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SCOPING ASSESSMENT ON MEDICAL ISOTOPE PRODUCTION AT THE FAST FLUX TEST FACILITY

S. W. Scott
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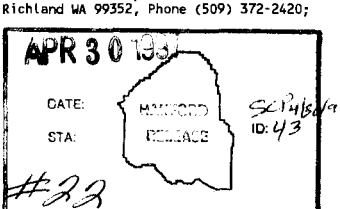
Abstract: The Scoping Assessment addresses the need for medical isotope production and the capability of the Fast Flux Test Facility to provide such isotopes. Included in the discussion are types of isotopes used in radiopharmaceuticals, which types of cancers are targets, and in what way isotopes provide treatment and/or pain relief for patients.



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Scoping Assessment On Medical Isotope Production At The Fast Flux Test Facility

October 25 1996

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Scoping Assessment On Medical Isotope Production At The Fast Flux Test Facility

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Scoping Assessment on Medical Isotope Production at the Fast Flux Test Facility

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Scoping Assessment on Medical Isotope Production at the Fast Flux Test Facility

1.0 Executive Summary

This scoping assessment addresses the use of the Fast Flux Test Facility (FFTF) to produce reactor medical isotopes. The FFTF is currently being evaluated as a tritium production reactor to help meet the defense needs for the United States. A restart of the FFTF would not only serve national defense needs but would also provide a unique opportunity for the production of medical isotopes.

Health care costs in this country exceed $1 trillion dollars annually. The costs for battling cancer alone have exceeded $150 billion a year and continue to grow.[1] The economic burden placed on our society by these costs is eroding the quality of our lives and preventing the country from focusing on other problems such as reducing the national debt and improving the quality of our environment.

Medical isotopes are an indispensable and growing component of this nation's health care system. The use of medical isotopes cuts the cost of health care and dramatically improves the level of patient care. The medical isotope market is expanding rapidly, yet domestic sources have lost considerable market share to foreign suppliers who are now dominating the industry.

There have been numerous studies (MIRC, Frost & Sullivan, Arthur Anderson, Tulane University) showing the growth potential of the radiopharmaceuticals market. These studies predict annual market growth rates from 8% to 23%. Currently the market is dominated by "diagnostic" isotopes such as molybdenum-99 and thallium-203, but experts believe that "therapeutic" isotopes will surpass the diagnostic market subsegment in the next five to ten years.

The FFTF can easily produce both diagnostic and therapeutic isotopes. It has an advantage possessed by no thermal reactor in that its energy spectrum can be tailored from fast neutron energies down to epithermal. Because the production of isotopes in the proper quality and quantity is sensitive to the neutron energy spectrum, there are certain therapeutic isotopes that can only be produced effectively in a fast reactor such as the FFTF. The FFTF also has the largest target volume of any reactor within the U.S. Department of Energy (DOE) complex. Its large volume and energy tailoring capabilities will allow the FFTF to make large quantities of a variety of medical isotopes.

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[1]Number extrapolated using 8% annual growth from 1990 figures, The National Economic Burden of Cancer Volume 82, No. 23, Dec. 5, 1990.

Several extremely promising therapeutic isotopes for the treatment of cancer and other diseases are generally not available to our medical community. This is because thermal reactors are not well suited for making them. As a result, the capital investment associated with obtaining these isotopes is cost prohibitive. On the other hand, the FFTF, with its flux tailoring capabilities and large target volume, is ideally suited for the production of these new isotopes. The use of the FFTF to produce tritium for this country's defense needs provides a special opportunity for the research and production of this new generation of medical isotopes that would not otherwise be available to the medical community.

As seen in this assessment, the FFTF can produce large quantities of a variety of radioisotopes concurrently with a tritium production mission. Once other primary tritium production facilities come on line, the FFTF can transition its role from a primary source to a supplementary/backup source and shift its focus to radioisotope production. Over the next 30 years, the country would benefit immensely in using the FFTF to produce medical isotopes by:

- increasing U.S. market share to at least 50% of the rapidly expanding radioisotope market.
- decreasing the trade deficit by at least $10 billion.
- decreasing health care costs by over $150 billion.
- saving over 100,000 lives a year.
- producing medical isotopes not available from other sources, thereby allowing the realization of new treatment technologies which could eventually result in the cure for cancer, AIDS, and other diseases.
- supplying medical isotopes for the treatment of over 20 million cancer patients. These isotopes will allow a vastly increased survival rate and dramatically improve the level of patient care when compared to other treatment modalities.
- generating a new regional industry, creating thousands of jobs, and the positioning of the Pacific Northwest as the international leader in cancer research and treatment.

Using the FFTF to produce medical isotopes in conjunction with the production of tritium provides a low risk, high return option to help meet the health care needs of this country.

2.0 The Need for Medical Isotopes

Health care costs continue to skyrocket in this country. From 1960 to 1993 national health expenditures had a 11.36% compounded annual growth rate and have now exceeded $1 trillion a year. The cost to treat cancer increased 45% from 1985 to 1990 to $104 billion a year. The number of cancer patients is equally staggering, with over 3 million people currently affected and 1.2 million new cases of cancer each year.[2]

The use of radioisotopes in the diagnosis and treatment of diseases has grown dramatically in the past 20 years. Medical isotopes are currently used in over 13,000,000 procedures each year and as therapeutic isotope technology advancements reveal new modalities of treatment, this number will grow significantly.

2.1 Diagnostic Isotopes

Diagnostic radiopharmaceuticals currently dominate the medical isotope arena. Diagnostic nuclear medicine involves the administration of very small amounts of radioactive substances, which are distributed within the body according to the product's physical and chemical properties. The radiopharmaceutical is selected based on its affinity for certain body organs or other sites of clinical interest. These radioactive materials "illuminate" the sites of interest in a manner that can be detected by appropriate instrumentation and subsequently provide an image for the physician to work with. These images can then be analyzed and correlated with clinical experience.

There are 17 different elemental groupings of radiopharmaceuticals compounds that have been approved for diagnostic procedures by the Food and Drug Administration (FDA). These 17 groups are produced in 51 different compounds, each one specific to a certain diagnostic application. Within these 51 compounds, 117 radiopharmaceuticals are approved for use. The most common product is technetium, which has 53 radiopharmaceuticals approved for use and constitute over 65% of all injections given.[3]

Nuclear medicine imaging procedures often identify abnormalities very early in the progression of a disease. For many medical problems this detection allows a disease to be treated early in its course, reducing the cost of treatment and allowing a more successful prognosis. Without question, diagnostic procedures using radiopharmaceuticals have dramatically improved the patient care in our health care systems and have also eliminated untold costs. Diagnostic radiopharmaceuticals have become an integral part of patient care. Supply of these radiopharmaceuticals, particularly technetium products, must be assured.

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[2]Cancer Facts and Figures 1994, American Cancer Society.

[3]Frost and Sullivan, The U. S. Market for Nuclear Imaging Equipment and Radiopharmaceuticals, 1990.

2.2 Bone Pain Relief

Over 50% of all prostate, breast and lung cancer patients eventually develop metastatic bone cancer. The pain related to this cancer is tremendous. In addition to progressive pain, the patients also suffer a host of other symptoms including neurologic deficits, immobility, and loss of independence, often associated with feelings of depression, fear, and isolation.[4] Interventions to palliate the pain include administration of narcotic and nonnarcotic analgesics, surgery, radiotherapy, second- and third-line hormonal agents, and radiopharmaceuticals. Of these interventions, radiopharmaceuticals are emerging as the treatment of choice due to their low cost, high pain relief ratios, and minimal side effects. Most recently, data from clinical trials suggest that, in addition to the palliative effectiveness of radiopharmaceuticals, treatment can also modify disease progression, reducing requirements for future interventions. Five radiopharmaceuticals are presently available for the palliative treatment of bone metastases, either in clinical trials or in general use:

Phosphorus-32 was introduced in the early 1940's. Its use paved the way for other isotopes but has been progressively abandoned because of its considerable hematological toxicity.

Strontium-89 is approved by the FDA for general use and is used most frequently. It has a relatively long half-life (50 days), has a maximum penetration range in tissue of 6.7mm, but has no useful gamma emission for imaging and subsequent dosimetric calculations.

Rhenium-186 is in Phase II and Phase III trials. It has a short half-life of 3.8 days and a maximum penetration range of 4.7mm. It provides excellent imaging capabilities with its 137 keV gamma emission.

Samarium-153 is also in Phase II and Phase III clinical trials. Its half-life is 1.95 days with a maximum penetration range of 3.4mm. It also provides good imaging capabilities with a 103 keV gamma emission.

Tin-117m is currently in phase I clinical trials. It has a half-life of 13.6 days and provides a 159 keV gamma for imaging.

It is important to note that any or all of these isotopes could emerge as the product of choice for the treatment of metastatic bone pain. They each have advantages and disadvantages for each particular case of treatment. With over 240,000 new cases of metastatic bone cancer in the U. S. each year, the demand for these isotopes will be quite large. The FFTF can meet this demand and has the flexibility to produce any or all of the above isotopes in the required amounts and purities.

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[4]Cleeland CS. The impact of pain on patients with cancer. Cancer. 1984;54:26, 35-41.

2.3 Therapeutic Isotopes

Recent events indicate tremendous growth potential and interest in the area of therapeutic isotopes:

- Dozens of clinical trials are showing extremely impressive results with the use of therapeutic isotopes. The use of these isotopes to treat cancer could in fact provide an eventual cure for this disease.

- The FDA granted approval of strontium-89 in 1995 and several other isotopes such as iodine-131 and rhenium-186 are nearing approval.

- A recent meeting attended by 37 nuclear medicine experts from around the world was held on the use of alpha emitters. The results of this meeting showed a great deal of promise in this new and exciting field.

- Clinical trials with the use of bismuth-213, an alpha emitter, have just started.

- Recent trials with the use of phosphorous-32, via infusional brachytherapy, have shown dramatic effects in destroying malignant tumors caused by pancreatic cancer.

Many industry experts expect the demand for therapeutic isotopes to surpass the demand for diagnostic isotopes in about five years. However, this demand increase will only occur if a supply of isotopes is available to perform clinical trials. It is apparent that the use of therapeutic isotopes to battle cancer, AIDS, arthritis, and other diseases is on the verge of becoming a major component of our health care system. The FFTF could provide a critical role in the research and production of these isotopes. This would benefit the country and the world in general. In fact, the FFTF could become a major player in the medical isotope arena and help to establish the Pacific Northwest as the international leader for the diagnosis and treatment of cancer.

Development of cell-directed radiation therapy is now at the forefront of cancer research. In this innovative treatment, radioisotopes are attached to monoclonal antibodies which are then injected into the patient's bloodstream. The antibodies seek out and attach themselves to the cancer cells and the radioisotope then kills the cancer cell with "cell-directed" radiation. This method of treatment spares the patient the horrible and debilitating side effects of external-beam radiation or chemotherapy.

Radioisotopes currently used for this application are generally beta emitters (unstable atoms that emit radiation in the form of beta particles) such as iodine-131 and yttrium-90. Beta emitter trials have been highly successful with up to a 93% success rate in otherwise terminal lymphoma patients.[5] However, because beta particles travel a relatively long distance in soft tissue they
waste cancer cell killing power by delivering radiation to non-targeted, healthy cells.

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[5]The Lancet, Vol. 346, August 5, 1995: Phase II Trial of ^{131}I-B1 (anti-CD20) Antibody Therapy with Autologous Stem Cell Transplantation for Relapsed B-cell Lymphomas.

The preferred isotope for cell directed radiation therapy is an isotope that emits alpha particles. Because alpha particles travel a relatively short distance (2 to 3 orders of magnitude less than beta particles) in soft tissue, they spend most of their energy killing cancer cells and cause very little damage to non-targeted cells. Alpha particles also cause much more damage to the targeted cancer cells than beta particles. This is because alpha particles typically are higher in energy and deliver this energy over a very short distance. In radiation biology terms, alpha particles have a high Linear Energy Transfer (LET) rate. Their high LET also corresponds to a high Relative Biological Effectiveness (RBE). This means that for a given radiation dose, alpha particles destroy many more cancer cells than beta particles.

The use of beta emitters in cell-directed radiation therapy has been more a matter of necessity than of choice. Although alpha emitters appear to be more effective than beta emitters and have fewer side effects, a supply to conduct clinical trials is not available to the medical community. This is why most studies are being conducted with beta emitters. If the FFTF were operating, it could produce isotopes to conduct clinical trials as well as meet the entire U. S. expected demand for alpha emitters, such as actinium-227/radium-223, and do so more cost effectively than the production of any beta emitter anywhere in the world. The demand for isotopes like actinium-227/radium-223 could be tremendous. As shown in a recent demand study, the total number of patients that are expected to be treated by actinium-227/radium-223 could approach 15 to 20 million over the next 17 years. This number is not unrealistic since it assumes only 50% of the available patients would receive treatment.

As clinical trials are conducted and the public becomes aware of the advantages of radioimmunotherapy with alpha emitters over other treatment modalities, they will demand immediate FDA approval and mass production of these isotopes. Without the FFTF, the U.S. does not have the capability to produce the required quantities of alpha emitters and will once again have to rely on foreign suppliers. With an estimated retail market of over $300 million per year, alpha emitter production and processing will create thousands of jobs. This country cannot afford to allow opportunities such as this to continue to go abroad.

3.0 Cancer Costs

If we look at the expenses involved in treating cancer, we find it will cost, on the average, $15,000 per surgery, $10,000 for chemotherapy and anywhere from $2,000 - $10,000 for external radiation treatments. If we look at the potential number of patients that could use cell-directed radiation therapy (at an average cost of $2,000 each) instead of the standard procedures, the cost savings are tremendous. The number of patients that could experience these costs saving for the next 30 years is at least 20 million. If we then assume a cost avoidance of $8,000 per patient, we could save $160 billion from our national health care expenditures. These potential cost savings from the use of radioimmunotherapy must be seriously considered and in themselves, easily justify the costs associated with operating the FFTF.

The other cost of cancer is the cost in terms of human loss and suffering. Over 550,000 people will die of cancer in 1996.[6] The U. S. has typically spent about $100,000 per life saved for programs dealing with highway safety measures, cancer screening, etc., and up to $2 billion per life saved on nuclear reactor safety improvements.[7] It is somewhat disconcerting to see that only $2.7 million was spent by the U. S. government in 1996 for radioisotope development.

4.0 Medical Isotope Availability

Currently, 95% of all medical isotopes are produced outside the United States. Foreign dominance of this high-tech business raises questions about the reliability of supply and our dependence on other governments for these critical health care tools.

The cornerstone of the U.S. radioisotope production capabilities is the Isotope Production and Distribution Program (IPDP) which is run by the DOE's Nuclear Energy Department. Since its establishment as a self-sufficient entity in 1990, the IPDP has had large, recurring losses.[8] This is due to several reasons:

- The IPDP was forced into a mode of full-cost recovery by Public Law 101-101. Although this law was in effect made moot by the passage of the 1995 Appropriations Act (Public Law 103-316), considerable damage was done to the U .S. market share and the credibility of the IPDP as a low cost, reliable supplier.

- The IPDP remains dependent on other programs of which many are being substantially reduced or eliminated.

- U.S. production facilities are old and funds for upgrading them are generally not available.

- Customers are not comfortable depending on the DOE for long-term supplies because past experience has shown that medical isotope production is not a major priority for the DOE.

The IPDP's losses are expected to continue over the next few years; despite the efforts of the Program, U.S. production capabilities and market share have declined over the last 6 years.

A large problem faced by the IPDP is that it has no production capability for molybdenum-99 (Mo-99). The daughter product of Mo-99 is technetium-99 metastable (Tc-99m). This isotope is of vital importance to our medical community. It is used in over 30,000 diagnoses every day. Currently, all of the Mo-99 used in the U. S. is made by a single reactor in Canada. This reactor , the National Research Universal (NRU), is nearly 40 years old and is

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[6]American Cancer Society, Cancer Facts and Figures, 1996.
[7]B.L. Cohen, American Journal of Physics, 55(12), December 1987.
[8]Arthur Andersen, Market Analysis Update, Nov. 1994.

scheduled for shutdown before the year 2000. The Canadians are planning to build two new reactors to replace the NRU but have been tied up with funding problems. Other sources of Mo-99 are available; however, most of these would need to get FDA approval before use in the U. S. Even then, they would not be able to meet our total demand. Relying on one old reactor for the supply of Mo-99 places our medical community at great risk. Because of this, the IPDP has focused much of its resources and efforts in trying to overcome this problem. The Program had planned to use the Omega West reactor at Los Alamos until a leak in its aging primary coolant system was found in January 1993. It is now the IPDP's intention to use the Annular Core Research Reactor (ACRR) at the Sandia National Laboratory to produce Mo-99. A Record Of Decision on this was issued on September 11, 1996. Although the ACRR can effectively produce Mo-99, it will serve as a backup supply with a normal production capacity of 10-30 % of the U. S. demand, with the capability to increase production rapidly to supply 100 % of the U. S. demand.[9] This still places the U. S. at risk, especially if the new Canadian reactors continue to slip their construction dates. The FFTF could serve as a large source of Mo-99. It was dismissed in the *Medical Isotopes Production Project: Molybdenum-99 and Related Isotopes Environmental Impact Statement*, April, 1996, as being too large to economically produce Mo-99. This is not the case if the FFTF is used to produce tritium and other isotopes. The FFTF was also dismissed because of the "required outage periods for a reactor of its size". With the research and testing mission in the past, the FFTF typically had outages in the 15-30 day range. There was, however, nothing that required its outages to be short. With a tritium and medical isotope mission, where maximum operating time is critical, the FFTF could reduce its outage times significantly.

The problems encountered by the IPDP in finding a suitable place for the production of Mo-99 mainly hinge on the fact that its facilities are getting old. As seen in Table 4.0, this is not a minor problem. As the IPDP struggles to fulfill its mission, considerable energy and resources will be expended in trying to reconfigure, patch-up, and upgrade old reactor facilities to meet the needs of the isotope industry.

[9]Medical Isotopes Production Project: Molybdenum-99 and Related Isotopes, Record of Decision, September 1996

Table 4.0
Reactor Facilities Used for the Production of Isotopes for the DOE

Name	Location	Date of Initial Operation	Remaining Lifetime	Future
Advanced Test Reactor	Idaho	1970	> 10 years	Operations should continue well into the next century
High Flux Isotope Reactor	Oak Ridge	1965	< 10 years	Operations should continue for a few more years
Annular Core Research Reactor	Sandia	1978* (1969)	> 10 years	ROD issued for Molybdenum-99 production mission
Omega West	Los Alamos	1959	?	Reactor is shutdown due to a leak in primary coolant system
K-Reactor	Savannah River	1954	?	Reactor is shutdown and not expected to restart
Fast Flux Test Facility	Hanford	1982	23-30 years	Currently scheduled for shutdown

* Note: The Annular Core Research Reactor (ACRR) was originally called the Annular Core Pulsed Reactor (ACPR) which began operation in 1969. In 1978, the ACPR was upgraded to the ACRR. Since the ACPR and the ACRR were operated at very low duty cycles the core is essentially new in terms of steady-state operation.

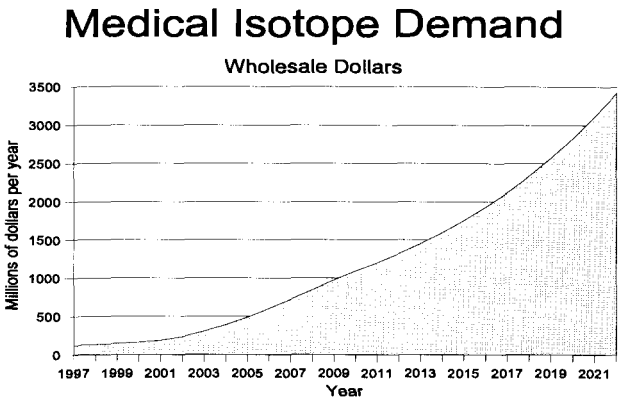
The IPDP has not been able to establish a much needed customer relations base. This is, in part, due to the fact the IPDP is part of the DOE . The DOE has been focusing on regulating the recovery from the defense mission and has at times, become entangled in the red tape and zero-risk thinking associated with this mission. Isotope production needs the freedom and ability to take reasonable risks associated with a vibrant research and market development for new technologies. Risk taking, which is an essential element in the quest for new technologies, has simply not been an acceptable practice within the DOE. This is especially true when relating to additional nuclear operations. Also, the IPDP has had conflicts between their original mission and vision and the way they were forced to conduct business under the guidelines of the "full cost recovery" of Public Law 101-101. The DOE and the IPDP are trying to overcome these problems.

In 1994 the IPDP developed the National Isotope Strategy, which clearly delineates the vision, goals and strategy for the Program. The Program also conducted a market analysis in 1992 (updated in 1994) that not only pointed out the direction and the growth potentials of the market but also looked at what the IPDP customers thought about the Program. The IPDP also sought and accomplished a change in legislation that allowed them to get out of the full cost recovery mode they were forced into in 1990. The full cost recovery mode caused the Program to deviate from its original goals for isotope production and distribution by narrowing the range of isotopes it could produce to those that it could earn a profit on. This did not allow for the fulfillment of the Program's primary mission of producing and distributing isotopes to meet our national research needs and supporting our health care system.

The IPDP is clearly moving in the right direction. With a restart of the FFTF, the IPDP would have a newer facility with more capabilities than the rest of their current facilities combined. The addition of the FFTF to the Program would clearly enable the U. S. to realize its rightful place as the supplier of choice in the radioisotope market.

5.0 The Medical Isotope Market

Several major studies have been devoted to the analysis of the radioisotope market. All of the studies predict significant growth, with some of the studies predicting a radiopharmaceutical wholesale market of $400-700 million per year within the next seven to ten years. As seen in the chart below, substantial growth is expected in the total market, with the bulk of the growth coming from therapeutic isotopes.[10]



The medical isotope market has not experienced the growth levels it is capable of due primarily to the fact that key isotopes needed for research, clinical trials, and eventual widespread application are simply not available to our medical community. This includes several extremely promising therapeutic isotopes for the treatment of cancer and other diseases. Without the FFTF, the capital investment associated with obtaining these isotopes is cost prohibitive. In effect, there is a potential for a very large market for these isotopes, but since their availability is questionable and the initial capital investment is high, the market potential is not being realized. The market for these isotopes depends upon their availability in smaller quantities to perform necessary clinical trials. Only when these trials are completed, and the isotope certified by the FDA for use, can the market grow. The availability of the FFTF is essential to provide as many isotopes as possible during the clinical trials. This will enable the unique therapeutic benefits offered by the isotopes to become available to those suffering and dying from cancer and other diseases. Testimony provided to the Energy and Water Appropriations Subcommittee (February 1996) by Robert Atcher on

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[10]Growth rates based on market growth estimates from *The FFTF Business Plan*, Tulane University, September 1993.

behalf of the American College of Nuclear Physicians and the Society of Nuclear Medicine stated that:

> "The nuclear medicine arena developed into a $10 billion dollar a year health service industry from a small research enterprise funded by the DOE and predecessor agencies. This industry has been a spectacularly successful example of the beneficial growth of an industry from federally funded research. At this time however, the flow of products and techniques into the marketplace and into the clinic is threatened by decreasing support and shrinking research budgets."

If the FFTF were operating to produce tritium, it could reestablish an influx of new medical isotopes which is crucial to the growth of this industry. It could also produce these isotopes with little or no additional cost to the taxpayer.

6.0 The FFTF

A restart of the FFTF will provide the DOE an outstanding opportunity to regain its research and production capabilities and reaffirm its commitment to help revitalize the regional and national economies.

6.1 Overview

The FFTF is the world's largest, liquid metal-cooled test reactor. This 400 megawatt reactor was designed to be operated as a prototype plant for the Clinch River Breeder Reactor, to test full scale components and to test fuels and materials for the Liquid Metal Fast Breeder Reactor development program. During the late construction phase of the FFTF, the nation's breeder program was abandoned, putting an end to the need for a breeder prototype and test reactor. However, because of its design and versatility, the U. S. decided to complete construction and operate the reactor to irradiate and test new reactor fuels and structural materials for U.S. and international agencies; to conduct operational, safety, and balance of plant testing; and to eventually produce medical and industrial radioisotopes. Examples of some of the FFTF's various missions include:

- Fusion program material testing,
- Space Isotope Program testing (Pu-238),
- Space Reactor Program materials testing,
- International Testing Program, specifically for Japan and the European Fast Reactor Programs,
- Liquid Metal Reactor (LMR) fuel testing, and
- LMR passive safety testing.
- Medical and Industrial radioisotope production.

The ability to perform the above tasks proves the flexibility, reliability, and safety of the FFTF and the capabilities of the Physics and Engineering staff.

The reactor operated for approximately ten years (1982-1992) before being placed in standby. The reactor's outstanding operational performance was achieved by the combination of a highly qualified and dedicated staff, and a superior plant design that has been repeatedly validated through testing and operation.

The term "fast flux" is indicative of the high energy (speed) of the neutrons within the reactor core. These high energy neutrons, coupled with the FFTF's relatively large power output, allow the FFTF to test a variety of materials and produce many isotopes in amounts and purity levels not attainable in other reactors.

The flux density of the FFTF is significantly higher than in a light water reactor. When producing medical isotopes, this will result in a high "specific yield" per target assembly. This means that fewer target assemblies are needed to produce the same amount of isotopes. This reduces costs, exposures to personnel, and the waste burden on the environment.

Radioisotope production has been extensively studied and demonstrated, with over 60 different isotopes produced for medical and industrial applications. In 1986, the FFTF produced gadolinium-153 of the highest purity ever made. This material, which is used to diagnose and detect osteoporosis, was made by the FFTF to avert a world shortage in 1988. During the late 1980's, the FFTF produced other isotopes which were delivered to physicians and hospitals for cancer treatment, diagnostic research, and cardiovascular and brain studies.

6.2 The FFTF's Role in Medical Isotopes

The FFTF is well suited for a dual mission of tritium and medical isotope production. Preliminary studies show that the FFTF can produce large quantities of a variety of radioisotopes with a minor impact on tritium production. Here, the flexibility of the FFTF and the experience in core configuration manipulation, test assembly design and isotope production comes significantly into play. One proposed core would produce 1.9 kg/yr. of tritium and allow the production of a majority of the market demand for several key isotopes. This proposal provides approximately 1500cc (three core positions) of in-core space for medical isotope production. This is just one example of what might be done in configuring for the dual mission. Further studies will be required to optimize tritium and medical isotope production.

The production of isotopes in a variety of both moderated and nonmoderated test assemblies has been well demonstrated in the FFTF:

- The Materials Open Test Assembly is a nonmoderated vehicle that has been used extensively for the production of a variety of isotopes.

- The Cobalt Test assembly was an isotope production assembly moderated with yttrium hydride. It was irradiated in Row 7 of the FFTF for 169 days and produced 163,000 curies of cobalt-60.

- The Multiple Isotope Production (MIP) Experiment demonstrated the FFTF's capability to produce plutonium-238, californium-252, and 25 other marketable medical and industrial isotopes.

Extensive effort has already been devoted to designing new types of assemblies to further enhance production capabilities at the FFTF. This experience base can be used to design and fabricate new isotope production assemblies tailored to market needs for a broad range of isotopes.

For the FFTF to be successful in the radioisotope market, it needs to be able to produce short-lived isotopes. For these isotopes the FFTF needs a rapid turnaround vehicle to produce a reliable product stream for its customers and meet the needs of the tritium mission. This vehicle will allow the insertion and removal of isotope targets while the reactor is operating. Detailed studies have already been performed on the feasibility of such a vehicle. Several options have been identified, including insertion/removal of targets using existing equipment and insertion/removal using a either a mechanical or pneumatic push/pull system. These vehicles, known as Rapid Radioisotope Retrieval (R3) systems, are estimated to cost between $2.5 and $10 million, depending on the option, and can be installed before the plant is restarted in July of 2000.

When compared to other domestic sources of radioisotopes, the FFTF has several advantages:

- The FFTF has the largest volume for irradiation and the highest total flux of any of the DOE reactors.

- The FFTF can produce high-specific-activity (hsa) isotopes for most of the high demand applications better than other suppliers. This includes all of the leading candidates in the therapeutic arena (phosphorus-32, scandium-47, strontium-89, tin-117 metastable, samarium-153, rhenium-186, actinium-227, iodine-131, and thorium-229). Some of these isotopes such as rhenium-186 require a very high hsa for certain applications. The FFTF can produce large quantities of these isotopes to the hsa specification required for such applications through optimization.

- The FFTF's flux spectrum can be tailored to give it a high degree of flexibility in the production of radioisotopes.

- The FFTF is much newer than other reactors within the DOE complex. It has only about eight years of runtime on the reactor and recent analyses have indicated that it has at least 22 years - and in all probability 30 years - of remaining life.

The Hanford Site has many strengths which would further enhance FFTF's production capabilities, such as:

- availability of excellent facilities for all phases of isotope production (hot cells, analytical laboratories, the Fuels & Materials Examination Facility, etc.) .
- scientific and engineering expertise in isotope production, separation, processing, analysis, packaging, and shipping.
- regulatory license/approval, administrative and technical procedures and expertise to handle large quantities of radioactive materials.
- employees involved with the isotope program are highly motivated and dedicated to the enhancement of lives through the use of radioisotopes.

7.0 Estimated Production of Top FFTF Isotopes

The challenges in estimating the exact size of the market potential for the FFTF are complex. There are over 40 major medical isotopes that can be produced in the FFTF. Possible emergence of new therapeutic isotopes depends on their availability for clinical trials and their availability in commercial quantities at the successful completion of these trials. Thus, it is vital to have a facility that can produce a wide variety of isotopes, as well as a large quantity of them. If either of these conditions cannot be met, the demand only becomes a function of availability.

For the purpose of this scoping assessment, conservative growth figures were used and only certain isotopes were evaluated. These are not necessarily the isotopes of choice for the FFTF. A much more in-depth review of customer needs and requirements and the formulation of a detailed strategic plan will be required to identify products and product schedule.

Calculations and analyses have been performed in a recent Pacific Northwest National Laboratory study to determine the production capabilities of the FFTF.[11] These calculations and analyses were performed assuming the primary use of the reactor was to produce tritium. The study reveals that the FFTF can produce large amounts of important medical isotopes. Further studies will be needed to determine volume availability (in all U.S. reactors), self-shielding effects, expected medical applications and competition with accelerator produced isotopes to fully comprehend the need of the FFTF for medical isotope production.

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[11]Medical Isotope Production in the Fast Flux Test Facility, June 1996, Pacific Northwest National Laboratory, R.E. Schenter and S.G. Smith.

It should also be noted that only a small portion of the FFTF reactor is required to provide a substantial quantity of medical isotopes. As seen in Table 7.0, the FFTF can meet the expected demands for a variety of isotopes. Table 7.0 shows annual FFTF production levels while producing up to 1.9 kg/yr of tritium. All the isotopes listed in Table 7.0 can be produced concurrently.

Table 7.0
FFTF Medical Isotope Production While Producing 1.9 kgs of Tritium

Isotope	Annual FFTF Production in Curies (000's)	Annual Demand in Curies (000's)	Irradiation Time	Core Location	Curie Yield per Gram of Target
Actinium-227/ Radium-223	22	3.5	100 days per cycle with 2.5 cycles	½ of 1 in-core position (250cc)	N/A
Rhenium-186	750	4.2	10 days per cycle with 5 cycles	R3-1 Assembly 1 carrier	14000
Strontium-89	2.2	0.36	100 days per cycle with 2.5 cycles	½ of 1 in-core position (250cc)	N/A
Samarium-153	481	5.25	10 days per cycle with 5 cycles	R3-1 Assembly 1 carrier	25000
Molybdenum-99	1037.3	707.2	5 days per cycle with 35 cycles	R3-1 Assembly 22 carriers	250
Iodine-131	2.7	5.0	20 days per cycle with 11 cycles	R3-2 Assembly 5 carriers	15.5
Phosphorous-32	3.09	3.0	10 days per cycle with 20 cycles	R3-2 Assembly 19 carriers	7.5

See Section 7.1 for Production Assumptions and further explanations of this table.

7.1 Demand and Production Assumptions

1) All production figures are based on a tritium production mission with standard (FFTF) 100 day reactor operating cycles. Three in-core positions are used for medical isotope production in this configuration.

2) Demand figures are based on best available information.

   - Patient numbers are from the National Cancer Institute and the American Cancer Society.

   - Dose figures are based on the Society of Nuclear Medicine procedure guidelines and clinical trial procedures.

3) Rapid Turnaround Vehicle (R3) data based on a mechanical system with an individual carrier target volume of 0.51 cm^3, or a total target volume of 12.24 cm^3 for a four foot carrier train, with 24 target carriers. Two R3 assemblies (R3-1 and R3-2), for a total of 48 target carriers, are used to maximize irradiation time flexibility.

4) Self-shielding factors have not been applied to production figures. Self-shielding can have substantial effects on production but will be minimized by small diameter targets within the R3 carrier trains. For non-R3 produced isotopes such as strontium-89 and actinium-227, excess production capabilities will more than make up for self-shielding effects.

5) Production numbers are strictly based on production calculations. Modification of targets or multiple targets per carrier assembly (R3) may be required to meet handling specifications and shipping restrictions.

7.2 Product Descriptions

Actinium-227/Radium-223

The daughter of actinium-227, radium-223, offers a unique combination of low cost and potentially high therapeutic ratios. This alpha emitter can be used in a number of applications and is predicted to be the isotope of choice in cell-directed radiation therapy for numerous types of cancers. A peak yearly demand of 8,400 curies is based on 2.2 million patients at 4 millicuries per patient occurring, on a national fast track program, somewhere around 2007. Steady State demand is predicted to be around 3,500 curies per year. The FFTF is ideally suited for the production of this isotope. Production would occur in an in-core hydride assembly.

Rhenium-186

This isotope requires a very high specific activity for specific applications. It can be used for the treatment of pain caused by metastatic bone cancer which occurs in about 50% of all lung, prostate, and breast cancer patients. It can also be used in cell-directed radiation therapy. Demand figures are based on three doses of 40 millicuries given to each of 35,000 new patients each year for palliation of bone cancer pain. The FFTF can produce large quantities of this isotope with required hsa's not readily achievable in other reactors. Unfortunately, some radiopharmaceutical development companies (NeoRx) have had to discontinue their research with rhenium-186 because without the FFTF running, they could not obtain this isotope at the required hsa.

Strontium-89

This isotope is also used for bone cancer pain relief. It has been approved for use by the FDA and demand should be strong for some period of time. Demand for strontium-89 should peak in four to six years but then taper off somewhat once rhenium-186, samarium-153, and alpha emitters are approved by the FDA. Demand figures are based on three doses of 4 millicuries given to each of 30,000 patients.

Molybdenum-99

Current U. S. demand is 3000 6-day curies a week.[12] This equates to about 13,600 per week or 707,200 curies per year. Significant growth in the use of Mo-99 has occurred over the last few years due to an increase in new diagnostic products which utilize technetium-99m, the daughter isotope of Mo-99. FFTF production would be via neutron capture in molybdenum-98. Typically, capture Mo-99 does not have a high enough specific activity to be used in standard technetium generators, so fission molybdenum is generally used. The FFTF, being a fast reactor, can produce capture Mo-99 at specific activities about 100 times that produced by thermal reactors. This will allow Mo-99 to be made at greatly reduced costs since the processing will not include waste disposal costs associated with transuranics and fission products.

Samarium-153

This isotope, along with strontium-89 and rhenium-186, is used for the palliation of cancer induced bone pain and is also used to treat brain cancer. Average dose is 70 mCi and can be given several times a year. Demand figures assume three doses to each of 25,000 patients.

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[12]Medical Isotopes Production Project: Molybdenum-99 and Related Isotopes, Environmental Impact Statement, DOE/EIS-0249-F, April 1996

Iodine-131

This isotope is in Phase III clinical trials for a number of medical procedures. Results with cell-directed radiation therapy have been outstanding. One trial resulted in an overall survival rate of 93% on otherwise terminal lymphoma patients while another trial killed up to 99% of the leukemia cells in myeloid leukemia patients. Supply of iodine-131 at this time cannot even keep up with clinical trials. Once the FDA approves its use, the FFTF will be needed for production. Demand figures are difficult to calculate. Current trials have used doses up to 785 mCi per patient. This is very high. This assessment assumes 200 mCi per patient with 25,000 lymphoma and leukemia patients treated each year.

Phosphorus-32

Phosphorus-32 is used for a number of applications. It is used for the treatment of cancer induced bone pain, in the treatment of Polycythemia Rubra Vera, and most recently, in infusional brachytherapy for the treatment of various cancers. Demand figures assume infusional brachytherapy treatments for 30,000 patients each year with an average dose of 100 millicuries.

As stated previously in this assessment, the mix of isotopes shown in Table 7.0 is only a representation of what could be made in the FFTF at any given time, while producing 1.9 kg of tritium. The diverse capabilities of the FFTF will allow it to produce a number of medical and industrial isotopes as the market dictates. Table 7.2 shows these medical isotopes and their uses.

Table 7.2
FFTF Medical Isotopes and Their Applications

Isotope	Medical Application
Actinium-227	Cell-directed radiation treatment for cancer
Carbon-14	Radiolabeling
Cadmium-109	X-ray fluorescence
Californium-252	Cervical, melanoma, and brain cancer treatment
Curium-244	Target to make Californium-252
Cobalt-60	Teletherapy and disinfection of surgical equipment
Copper-64	PET scanning
Copper-67	Cancer treatment/diagnostics, monoclonal antibodies
Dysprosium-165	Radiation synovectomy, rheumatoid arthritis treatment
Gadolinium-153	Osteoporosis detection and diagnosis
Iodine-123	Brain imaging
Iodine-125	Osteoporosis detection, diagnostic imaging, prostate cancer treatment
Iodine-131	Lymphoid tissue tumor/thyroid treatment, leukemia treatment
Iridium-192	Brachytherapy
Lutetium-177	Heart disease treatment (restenosis therapy), cancer therapy
Molybdenum-99	Parent for Tc99m generators
Osmium-191	Blood flow studies, heart disease diagnostics
Osmium-194	Monoclonal antibody attachment used for cancer treatment
Phosphorous-32	Polycythemia Rubra Vera and leukemia treatment
Phosphorous-33	Labeling metabolic compounds and alternative to P-32
Palladium-103	Prostate cancer treatment
Rhenium-186	"Magic Bullet" cancer treatment and bone cancer pain relief
Scandium-47	Bone cancer pain relief
Selenium-75	Radiotracer used in brain studies
Samarium-153	Brain cancer treatment and bone cancer pain relief
Tin-117m	Bone cancer studies
Strontium-89	Bone cancer pain relief
Thorium-228	Cancer treatment, monoclonal antibodies
Thorium-229	Grandparent for alpha emitter Bi-213 used for cancer treatment
Tungsten-188	Parent for monoclonal antibody (Re-188) attachment for treating
Xenon-127	Neuroimaging for brain disorders
Yttrium-91	Cell-directed radiation treatments for cancer

8.0 DOE, the IPDP and Private Enterprise

Past experience with the private sector has shown a reluctance to invest in nuclear reactors or other large capital projects to produce isotopes. Perceived liabilities, costs, licensing uncertainties, and market volatility have deterred private sector investment. If the FFTF were restarted for the purpose of producing tritium, the risks normally associated in the startup and operation, as well as the amount of capital investment, would be significantly reduced. This unique situation would allow private enterprise a chance to enter the market on an equal footing with foreign suppliers who are generally subsidized by their governments.

The operation of the FFTF in a combined tritium and medical isotope production mission offers a situation that is perfectly suited for the re-invention of government. Several options are open to the restructuring of the traditional organizational structure used in the past by the DOE. For examples:

- The DOE could continue to operate the FFTF with a Management and Operations contractor and write a separate contract with a consortium of private partners.

- The DOE could lease the facility to private enterprise and still provide oversight support.

- The IPDP could establish a Public/Private Partnership in which a Center for Government/Industry Cooperation and Technology Transfer would team with a partnership of privately financed corporations that would market the products from the FFTF.[13]

A partnership with private enterprise brings together the technical capabilities and experience of the DOE and the Hanford Site with key customer centered, business process skills of the private sector. This partnership is consistent with the National Performance Review objective of privatization of the Government's assets in order to cut red tape and be more customer oriented.

9.0 A Visualization of the Future

The Hanford Site is going through major changes. The post cold war cutbacks to the defense programs and transition from production to cleanup will have major economic impacts on the region. The funding levels at Hanford will be reduced drastically in the next ten years. The DOE is trying to diversify the economy and several programs have been initiated to lessen the impact when defense dollars stop making their way into the area. None of the proposed programs will have as positive an effect as a restart of the FFTF.

The operation of the FFTF for the production of medical isotopes will create a whole new industry in the Columbia Basin area. Direct production and processing of the isotopes at the FFTF will create approximately 1000 jobs. Add to this those jobs dedicated to marketing, sales, distribution, research, and education, and the direct job pool created through the generation of this new regional industry could easily be 3,000 to 5,000.

A problem with past studies is that no comparison was made of FFTF production rates with expected needs in a comprehensive plan that shows the engineering and operations realities. This visualization looks at a proposed scenario and how the FFTF will operate to meet production demands.

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[13] Details of this proposal can be found in The Fast Flux Test Facility Business Plan, September 1993, Tulane University.

The first step, which should be done immediately, is to develop a strategic plan. There has been considerable work done in this area in past years, but these strategies need to be revamped to accommodate the dual mission with tritium, market changes, and the structure in which the FFTF would operate. Since the future of the medical isotope market lies in the expansion of the therapeutic market, the FFTF should begin immediate work in this area. In today's rapidly changing marketplace, the strategic plan should concentrate on the enhancement of capabilities and not become too focused on specific isotopes for production.

In order for the FFTF to establish itself as the preferred supplier in the radioisotope market, it must establish itself as a reliable and efficient producer. Its first option should be to enter a pre-existing market as the lowest cost producer. This is possible since the initial costs of construction have already been incurred and the bulk of operating costs will be covered by the tritium mission. Once the FFTF establishes itself as a reliable supplier with competitive pricing and high quality products, it should be able to capture 30-40% of the market share within one to two years for a given isotope. A good candidate isotope for this market groundbreaking might be strontium-89.

As the FFTF asserts itself as a serious player in the radiopharmaceuticals market, it can then move forward with other isotopes in a similar manner, using both competitive pricing and superior product quality to leverage itself into the market mainstream. This period should also be used for the development of high growth potential isotopes such as actinium-227/radium-223 and rhenium-186. Laying the initial groundwork in this area requires the immediate production of research quantities of these isotopes. This will allow additional testing and clinical trials to begin. Establishing an early customer relationship by providing this service will assure long-term growth potential through first-mover technology advantages. This will be crucial in allowing the FFTF to gain a dominant market share position in the industry, which will be required by the time alternative tritium sources come on line.

Revenues from the production of medical isotopes at the FFTF have been projected in a number of studies conducted in the early 1990's. In general, these studies did not understand the significance of the therapeutic market potential and also discounted the production of Mo-99 due to the fairly long outage times (30 days) of the reactor. Recent successes in clinical trials now assure a significant market for therapeutic isotopes and production of Mo-99 at the FFTF will be via capture, not fission, which will all but eliminate any processing time (this will help offset reactor outage times). Also, the FFTF can team with another Mo-99 production base, such as the ACRR, in order to provide a continuous, reliable supply to the medical community. Based on current market information, the FFTF can generate well over $100 million a year (assuming a 50% market share) with the production of the medical isotopes in Table 7.0. Considering the FFTF's production advantages, it is reasonable to assume that it could capture considerably more than 50% of the market.

Although the FFTF can produce major portions of the country's needed medical isotopes, national strategies need to include other domestic supplies of isotopes from High Flux Isotope Reactor, the Advanced Test Reactor, the ACRR, and other production facilities within the IPDP umbrella. The FFTF has an outstanding operational record but, as in any industrial endeavor, potential operational problems are possible. Medical isotope production is too important to the nation to count on a single source. For this reason, the FFTF should be

teamed with the other facilities to provide redundancy and the best possible service to the medical community.

10.0 Conclusion

Medical isotopes are a major component of our health care system, yet we rely on foreign suppliers for 95% of these isotopes. The growth potential for this industry is large but, excluding the FFTF, the U. S. has very limited out year production capabilities. Current facilities within the IPDP umbrella do not have sufficient target volume capacity to meet the expected demands of the medical community. The FFTF could, with high confidence, provide a large portion of the world market demand for both diagnostic and newly emergent therapeutic radioisotopes. The ability to produce such a large variety and volume of high quality radioisotopes for the next 30 years makes the FFTF the only realistic choice this country has if it is to compete with foreign suppliers.

The FFTF, together with its sister facility the Fuels and Materials Examination Facility (FMEF), has the capability of forming the finest isotope production complex in the world. The FFTF would be unmatched in both target volume and flux tailoring capabilities and the FMEF has tremendous processing capabilities. With the production of tritium, the FFTF can be a major player in the medical isotope market. When other tritium production options become available, the FFTF has the capability of totally dominating the market for reactor produced radioisotopes. This market is expected to reach well over $1 billion per year by 2010.

The cost savings and dramatically improved patient care and survival rates through the use of therapeutic isotopes demands that the U. S. pursue the development and production of said isotopes as a national priority. The long-term operation of the FFTF for the production of medical isotopes would provide a key leverage point in this country's fight against cancer, skyrocketing health care costs, and the expanding trade deficit. Internal radioimmunology with the use of alpha emitters promises to offer the lowest cost, most effective treatment available in the battle against cancer. The FFTF is particularly well suited for production of these isotopes. Operation of the FFTF for the production of defense tritium and medical isotopes is a no-lose proposal for this country.

Considering the enormity of the problems faced by our health care industry, the costs associated with a restart of the FFTF are indeed very, very insignificant. In terms of lives saved and benefits to the national economy, the FFTF should be operated to produce medical isotopes even if other alternatives are selected for tritium production.