaluation of Medical Radionuclide Production with the Accelerator Production of Tritium (APT) Facility
Medical University of South Carolina, University of South Carolina and Westinghouse Savannah River Company, 15 July 1997
Page 4, Introduction

"Worldwide market demand for isotopes has grown steadily since 1992. The radioisotope market has grown by about 17% and now ranges between $92 million and $112 million. Stable isotope demand has risen to about $12 million despite declining prices. Estimated annual dollar growth is approximately 5%, with specific isotope markets expected to grow much more rapidly….one of the driving forces behind many of these growth isotopes is qualification for reimbursement under health insurance plans. As other procedures are approved for health insurance reimbursement, the market opportunity can become even greater."

Worldwide Isotope Market Update
Arthur Andersen & Co. SC, November 1994
Page 18, Summary

The Expert Panel believes that the expected growth rate of medical radionuclide usage during the next 20 years will be between 7-14% for therapeutic applications and 7-16% for diagnostic applications. These growth rates are attainable only if basic research and technological improvements in nuclear medicine are supported and encouraged by the collaborative efforts of both the DOE and NIH.

The Expert Panel was asked to develop a 'list' of radionuclides for the Department Of Energy to consider for production. Three lists are proposed. The first list contains ^{90}Y, ^{99}Mo, ^{111}In, ^{123}I, ^{186}Re. These isotopes were selected because of their proven clinical efficacy, and because they face supply and cost concerns that could dramatically affect the practice of nuclear medicine. The second list consists of ^{18}F, ^{32}P, ^{81m}Kr, ^{89}Sr, ^{103}Pd, ^{117m}Sn, ^{127}Xe, ^{125}I, ^{131}I, ^{153}Sm. These isotopes were selected because commercial and research applications have been developed or are being developed that require their use. The Expert Panel believes their lack of availability and high prices are inhibiting their

development toward clinical applications. The third list is for research materials that show promise as diagnostic and therapeutic materials, but are not being explored because of lack of availability or high price. List three includes: ^{47}Sc, ^{62}Zn, ^{64}Cu, ^{67}Cu, ^{68}Ge, ^{153}Gd, ^{168}Ho, ^{177}Lu, ^{188}Re, ^{211}At, ^{212}Bi, ^{213}Bi, ^{223}Ra.

The Expert Panel recommends that the stable isotope inventory be reviewed. There is great concern that the supply of high purity stable isotopes, used as target materials for isotope production and as stable tracers in metabolic studies, may be in jeopardy. The Department of Energy has historically provided this material from the Calutrons at Oak Ridge National Laboratory. The Calutrons have been shutdown. At present there is no domestic production facility to guarantee the continued supply of these very important isotopes.

To meet the current and future needs of the biomedical sciences the Expert Panel recommends that the United States develop a capability to produce large quantities of radionuclides to maintain existing technologies and to stimulate future growth in the biomedical sciences. The successful implementation of such a program would help insure our position as an international leader in the biomedical sciences well into the twenty-first century. The expert panel recommends that the U.S. government build this capability around either a reactor, an accelerator or a combination of both technologies as long as isotopes for clinical and research applications can be supplied reliably, with diversity in adequate quantity and quality.

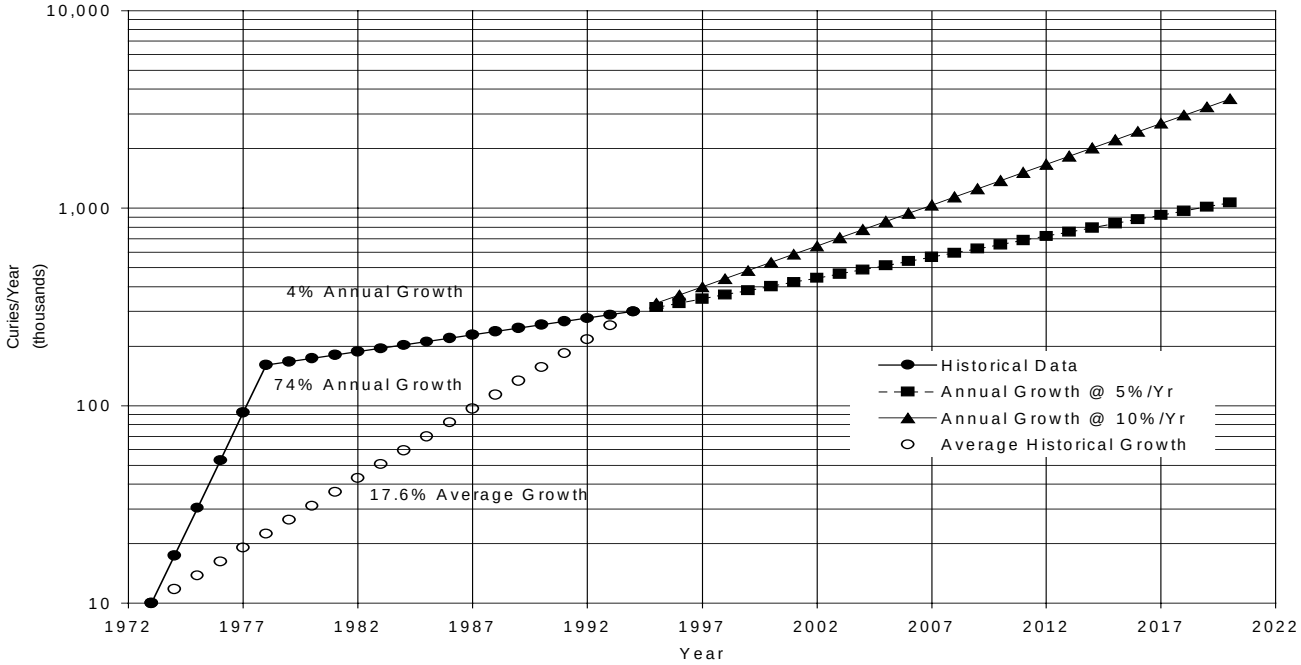
The basic science and clinical aspects must be integrated and equally represented at the highest levels of the DOE and NIH with industry collaboration to insure that both clinicians and researchers are able to take complete advantage of this capability. The expert panel recommends that the current Department Of Energy policy of privatization of all commercially applicable technological developments derived from their programs be incorporated and maintained in the ‘Charge’ to the Isotope Production and Development Program.

Economic Analysis

In forecasting the future demand for new medical radionuclides one can extrapolate from the experiences with ^{99}Mo, ^{201}Tl, ^{123}I and ^{60}Co. When these radionuclides were introduced for research and clinical testing the demand started slowly growing at a modest rate of 4-7% annually. After the efficacy of the radionuclide is demonstrated and it receives FDA approval the demand increased 20 to 30 fold over a short period, to meet clinical needs. Once a market is satisfied, growth continues at a 5-10% annual rate as further applications are developed.

The growth of ^{99}Mo best exemplifies this scenario (Figure 1). First introduced as a curiosity for research applications, the demand increased 20 fold over a 5-year period and then stabilized at a more reasonable growth rate. It would be impossible to meet the needs if action is not taken immediately. Clearly a shortage in supply would result in public outcry for needed isotopes. For these reasons the Expert Panel recommends that a diverse capability, whether they be reactors or accelerators be adapted to produce needed radionuclides.

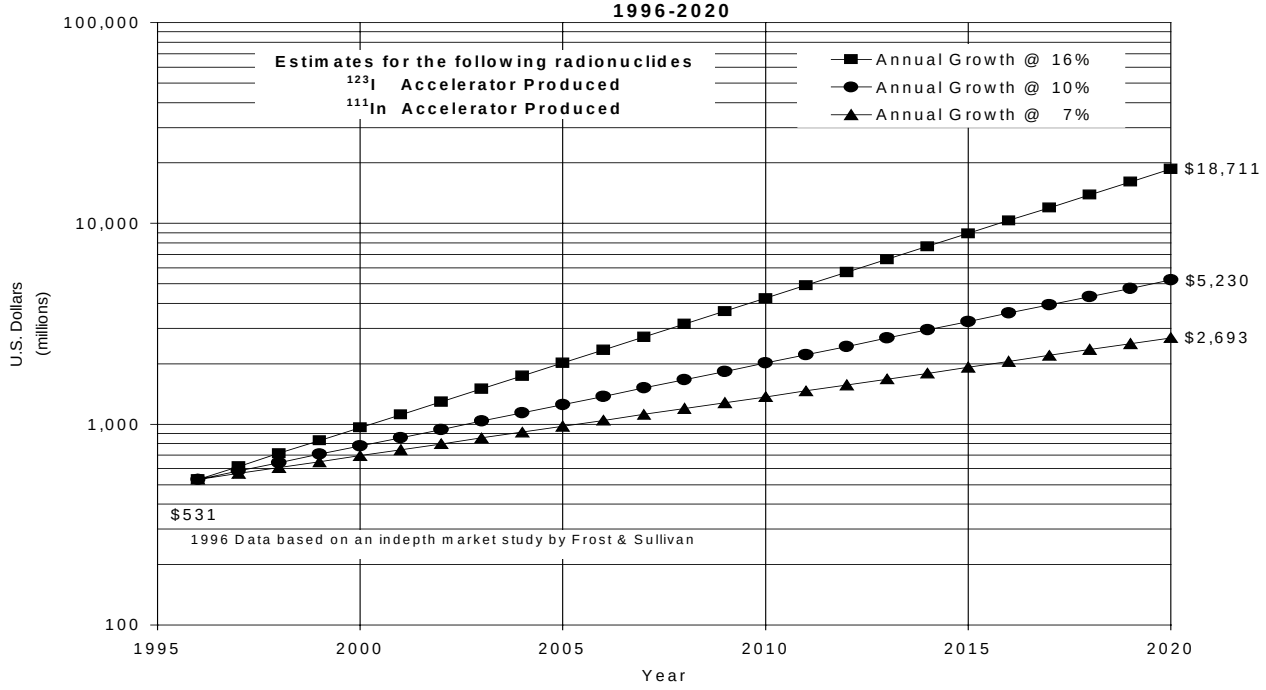
Figure 1
^{99}Mo Historical Demand and Outlook
1973 - 2020



Two major studies recently by Frost & Sullivan and MUSC forecast the market growth for new radionuclides. Frost & Sullivan, who specialize in the pharmaceuticals market, carried out a comprehensive analysis of medical radionuclides for diagnosis and therapy for 1996. These data were accepted as the basis for projecting the market growth to the year 2020.

The Frost & Sullivan report assumed an increase of 10 fold in medical radiopharmaceutical demand for therapy between 1996 and 2001. At this midpoint of time (end of 1998) the demand is not increasing as projected so we have used the 1996 database for our analysis. Frost & Sullivan has projected a 14%/yr increase in demand for therapeutic isotopes and 16%/yr increase for diagnostic isotopes. If one accepts the ^{99}Mo (Figure 1) scenario, the 10 fold increase in 5 years followed by mature growth, the average over 20 years is comparable to the Frost & Sullivan annual growth rate of 14-16%. Based on the more conservative projections by industry and the Arthur Anderson Report, the MUSC Report used the 7-10%/yr growth in demand. No effort was made to analyze the radiopharmaceuticals under development or now coming to market as discussed by Frost & Sullivan.

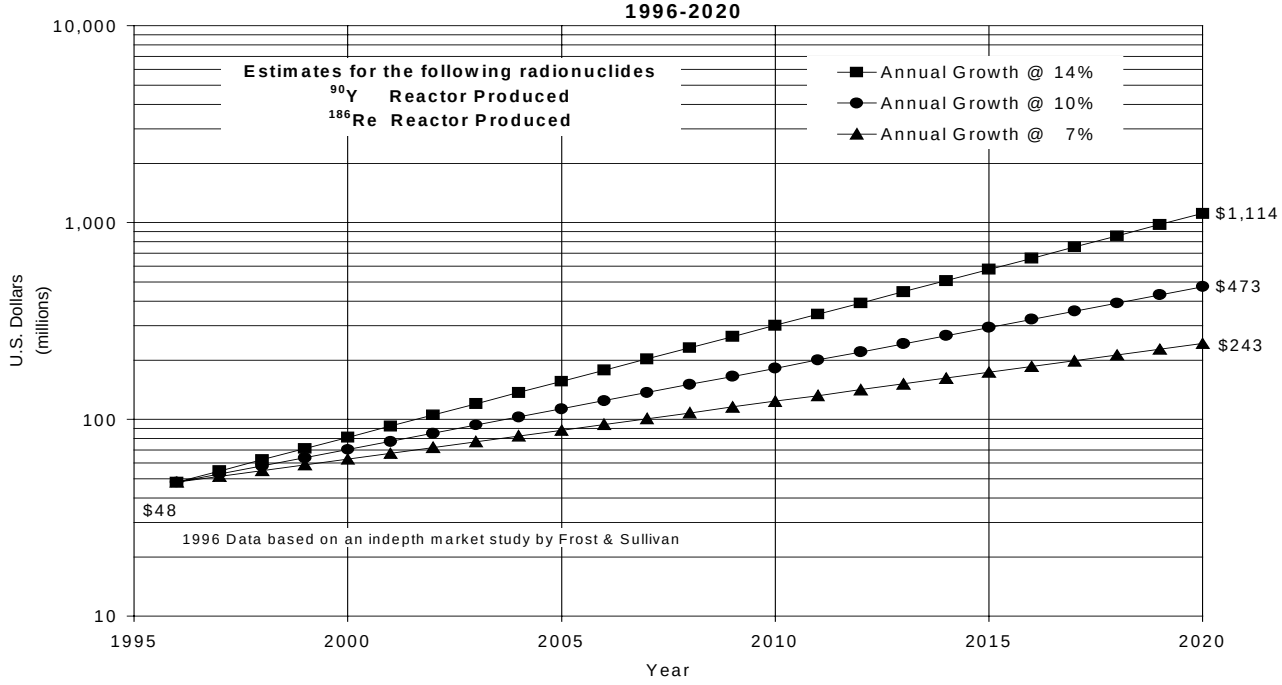
Figure 2
Diagnostic Radiopharmaceuticals Market Forecast
1996-2020



The members of the Expert Panel consider the demand over the next twenty years will lie somewhere between the Frost & Sullivan projections and those of MUSC Report. The diagnostic radiopharmaceuticals market (Figure 2) is forecasted to range from $2.7 billion (7%/yr) to $18.7 billion (16%/yr) by 2020. The major contributors to this explosive growth is based on the availability of the new diagnostic radiopharmaceuticals labeled with radioisotopes of:

^{123}I	Accelerator Produced
^{111}In	Accelerator Produced
^{18}F	Accelerator Produced
^{81m}Kr	Accelerator/Reactor Produced

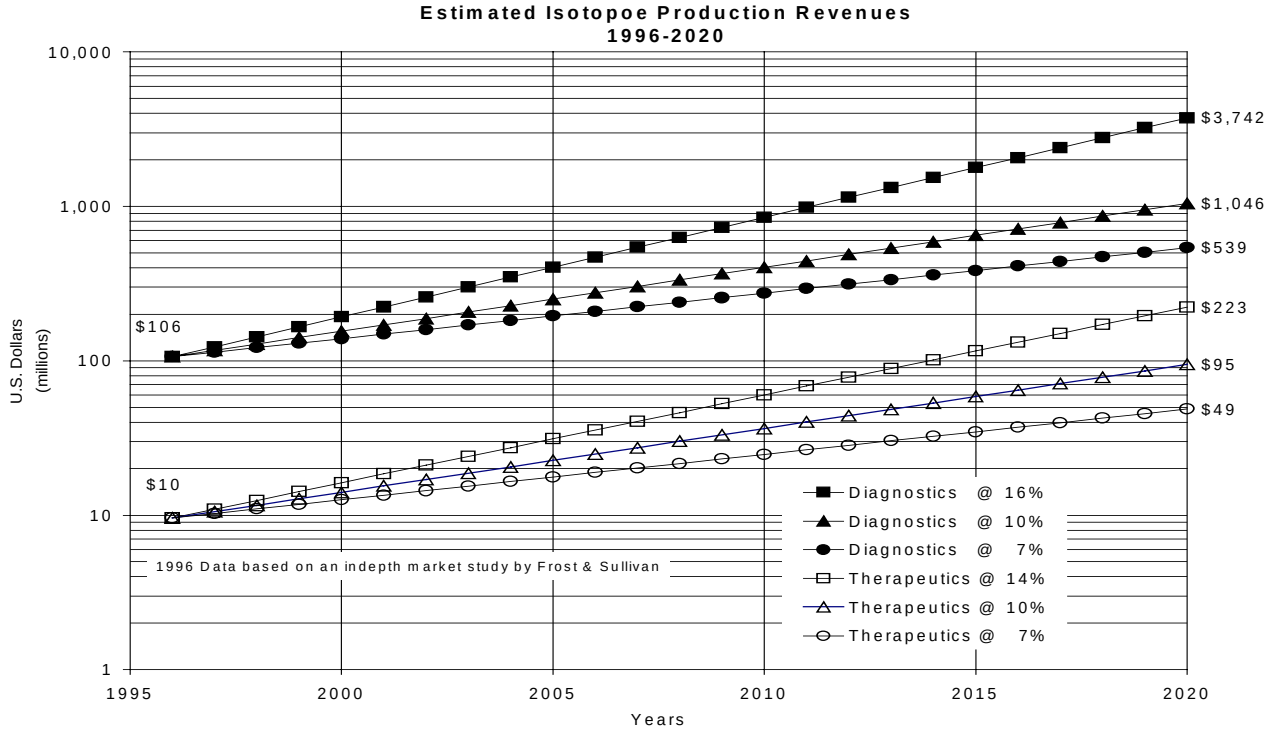
Figure 3
Therapeutic Radiopharmaceutical Market Forecast
1996-2020



The therapeutic radiopharmaceutical market (Figure 3) will range from $244 million (7%/yr) to $1.11 billion (14%/yr) by 2020. The major contributors to the growth in therapeutic isotopes are:

^{90}Y	Reactor Produced
^{186}Re	Reactor Produced
^{32}P	Reactor Produced
^{89}Sr	Reactor Produced

^{103}Pd	Reactor/Accelerator Produced
^{117m}Sn	Reactor/Accelerator Produced
^{131}I	Reactor Produced
^{153}Sm	Reactor/Accelerator Produced



Both the Frost & Sullivan and MUSC reports show revenues for the production of isotopes at 17-20% of the radiopharmaceutical revenues. As shown in Figure 4 a 7%/yr annual growth would generate almost $600 million dollars by 2020 and at the 14-16%/yr annual growth it would increase to almost $4 billion. Production revenues of these magnitudes would justify the adaptation of an existing accelerator/reactor capability to be available to produce medical radiopharmaceuticals. As long as these facilities exist with the capability included in their design to produce radionuclides, the time and costs to add targets and production is significantly smaller than the time and cost of building a *de novo* mega capability.

Appendix A

Historical Outline

Neither biochemistry and biomedical science, nor the use of radioactive materials in the practice of medicine would exist as we know it today if it were not for the contributions derived from the Manhattan District Project, its inclusion into the Atomic Energy Commission and it's successor, the Department of Energy. Under the leadership of Paul Abersold, the by-products of nuclear reactors were made available to the biomedical community immediately after the declassification of the information and facilities developed during World War II.

One can only conjecture what the world would be like if the Manhattan District Project had never come into being. The shorter half-life of accelerator produced ^{11}C would not have been able to meet the needs of scientists that could be met only with reactor produced radiotracers.

Reactor-produced radionuclides, particularly ^{14}C and tritium, gave birth to biochemistry, extending the preliminary results with cyclotron-produced radionuclides, ^{11}C and ^{32}P. Reactors provided an inexpensive supply of radionuclides that were not available in the few accelerators available prior to the war.

As has been the case in nearly all technological advances – radio, telegraph, television, radar, antibiotics, blood transfusion, trauma centers, blood vessel surgery, computers, and, most recently the Internet – have depended on basic and developmental research supported by the federal government in the primary interest of national security.

Leo Szilard, the Hungarian-American scientist, who persuaded President Roosevelt to build the atomic bomb, came to regret the horror of possible nuclear warfare that he had unleashed on the world. But he constantly advocated what became known as the "peaceful uses" of atomic energy.

The world's first nuclear reactor was built by Enrico Fermi and his colleagues at the University of Chicago. On December 2, 1942, the secret experiment code-named CP-1 proved that nuclear fission could be initiated and controlled.

The first reactor-produced radionuclide for biomedical use was ^{14}C, produced at the Oak Ridge Graphite Reactor in 1946. Located at the Oak Ridge National Laboratory (ORNL) near Oak Ridge, Tennessee had begun operation on November 4, 1943, for the

production of ^{239}Pu. After plutonium-239 production had been shifted to Hanford Washington, the Oak Ridge Reactor was used to develop and produce radionuclides for use in medicine, agriculture, and industry. One of Noble-laureate Ernest Lawrence's graduate students, Paul Abersold, was named director of the new 'Isotopes Program' of the also new Atomic Energy Commission, and arrived in Oak Ridge in January 1946. Abersold was the person most responsible for making radiotracers available to the biomedical and other scientific communities.

In the June 14, 1946 issue of Science magazine, the first radioisotope catalogue was published. On the historic date of August 2, 1946, ^{14}C was shipped from the Oak Ridge Graphite Reactor to the Barnard Free Skin and Cancer Hospital in St. Louis, Missouri. This reactor was operated up to its decommissioning in 1963, at which time it became a National Historic Landmark.

Another Atomic Energy Commission sponsored reactor, the Brookhaven Graphite Research Reactor, was also of historic importance, operating from 1950 until 1968. The Oak Ridge High Flux Isotope Reactor (HIFR) began operation in 1966, and remains an important source of radionuclides for research and commercial use. The High Flux Beam Reactor (HFBR) at Brookhaven National Laboratory began operation in 1966 and is another source of radionuclides. The commercial reactor of Nordion in Canada now supplies radionuclides such as molybdenum-99, used to produce the widely used radionuclide, technetium-99m. Despite the pioneering work in the U.S. today, 90% of biomedical radionuclides are produced outside of the U.S., a situation that is deplored by the biomedical community in the U.S. For example, a strike at Nordion threatened to shut down much of the use of technetium-99m radiopharmaceuticals in the U.S.

In the past, most radionuclides used in medical practice and biomedical research were produced in nuclear reactors using the (n, gamma) nuclear reaction for their production. These radiotracers are of low specific activity that limits their use. By bombarding targets with charged particles in an accelerator one can produce neutron deficient radionuclides in a carrier free state, which is not possible using the (n, gamma) reaction. In the U.S. today there are approximately 50 small cyclotrons, many in hospitals, which produce radionuclides, such as carbon-11 and flourine-18, that cannot be made in a nuclear reactor. These cyclotrons have been greatly improved and simplified since their invention by Ernest Lawrence in the early 1930's.

In addition to the unique radionuclides that can be made with accelerators, the high specific activity of accelerator-produced radionuclides are essential for ligands that bind to receptors and other recognition sites, that have limited capacity for binding ligands. Small amounts of carrier often saturate these recognition sites before sufficient radioactivity is bound to the receptors to permit their detection and quantification.

Positron emitting tracers are increasingly being provided by regional suppliers, either academic medical centers or commercial radiopharmacies, but the supply remains quite limited. As the economist Keynes has said: “The difficulty lies not in ideas, but in escaping the old ones.” The time has come to add a capability to the nuclear reactor capability of producing radionuclides at a larger scale then at present. Reactor produced radionuclide products are inadequate at present and should be expanded as well.

The ability to carry out radiotracer whole body imaging of patients at high risk of developing cancer, for example, studies in those persons with a family history of cancer, is helpful in early diagnosis, which makes possible the beginning of specific treatment. A diagnosis based on regional biochemical abnormalities leads to the design and validation of better drugs, as well as making possible better diagnosis.

Today advances are being made in the use of radiotracer methods in oncology, cardiology and neurosciences. In the present climate of changing medical practice, it is increasingly evident that better information leads to better medicine. Treatment can be much more specific, whether it is surgery, radiation therapy, or chemotherapy. Revolutionary advances are also being made in the assessment as well as the planning of treatment. History repeats itself because no one listens the first time. Radiotracer technology is achieving the hopes of the early pioneers in “atomic medicine”.

Appendix B

Impact of Current Regulations On Nuclear Medicine

Nuclear Regulatory Commission (NRC)

The Nuclear Regulatory Commission (NRC) is revising 10-CFR-35, which governs how all of nuclear medicine is regulated from a radiation safety perspective. The revisions, which become effective in June 1999, will result in a scaling back of some of the regulations that have hampered nuclear medicine. These revisions should result in reduced costs for compliance and inspection by lowering fees levied by the NRC. Currently these fees range from $1500 to $35,000, depending on the scope of the operation, and are not recoverable. These costs are significant in the cost effectiveness equation.

NRC regulations translate into additional requirements for the states. Currently 30 states are self-regulating through an agreement with the NRC, 20 states are under direct NRC control. Nuclear Medicine has encouraged the NRC to be as lenient as possible when requiring states to adopt certain regulations, preferring states to write regulations which are suitable for its residents.

Food and Drug Administration (FDA)

The FDA Modernization Act, passed last year, has provisions affecting approvals of radiopharmaceuticals, treating them differently from conventional pharmaceuticals. The nuclear medicine community took issue with the revisions dealing with drug compounding to assure that physicians and pharmacists will be permitted to compound under state law, rather then under federal regulations.

The cost of regulations that apply to the drug approval process is of great concern to the nuclear medicine community. The Center for Drug Evaluation and Research (CDER) has been excessively conservative in approving radiopharmaceuticals and often requires information that is not pertinent to the evaluation of the drug. Both of these circumstances escalate the cost to the manufacturer to develop the drug, which can lead companies to develop alternative drugs due to cost. The high cost of research with radiopharmaceuticals

is considered prohibitive by companies, unless enough initial research already has been completed and the drug shows promise in the marketplace. This is one of the primary reasons that the government should be involved with producing isotopes for use in biomedical research.

Environmental Protection Agency (EPA)

The EPA impacts the practice of nuclear medicine by establishing patient and public radiation exposure standards. The EPA often conflicts with the NRC in radiation exposure standards and air emission standards. This dual regulatory responsibility with NRC drives up the cost of compliance with the regulations. In addition EPA uses extremely conservative estimates which often require significant resources to mitigate.

Other federal agencies we are dealing with that could create barriers to nuclear medicine include the Health Care Financing Administration (HCFA) with reimbursement related to Positron Emission Tomography and Ambulatory Patient Classifications. Medicare reimbursement, which is a significant portion of the nuclear medicine payment class, continues to be reduced with payments shrinking throughout the nuclear medicine system.

These regulations drive up the cost of providing quality health care service utilizing nuclear medicine. The regulatory burdens, due to the use of radioactive material, are higher than any other medical specialty and for the most part go unreimbursed by the third party payor. While progress is being made in the attempt to modify these regulations, it is moving at a pace much to slow to prevent reorganization of the field and possibly limiting patient access to this specialty modality.

Appendix C

Industry and the Department of Energy

The commercial radiopharmaceutical manufacturers and biomedical researchers have not been pleased with the performance of DOE in the past with the reliable and consistent supply of radionuclides. There have been several reasons for these concerns.

Both biomedical researchers and commercial radiopharmaceutical manufacturers need to have a reliable supply of radionuclides. The commercial manufacturers are expected to have finished radiopharmaceutical products available on a continuous basis. The practicing physicians expect to be able to order any product on any day and have it in their hospital the following morning. With a reliable supply of the radionuclides that go into these products, that is very achievable. However, if shipments of these radionuclides from DOE or other suppliers are missed or even late, delays in getting the finished products to the physicians are almost certain. Other commercial radionuclide suppliers have proven to be very effective even under adverse weather, labor or other operational problems. DOE has not demonstrated this reliability. A similar problem arises when a biomedical researcher does not get their radionuclides when expected. Key research studies are scheduled long in advance and require the radionuclides to be in the research lab at the scheduled time of the research. If a shipment is late, often research data is lost and work has to be redone once the radionuclides are received. This can dramatically delay research timetables and create duplicative work.

The nuclear medicine community realizes that many of DOE's problems in the past have been from their lack of control of the reactors needed to produce these radionuclides. However, other delivery problems have been caused by shutdowns over national and government Holidays. These shutdowns are not acceptable in the commercial manufacturing or research communities, and should not be part of a reliable radionuclide supplier world. The industry is also aware of funding problems that DOE has faced in the past. Operations have been temporarily shutdown after funding has been cut or suspended.

One last perceived cause of these delivery problems has been the lack of a hard and fast commitment to honor delivery schedules and timetables. In commercial contracts

there are usually delivery guarantees and penalty clauses for missed or late deliveries. In the past DOE has refused to accept such delivery guarantees in their supply contracts. If commercial radionuclide suppliers can honor these delivery clauses, DOE should be able to as well.

Even though many of these delays in shipments can be explained, it is still not acceptable. In order to be a viable supplier DOE will have to find a way to overcome these problems that have burdened them in the past. Until DOE can do this, the will not become a true world class supplier.

Appendix D

Current Chemistry and Biology Tools: Potential Impact on New Drug Research and Development

Over the past decade major advances have been made in the capabilities that new drug researchers have at their disposal for the identification of new pharmacologically active compounds. Improvements in chemical and bioengineering techniques have revolutionized both the speed and quality of new drug development. For example, the capabilities of combinational chemistry have dramatically increased the rate of compound synthesis and reduced the time required to identify pharmacologically active compounds. High throughput biological screening techniques used in concert with the combinational chemistry has allowed thousands of small molecules to be synthesized, screened and isolated in a few weeks time, where it would have required years previously.

With the rapid identification and isolation of compounds, the potential exists today for the radiopharmaceutical sciences to capitalize on the joining of medical isotope technology with these high-potency biomolecules directed at specific biological targets. This opportunity may provide answers that address both unmet medical needs in the area of more specific diagnostic imaging tools as well as therapeutic radiopharmaceuticals.

These advances should lead to specific benefits in the following major areas of diagnostic clinical need: the detection of thromboembolic disease throughout the body, the differential detection of infectious disease, the detection and differentiation of malignant from benign diseases anywhere in the body, and the differential diagnosis of a variety of psychiatric disorders. The probable isotopes of choice of these diagnostic radiopharmaceuticals will be ^{99m}Tc, ^{111m}In, and ^{123}I.

Of equal importance is the potential of developing radiolabeled cancer-specific compounds to deliver cytotoxic quantities of radiation in-situ. Indeed, the first developments of targeted antibodies and somatostatin-receptor targeted peptides are already showing impressive results in clinical trials for the treatment of lymphomas and neuroendrocrine tumors. There is likely to be further growth seen in the number of clinical trial candidates, and resultant new drug products that are directed at cancer targeted therapies utilizing cytotoxic radioisotopes. These isotopes will be bound to the high

potency compounds which are identified from the tools of combinational chemistry and high-throughput biological screening. Among the isotopes of specific interest in this regard will be those beta emitters with moderate half-lives (e.g. 2-7 days) and high specific activity for efficient labeling of these biomolecules. Among these isotopes are: ^{47}Sc, ^{64}Cu, ^{67}Cu, ^{90}Y, ^{117m}Sn, ^{153}Sm ^{166}Ho, ^{177}Lu.

Appendix E

Isotopes Selected For Their Proven Efficacy That Face Supply And Cost Concerns

Isotope	Pharmaceuticals	Applications
90-Y	90Y-DOTA-biotin	Therapeutic agent for any malignant neoplasm that demonstrates an immunohistologic reaction (NR-LU antigen) including: Breast, Colon, Kidney, Lung, Ovarian, Prostate and Pancreatic cancers.
	Thersphere®	Inoperable liver cancer
99-Mo		Mo-99 is the parent of Tc-99m, the most widely used radioisotope used in nuclear medicine imaging.
	This list of pharmaceuticals is representitive of Tc-99m imaging agents, the complete list is too extensive to include in this document	
	Myoview	Cardiac Imaging
	Cardiolite	Cardiac Imaging
	Miraluma	Breast Cancer Imaging
	Verluma	Non-small-cell-lung-cancer (NSCLC) Imaging
	CEAScan	Colorectal Cancer Imaging
	Leukoscan	Infection Imaging
111-In	OctreoScan®	Somatostatin receptor imaging for gastro-entero-pancreatic neuroendocrine tumors
	In-oxine	
123-I	I-123 beta CIT (DOPASCAN)	Parkinson's (radioimmunoscintigraphy)
	IBZM	Schizophrenia (diagnostic)
	IQNB	Alzheimer's (diagnostic)
	I-123 estradiol	Breast Cancer Imaging
	I-123 MIBG	Cardiac Imaging
	IPPA (ViaScint)	Cardiac Imaging
	BMIPP (fatty acid)	Cardiac Imaging
	Hippuran®	
	This is an important research isotope.	
186-Re	Re-186-HEDP	Pain pallation for metastatic bone cancer Rheumatoid arthritis

Appendix E

Isotpes That Are Being Developed Toward Clinical Applications That Face Availablity and Cost Concerns

Isotope	Pharmaceuticals	Applications
18-F	FDG	PET Scans
32-P	sodium phosphate	Bone pain therapy Cancer treatment, cell metabolism studies, kinetics studies and genetics research in biochemistry, microbiology and enzymology
81m-Kr		Ventilation perfusion scintigraphy
89-Sr	Metastron	Bone pain therapy
103-Pd	TheraSeed®	Prostate cancer implants
117m-Sn	117m Sn stannic DTPA	Bone pain therapy Various radio-immunotherapies (RIT) and imaging applications
131-I	MIBG 131I	Various therapeutic applications (RIT)
153-Sm	Quadramet	Bone pain therapy Various therapeutic applications (RIT)

Research Isotpes

Isotope	Application	Isotope	Application
47-Sc	Radio-immunotherapy (RIT) Various therapies are being explored	153-Gd	Various therapies are being explored
62-Zn	62 Zn/ 62 Cu Generator for PET	166-Ho	Bone marrow ablation Radiation synovectomy agent
64-Cu	Clinical diagnostic agent for cancer and metabolic disorders Potential PET tracer	177-Lu	Various therapies are being explored
67-Cu	Non-Hodgkins Lymphoma	211-At 212-Bi 213-Bi 223-Ra	Alpha emitters are being studied for a variety of theapeutic applications
68-Ge	PET Calibration Potential antibody label		