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FAST FLUX TEST FACILITY (FFTF)

BRIEFING BOOK 3

OTHER KEY REFERENCES

Technical and Economic Viability of Future FFTF Operation

U.S. Department of Energy
Office of Nuclear Energy,
Science and Technology
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Medical Isotopes Production at the Fast Flux Test Facility

A Technical and Economic Assessment

Hanford Site
Richland, Washington

November 1997

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Medical Isotope Production at the Fast Flux Test Facility - A Technical and Economic Assessment

November 1997

This report was prepared by staff at the Pacific Northwest National Laboratory and the Babcock & Wilcox Hanford Company, with technical contributions from staff members of the Fluor Daniel Northwest Company and Numatec Hanford Corporation.
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Executive Summary

The Fast Flux Test Facility (FFTF) is a 400-MW, liquid sodium-cooled reactor located at the Hanford Site in Richland, WA. FFTF was built as part of the U.S. liquid metal reactor program in the 1970s, and operated successfully from 1982-1992 performing tests of reactor fuel assemblies and materials, studies on operational safety and reliability of liquid metal reactors, and tests of the ability of FFTF to produce a wide variety of radioisotopes for applications in medicine, industry and research. Although FFTF achieved an outstanding record of performance and operational safety during its decade of operation, the lack of a long-term mission forced DOE in 1993 to place the reactor in a standby condition during preparation for a phased shutdown.

In 1995, recognizing the potential of FFTF to serve as an interim supplier of tritium for nuclear warheads while simultaneously producing valuable medical isotopes, the Secretary of Energy ordered that all irreversible deactivation activities be temporarily halted. During the following year, five independent studies confirmed that FFTF had the capability of producing at least 1.5 kg of tritium per year with reasonable confidence, and that the concept of a dual mission to produce both tritium and medical isotopes was reasonable. Based on these studies, the Secretary issued a decision on January 17, 1997, that FFTF should continue to be maintained in a standby condition while environmental and safety studies are conducted on tritium production and an assessment is performed on the technical and economic feasibility of producing medical radioisotopes in parallel with the primary tritium mission.

This report was prepared in response to the Secretary of Energy's directive and addresses both the technical and economic feasibility of using FFTF to produce medical radioisotopes.

Medical Isotope Production Capabilities

Because of its high neutron flux, large target volume, and broad neutron energy spectrum, which extends from thermal levels to about 1 MeV, the FFTF has the ability to produce large quantities of a wide variety of medical isotopes. Previous studies on radioisotope production at FFTF have demonstrated the ability to produce 39 different isotopes, of which 25 have medical applications. Irradiation cycles can be varied from 10 days to several hundred days depending upon the cross-section for isotope production and the half-life of the desired isotope product. For short-lived isotopes with half-lives of several days, 10 to 25 day irradiation cycles can be carried out using a rapid radioisotope retrieval system to remove targets while the reactor is at full power. For isotopes with longer half lives, irradiation cycles of 100 or more days can be utilized in synchrony with the tritium production cycle. Although initial production of medical isotopes will initially be limited to three in-core positions, and possibly one or more positions in the reflector region, calculated production yields of 30 different medical isotopes are impressive. Initial operations will focus on 20 medical isotopes for which there is expected to be a large market demand, with limited production of 10 other isotopes for which there will be a smaller demand.

Radiochemical Processing

The radiochemical separation and purification processes have been analyzed for 30 medical isotope products. A variety of separation techniques will be required for these diverse isotope products, including ion exchange, electrochemical separation, and gas-phase trapping. In many cases, the valuable target materials will be retrieved during the processing cycle and reutilized in new targets for subsequent FFTF irradiations.

All of the radiochemical separation and purification procedures will be carried out in the 325 Building under conditions that are in compliance with current Good Manufacturing Practices (cGMP) for medical-grade isotope products. Special hot cell facilities are available for work with isotopes that require extra shielding, especially Gd-153 (Figure ES-1). In addition, a laboratory in which all of the glove boxes, fume hoods, and the hot cell are connected to a radon gas capture system is available for storage and preparation of Ra-226 target materials, and for processing the isotope products that result from irradiation of Ra-226 (specifically, Ac-227, Th-228, and Th-229). Many of the isotope products to be produced at FFTF and processed in the 325 Building have previously been produced and processed at Hanford during the period 1982-1992 when FFTF was operational.

Facilities and Equipment for Isotope Production and Processing

Extensive laboratory facilities are available at the Hanford Site for the preparation of FFTF targets and the processing of medical isotopes produced by irradiation for cycles ranging from 10 to 200 days. Laboratory facilities at the 325 Building will be made available and upgraded to provide 22 different isotope processing lines. A large, heavily shielded hot cell will be used for receipt and disassembly of irradiated targets, and a second heavily shielded hot cell will be used for the initial steps in processing Gd-153 targets. All isotope processing lines contain a small hot cell, shielded glove box, fume hood, and laminar flow hood fully equipped with standard laboratory utilities. A reagent preparation laboratory, analytical laboratory, and final product processing laboratory are also available in close proximity to the isotope processing laboratories. All laboratory facilities will be designed to meet the rigid requirements of cGMP.

The preparation of cold FFTF targets will be performed at the 306E Building, which has extensive facilities for preparing radioisotope target assemblies and performing nondestructive examination (NDE) of their integrity. Radioactive targets (e.g., Ra-226) and targets containing recycled target material with residual radioactivity will be fabricated in the 325 Building, which also has NDE capabilities.

Target pins and capsules prepared at the 306E Building and the 325 Building will be shipped to the Fuel and Materials Examination Facility (FMEF), where they will be assembled into bundles for long-irradiation vehicle (LIV) targets (for irradiation cycles up to 200 days). For short-term irradiation targets (10 to 25 day cycles), capsules and carrier trains will be assembled at the 306E Building ("cold" targets) and the 325 Building ("hot" targets) for insertion into the FFTF using two different rapid radioisotope retrieval systems. FFTF has extensive capabilities for insertion and removal of target assemblies, and for

Figure ES-1. Processing of medical isotopes in a hot cell at the 325 Building.

removing sodium from the targets prior to transport to the isotope processing facilities in the 325 Building. Major existing facilities at FFTF include the Closed Loop Ex-Vessel Handling Machine (CLEM) and the Interim Examination and Maintenance (IEM) Cell.

The overall flow of materials from the initial target preparation through final processing and shipping of medical isotope products is depicted in Figure ES-2.

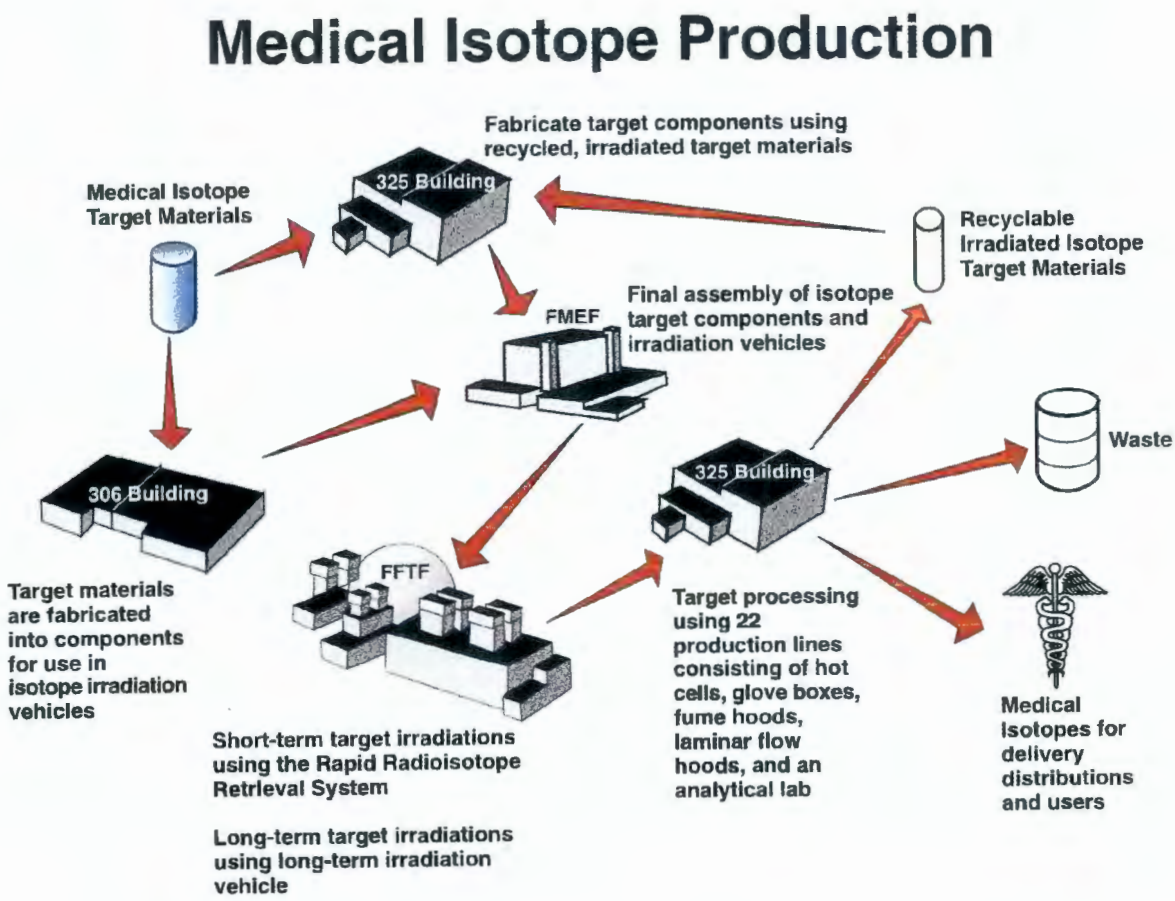

Figure ES-2. Flow chart showing facilities used for FFTF target production and for processing of final medical isotope products.

Operations Support

Estimates have been made of the staffing required to implement medical isotope production at FFTF upon startup of full-scale operations in 2002. The preparation of targets and the handling of irradiated targets is expected to require 20 full-time equivalent (FTE) staff. The radiochemical processing of targets from both long-term irradiations (100 days or longer) and short-term irradiations (10 to 25 days) is estimated to require 17 FTEs. Based on extensive experience in the production of medical radioisotopes, the packaging, shipping, marketing, sales, and administration tasks for FFTF isotope products are expected to require 13 FTEs. The overall project staffing is therefore 50 FTEs. Other operations support activities include radionuclide and chemical analysis of isotope products, waste disposal, and on-site transportation of targets and isotope products.

Cost and Schedule

The cost of facilities upgrades and equipment fabrication/procurement for target preparation and processing in the 306E and 325 Buildings is estimated to be $51.2 million. The construction of two rapid radioisotope retrieval systems and other equipment associated with target irradiations at FFTF has an estimated cost of $19.0 million. These cost estimates include engineering design work, procurements, special equipment fabrication, laboratory upgrades, and task management activities.

Annual operating costs have been estimated to be $10.93 million, independent of the purchase of target isotope materials. Of this total, $9.16 million is for support of 50 FTEs involved in target fabrication, target irradiation operations, post-irradiation target processing, product packaging and shipping, and marketing, sales, and administration. The remainder of the costs are for radionuclide and chemical analysis of the isotope products, waste disposal, and on-site transportation of targets and isotope products. Additional costs arise from the initial procurement and periodic replenishing of target materials. These costs vary with the choice of isotopes to be produced and the volume of isotopes produced in response to market demand. An effort will be made to minimize the costs of target materials by recovering a large fraction of the material following each irradiation cycle and reutilizing it in new targets. An initial investment for 20 selected isotope products that are expected to have a large sales volume has been estimated to be $14.5 million assuming full market penetration, and $2.9 million for a 20% market penetration.

The schedule for implementation of medical isotope production at FFTF is consistent with that of the primary tritium mission. If a DOE Record of Decision is issued in the first quarter of FY 1999, final conceptual designs will be completed for all facilities and equipment during the following two years. The construction and testing of equipment, including the two rapid radioisotope retrieval systems, and the laboratory upgrades will be carried out during the period extending from the second quarter of FY 1999 through the first quarter of FY 2002. Fabrication of isotope targets and verification of operational readiness for medical isotope production will occur during the second and third quarters of FY 2002.

Market Forecasts for Medical Isotopes

Five major studies of the medical isotopes market have been conducted since 1993, all of which project significant near-term growth. The most recent study was performed by Frost & Sullivan, Inc., and focused on reactor-generated isotope products. This study projected that the market demand for radiopharmaceutical products used in medical diagnostic and therapeutic procedures will grow by 7 to 15% per year over the coming two decades. The revenues from sales of diagnostic agents is expected to grow from $530 million in 1996 to about $17 billion in 2020. For therapeutic agents, which have a much smaller share of the pharmaceutical market, the growth in demand was projected to grow at an even faster pace. For therapeutic radiopharmaceuticals, the growth in sales revenues is expected to grow from $48 million in 1996 to about $6 billion in 2020.

It was concluded by Frost and Sullivan that additional U.S. isotope production capacity will be required over the period 2001-2020, and that FFTF can become a major U.S. source of medical isotopes. The FFTF's high neutron flux and large target volume make it well suited for this role.

Conclusions

The technical feasibility of producing at least 30 medical isotopes in parallel with the primary FFTF tritium production mission has been confirmed by this study. It has been established that sufficient capacity exists within the FFTF reactor core region to begin the production of 20 of these isotopes at the onset of operations in year 2002. Using realistic estimates of the revenues that can be obtained from the sale of FFTF medical isotopes during the first two decades of the 21st century, it has been concluded that: 1) the annual cost of production and processing of medical isotopes can be recovered at the start of operations in 2002; 2) after 10 years of operation, approximately 50 to 60% of the cost of operating the reactor can also be subsidized from the sale of medical isotopes; and 3) by 2015 to 2020 it is anticipated that FFTF can be operated in a full-cost recovery mode as a major source of medical isotopes.

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1.0 Background

FFTF is the world's largest liquid metal-cooled test reactor, which was originally designed and built in the 1970s to test fuel and key components to be used in the proposed Clinch River Breeder Reactor. Although the U.S. breeder reactor program was put on hold during the final phases of FFTF construction, the reactor nevertheless operated successfully from 1982-1992. During that period the FFTF performed numerous tests of reactor fuel assemblies and materials, studies on the operational safety and reliability of liquid metal reactors, and tests of the ability of FFTF to produce a wide variety of radioisotopes for applications in medicine, industry and research.

Although the FFTF achieved an outstanding record of performance and operational safety during its decade of operation, the lack of a long-term mission forced DOE in 1993 to order that the reactor be placed in a standby condition in preparation for a phased shutdown. Removal of fuel from the reactor vessel was initiated in 1994 and completed in April, 1995. During 1995 an environmental assessment (DOE/EIS 0993) was prepared on the impacts of disposing of radioactive wastes and other hazardous materials during the course of safely shutting down the FFTF. In addition, an on-site liquid sodium storage facility was built and preparations were made to begin withdrawing sodium from the reactor.

In November 1995, in response to a directive from the Secretary of Energy, plans to drain sodium from the FFTF and all other irreversible deactivation activities were temporarily halted. The basis of this action was to provide time for DOE to carefully explore the possibility of FFTF serving as an interim supplier of tritium for nuclear warheads. A Programmatic Environmental Impact Statement (PEIS) issued by DOE in 1993 on the subject "Tritium Supply and Recycle" (DOE/EIS-0161) had rejected FFTF as an adequate long-term source of tritium for defense weapons. However, the Secretary of Energy was responsive to the suggestion made in November, 1995, by a private consortium[a] that FFTF could rapidly undertake the dual mission of serving as an interim supplier of tritium for defense applications, while simultaneously producing medical radioisotopes that are needed to bolster the U.S. supply. The underlying concept to be explored was the possibility that FFTF could be reactivated by the year 2002 as a temporary source of tritium, thereby extending the period for implementing a dual track strategy that would provide a long-term U.S. supply of tritium for nuclear weapons. This dual-track plan, described in a 1995 Record of Decision (60 FR 238), consisted of either purchasing a commercial light-water reactor for tritium production, or constructing an accelerator system for tritium production at the Savannah River Site. Because of the long period of time required to implement this dual-track strategy, the possibility of reactivating FFTF as a temporary source of tritium was considered by DOE to be an attractive option worthy of additional study.

(a) Advanced Nuclear and Medical Systems, Richland, Washington.

During 1996 a total of five independent studies were conducted at the request of DOE to explore the feasibility of utilizing FFTF as an interim supplier of tritium:

- DOE Office of Nuclear Energy, Science and Technology study on "Tritium Production at the Fast Flux Test Facility" (issued February 1996)

- DOE Office of Defense Programs study entitled "Technical Assessment of Tritium Production Capability of the Fast Flux Test Facility" (issued March 1996)

- A report by R. Savoie et al. commissioned by DOE on "Independent Assessment of Cost and Schedule Estimates for the Production of Tritium at the Fast Flux Test Facility" (issued September 1996)

- JASON Panel report #JSR-96-325 on tritium production at FFTF (issued October 1996)

- A report by Putnam, Hayes and Bartlett, Inc., commissioned by DOE, entitled "DOE Tritium Production: Final Briefing on FFTF and ATR Cost Analysis" (issued January 1997).

The conclusions of these independent studies were consistent, and supported the concept of utilizing FFTF as an interim supplier of tritium for national defense applications. Specific conclusions and recommendations were: 1) FFTF was considered capable of producing at least 1 kg of tritium per year with a high degree of confidence, and 1.5 kg of tritium per year with a reasonable level of confidence; and 2) the concept of a dual mission to produce medical radioisotopes in addition to tritium was considered feasible, and the revenues from sales of these isotopes were considered a practical means of defraying part of the FFTF operating costs.

Based on the conclusions of these 1996 studies, the Secretary of Energy issued a decision on January 17, 1997, to maintain FFTF in a standby condition while environmental and safety studies are conducted on tritium production and an assessment is performed on the technical and economic feasibility of producing medical radioisotopes in parallel with the primary tritium mission. The Secretary specified that a decision on the future role of FFTF in the U.S. tritium production strategy would be made in 1998. The commitment to study FFTF as an interim supplier of tritium, and the time frame for a DOE decision on this issue, were reaffirmed in a May 5, 1997, letter from the Secretary of Energy to the Chairman of the U.S. Senate Committee on Armed Forces.

This document addresses the requirement in the January 17, 1997, letter from the Secretary of Energy that a feasibility study be performed on the production of medical isotopes at FFTF in parallel with the primary tritium production mission. Both the technical and economic feasibility of using FFTF to produce medical radioisotopes are addressed in this report.

2.0 FFTF Production Capabilities

2.1 The FFTF

2.1.1 Facility Description

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
- 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 for the diagnosis of osteoporosis, was made by the FFTF to avert a world shortage. 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.

2.1.2 Age and Condition

The FFTF began 400 MWT power operation in April 1982. The plant was designed and analyzed for a 20-year lifetime (at 400 MWT and 75% capacity factor). Several replaceable components in the reactor vessel (in the high neutron flux) were analyzed for 10 years of operation with the intent that they either be replaced or re-analyzed if operation after 10 years was desired.

In 1985, as the 10-year limit was approaching, the project 1) began analysis to extend the life of the 10-year components, based on actual core structural specimen radiation damage data and 2) revised (updated) flux profiles using more recent in-core dosimetry measurements. In 1986, a significant study was undertaken to consider using FFTF for electrical power generation and/or liquid metal reactor (LMR) steam generator testing. Thus, an additional 20 years of operation beyond the 10 years at projected restart for the new mission was desirable.

In April 1990, the analysis of the 10-year components for 30-year life was completed and transmitted to Department of Energy-Richland Operations (DOE-RL) for their review and approval. All analysis was based on the latest LMR design/analysis criteria and all reports were peer-reviewed by Stone and Webster. DOE-RL approved the 10-year component life extension documentation in January 1991.

The 20-year reactor component extension to 30 years was completed in December 1992, using the same analytical methods followed for the 10-year components. This documentation was not sent to DOE-RL for their action since the FFTF was already in standby awaiting the shutdown order.

The lifetime of the remainder of the FFTF components is reported in WHC-SP-0789, Thermal and Pressure Transient Events During Cycle 11, which was updated for actual pressure and thermal transient history before the last reactor cycle began. A review of the analyzed transients (assumed to achieve an original 20-year life in the technical specifications) showed less than 10% of the planned transients allocated for the balance of plant have been used, thus assuring at least a 30 year life.

All of the analysis has now been completed to show the FFTF has at least a 30-year life. When the plant was shut down in March 1992, after 10 calendar years, FFTF had used an equivalent lifetime of 8 years at 400 MWT and 75% plant capacity factor. This leaves 22 years of life remaining, based on the previous core arrangement and operating conditions.

Tritium production **will extend the usable life of FFTF beyond 22 years!** This "benefit" arises from the attenuation characteristics of the tritium targets. Fewer neutrons will be able to reach the life-limiting core components in both the radial and axial dimensions (radial reflector, core basket, etc). Estimates forecast **additional life extension of 8 years for a total remaining life of 30 years**. By continuing the coupon irradiation surveillance program to provide additional information, the possibility exists for life extension beyond the 30-year forecast.

2.1.3 Safety and Operational Record

The FFTF reactor is positioned in a heavily shielded cell at the center of a domed containment building. Heat is removed from the reactor by liquid sodium circulating under low pressure through three primary cooling loops. Intermediate heat exchangers separate the radioactive sodium in these primary loops from the nonradioactive sodium in the secondary system. Three secondary sodium loops transport the heat from the intermediate heat exchangers to twelve dump heat exchangers, which are cooled by air.

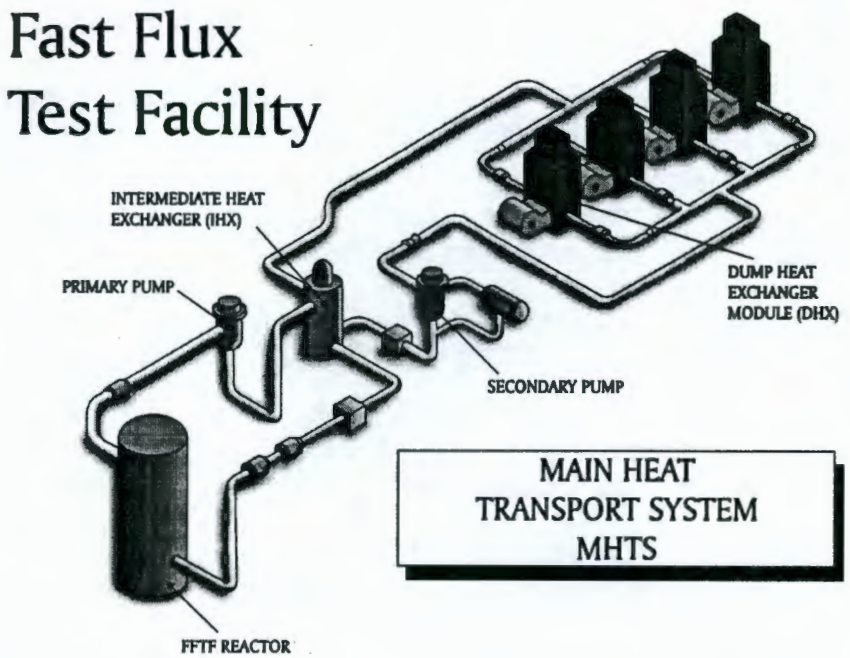

Figure 2-1. Major components of FFTF's heat transport system using liquid sodium to cool the reactor.

The FFTF does not have steam generators or a turbine plant like that found in a commercial reactor plant. This fact is considered a benefit to a tritium and medical isotope production mission because operation and maintenance costs will be lower, and production rates will not be tied to steam plant operations or availability.

Sodium, with its excellent heat transfer capabilities, is used at the FFTF as the reactor coolant because it does not appreciably slow down the fast neutrons. It has a high boiling point which permits the use of a low pressure system and minimizes the concern for pipe failure accidents.

Additionally, sodium is non-corrosive. This increases plant life and reduces activated corrosion products in the coolant systems, which results in reduced personnel exposure to radiation during plant operations and during reactor outages.

The design of the FFTF incorporates many of the passive inherent safety features that have been included in the design of future generations of reactor plant designs. The core design features include stability and negative feedback mechanisms and the heat transport system is designed to assure natural convection heat removal.

For example, during a total loss of onsite and offsite power, the FFTF will automatically shut down and in this emergency situation it will be cooled by natural circulation (i.e., no coolant pumps are required to remove decay heat). There is also a redundant emergency power source (1-E battery systems) that will provide reactor plant monitoring capabilities for essential parameters.

Another example of the FFTF's safety oriented design is the main heat transport piping and the reactor vessel. These two major systems were engineered to minimize the potential for a leak. Even if a leak occurs, the plant was designed to keep the reactor core covered and to maintain cooling to the reactor by the use of elevated piping and guard vessels around all major components. These unique design features help assure safety of the public and the environment.

Instrumentation monitors and controls the reactor and heat-removal systems. The reactor is designed and operated to be automatically shut down if pre-set limits on crucial parameters are exceeded. Collection, processing, and retrieval of operation and test data are fully computerized.

One example of reactor plant monitoring and controls is the Plant Protective System. It includes engineered safety features such as:

- the Reactor Shutdown System, providing redundant reactor shutdown signals
- the Containment Isolation System, which provides signals to containment isolation valves to prevent unacceptable radiation releases
- the Post Accident Monitoring instrumentation, used to monitor key plant parameters
- miscellaneous features including Control Room Habitability and emergency dump heat exchanger controls.

The FFTF includes facilities for receiving, conditioning, storing, installing and removing all routinely removable core components and test assemblies and for storing irradiated fuel. Examination

and packaging capabilities (for offsite shipment) are also included within FFTF, as are utilities and services such as emergency electrical power generation, heating and ventilation, radiation monitoring, fire protection, and auxiliary cooling systems.

The FFTF has been noted as the premier test reactor for the DOE. Beginning with its nuclear startup in 1980, this reactor has been a model of safe and efficient operation. The irradiation test record of the FFTF reactor has far exceeded the original scope and intent of its designers.

During initial construction and throughout the reactor's ten-year operating life, numerous reviews which focused on safety and conduct of operations have been conducted on the plant and its staff. These reviews, several of which are detailed below, have pointed out the rigors of safety built into the physical plant and its training and administrative programs. As a primary goal in the design of the plant, safety was built-in through passive, plant protective, and engineered safety systems. The certified operating staff have always held, and continue to hold, safety as their top priority.

2.1.3.1 Personnel Radiation Exposure and Tritium Release to the Environment

Another indicator that safety has a top priority at the FFTF can be seen in radiological controls and health physics, which include aggressive as-low-as-reasonably-achievable (ALARA) programs. The extremely low personnel exposure history speaks well of the design and engineering of the facility (i.e., shielding, relative ease in maintenance and refueling operations, and multiple layers of contamination confinement). From 1985 through 1990, the FFTF average total exposure was just below 1.4 man-rem per year. The average number of skin contaminations per year was 1.3 (1982-1995). These numbers are orders of magnitude below the 348 man-rem per year total exposure average and the 100+ skin contamination figures seen in commercial light water reactors (NUREG-0713, Vol. 15, Occupational Radiation Exposure at Commercial Nuclear Power Reactors and Other Facilities 1995, Summary of Annual Information Reported by Commercial Boiling/Pressurized Water Reactors and FFTF Performance Monitoring Management Information, July 1995).

The effect of increased tritium entering the FFTF primary sodium due to the production mission has been evaluated by plant personnel. Potential increased gaseous releases, potential hazard to personnel, and cold trap loading were considered. It is anticipated that the tritium concentration in the FFTF sodium can double or even triple as a result of tritium production. Nevertheless, the tritium released in the Plant's combined exhaust will be several orders of magnitude less than the release limit. A tritium production mission will result in emission of 183 curies per year of gaseous tritium, based on a 0.5 curie/day release rate.

Radioactive releases associated with the production of tritium will result in an annual dose increase of 0.003 person-rem to the 50-mile population.

There will also be a slight increase of exposure to the plant workforce due to handling additional fuel and target assemblies. Exposure levels are expected to increase by less than 2 person-rem. This will be an increase of less than 10 mrem per employee.

2.1.3.2 Low Level Waste

The FFTF produces very little Low Level Waste (LLW). During past reactor operation, the average LLW generated was only 35 yd^3 per year. This number is not expected to increase significantly when operating in a tritium and medical isotope production mode.

2.1.3.3 Review by the NRC

The FFTF is the only reactor in the DOE complex to undergo a Technical Safety Review conducted by the NRC. The Final Safety Analysis Report for the FFTF issued in 1975 was reviewed by the NRC Advisory Committee on Reactor Safety. The NRC Safety Evaluation Report and recommendations were issued in 1979, and all open issues were resolved prior to the start of operations.

Additional reviews conducted include the following:

- Five DOE-HQ topical reviews since 1980, including a review centered on Three-Mile Island issues and two technical safety appraisals
- National Academy of Sciences review in 1988
- DOE Advisory Committee on Nuclear Facility Safety review in 1988
- Three Institute of Nuclear Power Operations assist visits in 1988-1989
- Westinghouse Government Operations Nuclear Safety and Environmental Oversight Committee review in 1989.

The FFTF initial licensing review with the NRC required innovation and leadership to address the numerous "first in kind" issues. The lessons learned from this process can be directly applied to future review activities either through the NRC or DNFSB, whichever is designated. Recognizing the complexity of issues and the lack of industry experience, we propose that a memorandum of understanding be drafted early with the review authority 1) to establish the necessary and sufficient set of requirements, 2) to establish the training and familiarization programs for review authority staff, and 3) to develop the process for transition from a test reactor to a production reactor.

2.1.3.4 Cost and Schedule Performance

FFTF performance on cost and schedule throughout its operating history has been excellent. Cycle performance is measured by capacity factor. Although the FFTF was not a power production reactor, it achieved 4 years with a capacity factor greater than 70%. This is considered to be a benchmark of excellent operations.

Considering the FFTF test mission, a better measure of performance is the Operational Efficiency Factor (OEF). The OEF measures FFTF performance to schedule. All scheduled activities met on or ahead of schedule are radioed to the total number of activities planned. This ratio, expressed as a percentage, measures FFTF performance. FFTF consistently achieved above 98% performance, and achieved 100% in 1987 and 1991.

As indicated by its capacity factor and OEF, the FFTF and her staff have continuously demonstrated their ability and commitment to meet and exceed customer expectations. Given the commitment to technical discipline and operational excellence during the operational portion of FFTF's history, it is reasonable to assume that the same levels of high performance can be achieved in a tritium/medical isotope mission.

2.1.4 Production Advantages

2.1.4.1 Target Volume Considerations

Long Irradiation Vehicle. Several options are available for irradiation vehicles to produce isotopes with irradiation times of one or more 100 day cycles. Flexibility exists to tailor the vehicle to the production requirements for the desired isotopes. Options range from unmoderated assemblies with large target volumes to moderated assemblies with smaller target volumes.

The components of an irradiation vehicle in the active core region include the sodium coolant, a steel duct, pin cladding, and target material. If spectral tailoring is desired, then the addition of moderator material must displace some of the target material. The duct is a standard fixed component. The target heat generation rate coupled with the heat transfer capability and temperature limitations will impose limits on target pin size and spacing. Concerns for pin pressurization from gas generation or reactions with the steel cladding material will also impact the cladding thickness and the need for liners or internal target capsules. All of these concerns make it difficult to prescribe specific available target volumes without examining each target material and its unique requirements.

The following describes some options for irradiation vehicles and potential target volumes, with the caveat that careful consideration of the above issues shall be addressed before production target volumes are specified.

Unmoderated Assemblies. Assemblies like the Material Open Test Assembly (MOTA) have been used in the past for isotope production, and were designed for multiple samples at specific axial elevations and for target retrieval and reconstitution. These MOTA assemblies consist of a central stalk with nine axial levels, with six sample canisters per level. The specimen region in each canister is about 78 cc, for a total sample volume of approximately 4200 cc. Following irradiation, the canisters can be detached from the stalk for processing or reconstituted on a new stalk to continue irradiation.

Normal pin assemblies make more efficient use of the assembly target volume. The available target volume depends on the pin size and spacing. Options on the pin size range from assemblies containing

217 small diameter (0.23 inch) pins to assemblies containing 19 large diameter (0.7 to 0.9 inch) pins. These and other pin sizes in between have been successfully used in FFTF for isotope production and other types of test assemblies. For unmoderated assemblies, target volume fractions can range from 35% to 80% of the available space inside the duct. Over a 48 inch target length, these translate to between 5000 and 10,000 cc of target per assembly. The 10,000 cc value should be considered an upper bound, since this assumes the largest pin size, leaves no room for liners or thicker cladding, and leaves minimal coolant flow area. A value of 8000 to 9000 cc is more reasonable.

Moderated Assemblies. Moderator material can displace target material to provide spectral tailoring for specific isotope production requirements. This technique has been used in FFTF in several test assemblies, including the Cobalt Test Assembly and the Multiple Isotope Production Test Assembly (MIP). These two assemblies took different approaches in combining moderator and targets.

The Cobalt Test Assembly contained 19 large diameter yttrium hydride moderator pins and 36 small diameter target pins containing either Co-59 for producing Co-60, or natural europium for producing Gd-153. The target pins comprised only about 10% of the available volume inside the duct. If the Cobalt Test Assembly were used as a model for future target assemblies, this will provide about 1300 cc of target volume per assembly, based on a 48 inch target length. The relative sizes of the target pins and moderator pins can be varied, depending on the degree of moderation desired and amount of target material. Therefore a range of target volumes from 1000 cc to 5000 cc is reasonable to expect for this type of assembly.

The MIP test assembly contained 19 large diameter pins. Each pin contained axial segments of different materials. The center of selected segments contained capsules of isotope targets. Thus, there were no separate target pins. This technique makes optimum use of spectral tailoring, but minimizes the available target volume. The close coupling between the moderator and target in this type of assembly allows more thermalization than in separate target and moderator pins. This concept does allow a combined approach, however, where some of the large pins can contain moderator, some can contain moderator plus targets, and others can be just large target pins. Target heating concerns may limit the amount of target material inside the large pins. Target volumes for this type of assembly can range from 500 cc to 5000 cc, depending on the moderator to target ratio.

These are just two options, and other creative uses of moderation may be possible. Ultimately, the choice depends greatly on the characteristics of specific target materials, and how different targets are combined in a single assembly.

Rapid Retrieval Assembly. The assembly for inserting and removing targets in the core without shutting down has not been designed. Target insertion and removal methods, target capsule design, the amount of moderation, and concerns on neutron streaming and target heating will all need to be addressed to determine the available target volume. Some preliminary concepts exist, which can be used to estimate the likely target volumes. One concept is for the targets to be enclosed in silica capsules. Two or more isotope target capsules may be installed in a single metal capsule carrier, which then becomes part of a string of capsules inserted in the reactor. Padding and connectors will be needed to

protect and link the capsules. Depending on the overall length of each target capsule, as many as 38 target capsules might constitute one string. Limited heat removal capability and neutron streaming concerns limits the size of the delivery tube. Although the nominal concept is for one delivery tube per assembly, it may be possible to include more than one tube in each assembly. The need for the delivery tube to be a pressure boundary for the reactor places some limits on physical size and wall thickness. Estimates for target diameter have been in the range of 0.18 to 0.375 inches. Allowing for target length, capsules, padding, linkages, etc., the target volume for a single 48-inch string of targets will likely range from 10 cc to 25 cc. Other concepts of target packaging that make more efficient use of the axial spacing, or that allow more than one target string per assembly might increase these values.

2.1.4.2 Neutron Flux Level Considerations

The FFTF was designed to produce a high neutron flux. The nature of fast spectrum reactors is that there is a large excess of neutrons over what is needed to maintain the neutron chain reaction. Thus, neutron absorption to produce isotopes can be easily accommodated without making major changes in the system. Neutron flux levels vary with core location, with the highest flux levels in in-core locations. Typical neutron flux levels range from 2 to 4 x 10^{15} neutrons/cm^2/second in the core region to 2 to 4 x 10^{14} neutrons/cm^2/second in the ex-core region. Over a 48 inch axial region, the neutron flux can vary by about a factor of 1.5 from peak to average. However, flux level alone is not the only consideration for optimizing isotope production. Taking advantage of the varying flux spectra available in different regions of the reactor or specifically tailoring the neutron spectrum within an assembly can make tremendous differences in isotope production rates. For target isotopes with large absorption cross sections in the epithermal energy range, much higher reaction rates can be achieved in lower flux levels where the spectrum has been softened. Softening the spectrum increases some target reaction rates, but also increases parasitic absorption in fuel and structural materials.

2.1.4.3 Flux Tailoring Capability

There are several cases in which a fast reactor neutron spectrum is quite advantageous for the production of isotopes. Most of the isotopes that are planned for production in the FFTF fall into one of the advantageous categories as described below.

The first category is one in which the product isotope is formed from the target isotope by an (n,p) reaction. The Zn-67 (n,p) Cu-67 is an example of this type of reaction. Generally, (n,p) reactions involve neutrons with energies significantly above the epithermal region, in the tens to hundreds of keV energy range. The neutron spectrum from a fast reactor will yield a much larger reaction rate for this type of reaction than the spectrum from a thermal reactor. Neutrons of this energy can also be produced in an accelerator, but the flux level is much lower and yields a lower reaction rate.

The second category is one in which the parent isotope possesses a large resonance integral and a small thermal cross section, or has a reasonable thermal cross section but possesses an advantageous resonance integral for use in a fast reactor neutron flux spectrum. In this case, irradiation in a fast reactor

spectrum produces a greater reaction rate, and hence produces more of the product isotope for a given quantity of target material and irradiation time. Since both of these situations are similar, they are categorized as one case.

An example of a target possessing a small cross section and a much larger resonance integral will be Cd-109 production from Cd-108. The resonance integral of Cd-108 is 15 times larger than its small thermal cross section (1 barn thermal). Re-186 from Re-185 is a case where the target possesses a reasonable thermal cross section (112 barns), but has an advantageous resonance integral (1700 barns). Sm-153 production from Sm-152 is another example of an advantageous resonance integral (210 barn thermal, 3000 barn resonance integral).

The third category is one in which the daughter has a relatively long half-life and the thermal cross section of the daughter product is much larger than the thermal cross section of the parent target isotopes. With this combination in a thermal spectrum, the removal coefficient due to neutron absorption is large, and the quantity of product isotope produced per parent irradiated is small. The product daughter "burns out" by neutron absorption rapidly, establishing a lower daughter equilibrium level. Se-75 production from Se-74 is an example of a long-lived product with a much larger thermal cross section than the target isotope. Se-75 has a 120 day half-life and a 300 barn thermal cross section, while Se-74 possesses only a 48 barn thermal cross section. Se-75 has a small resonance integral while Se-74 possesses a 600 barn resonance integral, yielding much more product if irradiated in a fast reactor flux spectrum.

If the target isotope is irradiated in a fast reactor spectrum, the cross sections are most probably equilibrated in the epithermal region, yielding a greater product daughter equilibrium level for the same quantity of parent irradiated. With this knowledge, a fast reactor spectrum can be "tailored" to take advantage of production by the second category without causing significant impact to either the first or third category. This is done by using a calculated amount of moderating material around the target to develop the desired flux spectrum. In a fast reactor, this is not a difficult task. Conversely, this type of flux tailoring cannot easily be done in a thermal reactor.

This technology is not theoretical, but is mature and has been implemented in the past at the FFTF for the production of both Co-60 and Gd-153. Yttrium hydride was used as the moderator in this case. Figure 2-2 depicts the actual configuration in which the yttrium hydride was used to tailor the flux spectrum for production of the two previously mentioned isotopes from Co-59 and natural europium target materials, respectively. This configuration is very similar to what is proposed for the long-term irradiation vehicles (LIV) during the isotope production campaigns. The Cobalt Test was irradiated for 169 full power days, with no observable degradation of the yttrium hydride moderator effectiveness. These irradiations proved to be very successful, and production levels were close to those predicted by calculations. This demonstrated that both the technique and the modeling capabilities were excellent. MCNP was the modeling code used in conjunction with the ENDFB-5 cross section library.

Figure 2-3 gives the representative flux spectrum achieved by using yttrium hydride to moderate the neutron energy. As can be seen, the flux from a few eV to about 10^4 eV is significantly boosted to take

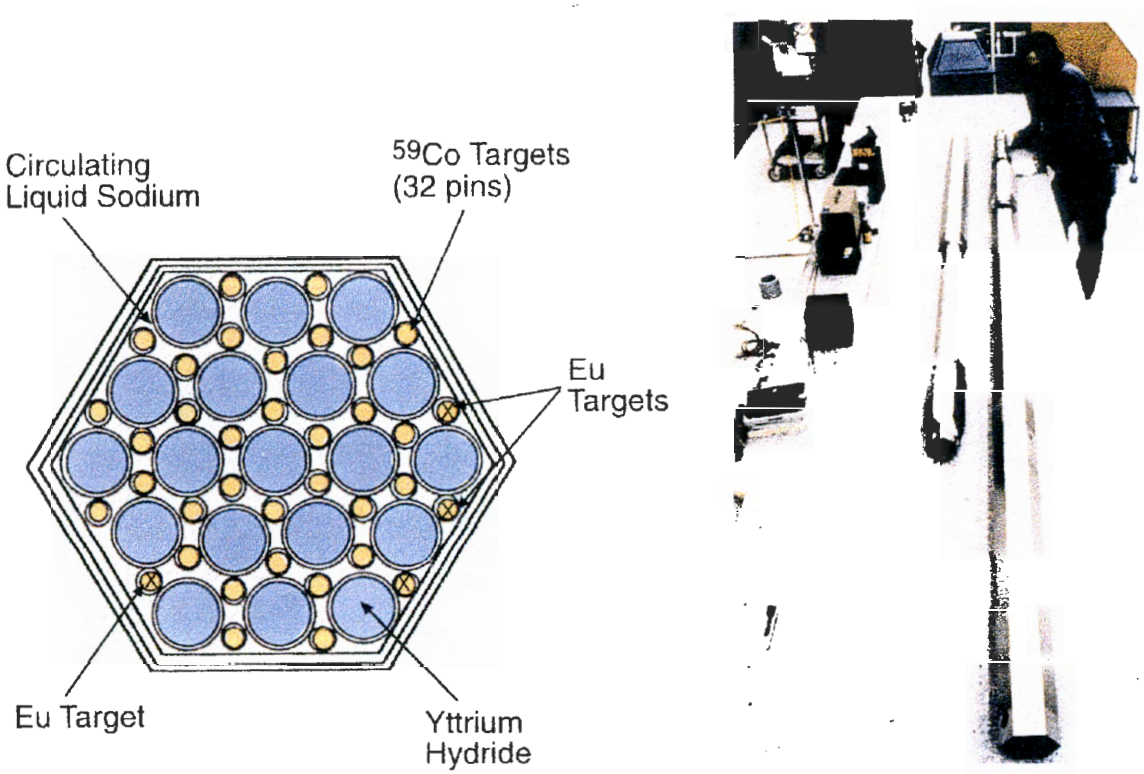

Figure 2-2. Isotope target assembly for Co-60 and Gd-153 production using yttrium hydride to moderate the neutron energy.

advantage of the resonance integrals in the target materials. This amplification of the flux over these energies increased the reaction rates significantly. It shall be noted that the flux in the ten thousand keV range is not impacted, and ample flux of higher energies exists for the targets that yield their product through (n,p) reactions.

Comparison calculations have been performed on reaction rates for Cu-67 production from Zn-67 targets in a hydrided and a normal FFTF spectrum. Production rate of the Cu-67 through the (n,p) reaction in the hydrided spectrum is about 94 % of the production rate in the unhydrided spectrum. Similar comparison calculations were performed on the production of P-32 from S-32 by an (n,p) reaction. In this case, production in the tailored flux spectrum was decreased to 82% of the production rate achieved in the unhydrated spectrum. This small loss of production rate for (n,p) reactions is a minor cost to pay for the tremendous gain in reaction rates realized by target isotopes that possess large or advantageous resonance integrals.

Figure 2-2 shows the yttrium hydride as the large pins, with the target pins being the small diameter pins. Depending on the amount of flux thermalization desired for a specific target material, the diameters of the respective pins can be altered to achieve the desired flux spectrum.

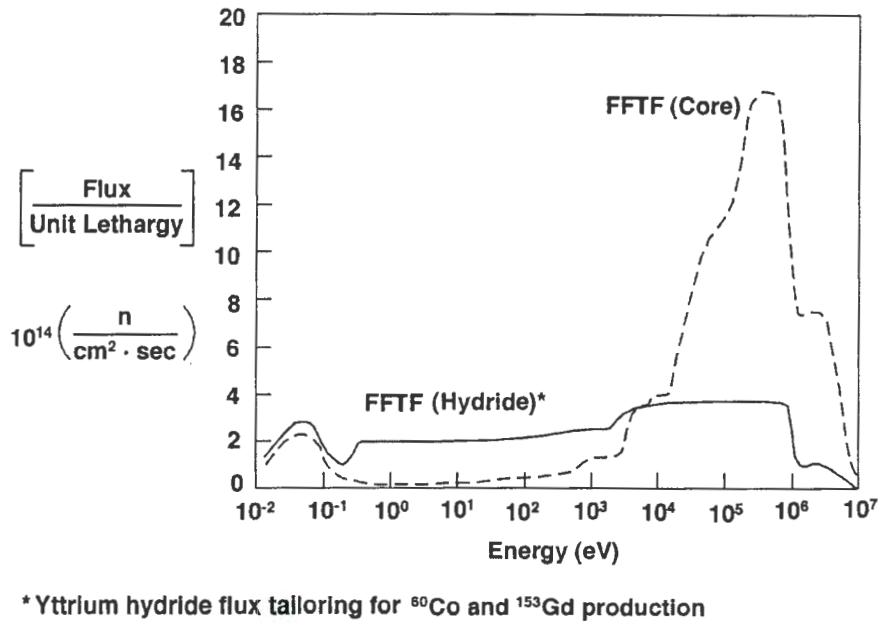

Figure 2-3. Change in neutron energy spectrum resulting from the insertion of yttrium hydride pins for energy moderation.

Axial flux tailoring is also possible, and was used in the MIP (Multiple Isotope Production) test that was conducted at FFTF in 1988. This assembly consisted of 19 large pins (48 inches long). The outer row of pins were tungsten with an upper region of yttrium hydride. The middle row of pins were yttrium hydride, with target capsules inside the yttrium hydride rods.

The center pin contained 6-inch segments of various materials (iron, nickel, chromium, zirconium, tungsten, yttrium hydride), with dosimetry targets inside each segment. This was a sophisticated physics test of the calculational ability to predict the neutronic environment in complex moderated assemblies in FFTF. Each region in this test created its own unique neutron and gamma spectrum, which was verified by extensive neutron dosimetry and spectrum unfolding techniques.

Although it was not intended for the production of medical isotopes, the MIP test did include a number of medical and other beneficial isotope targets (Re-185, Os-190, Tm-169, W-186, Se-74, I-129, Tc-99, and Li-6), which were processed and analyzed following irradiation. These targets were located in the upper yttrium hydride region. The W-186 target was analyzed for W-188, and was used to establish that the W-187 resonance capture cross section was significantly in error.

Axial flux tailoring is an inevitable outcome of the inherent design of the FFTF. Axial Inconel (nickel) reflectors on the fuel assemblies soften the spectrum outside the 36-inch fuel region. In an unmoderated assembly, there is capability to take advantage of this enhancement of resonance energy neutrons above and below the active core region. During the tests conducted with the materials open test assembly (MOTA), certain targets were located above or below the core for this reason (the fusion MOTA canister was located below the core region). Medical isotopes have been produced in a MOTA,

and have been located to take advantage of the increased resonance energy neutrons above and below the core region. It shall be noted that adding moderator to the assembly removes much of this tailoring effect seen in the Inconel reflectors.

Similar axial flux tailoring can be performed for the commercial production of medical isotopes, yielding a gradient of thermalization. A given target can be split into zones, each taking advantage of a different amount of thermalization. Figure 2-4 shows the resonances of Re-185 and Mo-98. These are shown only as examples. As can be seen, the Rhenium target uses the neutron energy spectrum from about 1 eV to about 100 eV, and the molybdenum target uses the energy spectrum from a few hundred eV to about 8,000 eV. These two targets benefit significantly from flux tailoring, but differ in the amount of thermalization desired for optimum reaction rates. The production of isotopes from both targets will benefit greatly from the hydride flux spectrum shown in Figure 2-3.

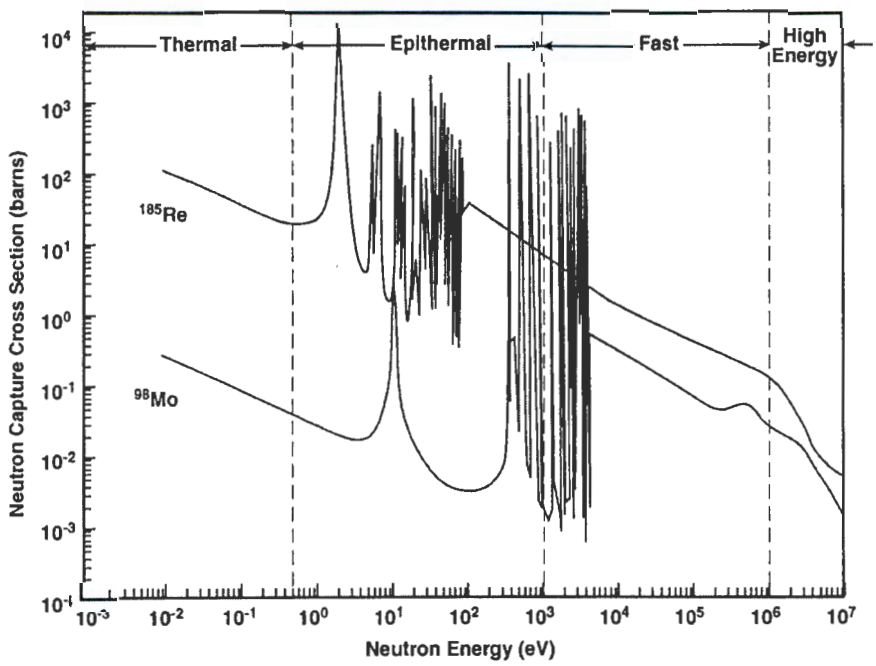

Figure 2-4. Neutron capture cross sections for Re-185 and Mo-99 targets as a function of neutron energy.

Tailoring can also be performed, if deemed desirable, in the rapid retrieval vehicle system. Decisions regarding what tailoring is desired, and what degree of thermalization is desired, will be based on market demand for the various isotopes to be produced at FFTF.

Since the LIVs will be removed at the end of each cycle, new flux tailoring plans can be implemented in each cycle, if desired. In the rapid retrieval vehicle, the target assembly is planned to remain in place for several cycles, so a decision to perform flux tailoring in this irradiation facility will be a long-term impact, and these decisions must be made carefully.

Spectrum modification is not limited to only what can be achieved in a single assembly. Localized environments can also be created using clusters of assemblies. Locating targets in the reflector region allows flexibility to create larger regions of modified neutron and gamma spectra. This type of flux tailoring was demonstrated with the MIP test, where adjacent reflector assemblies were changed to low-mass assemblies.

Care must be taken to preclude the spectrum from becoming too soft. If the thermal Maxwellian is increased significantly, an impact on fission rates in the surrounding bundles may be experienced. This tends to limit the degree of thermalization that can be achieved, but it is not a very significant constraint. As can be seen from the spectra in Figure 2-3, although a very significant boost is obtained between 1 eV and 1 MeV, the thermal Maxwellian is not significantly impacted by this degree of tailoring.

Figure 2-5 shows a comparison of spectra from various isotope production reactors with two spectra from the FFTF, one with flux tailoring by yttrium hydride pins. As can be seen from the figure, the FFTF hydrided flux from about 1 eV through 1 MeV is greatly amplified over the other isotope producing reactors. It shall again be mentioned that these other reactors lack the capability of easily developing a flux boost in this energy region. In the FFTF, it is a facile task, which has been carried out successfully during prior operations from 1982-1992.

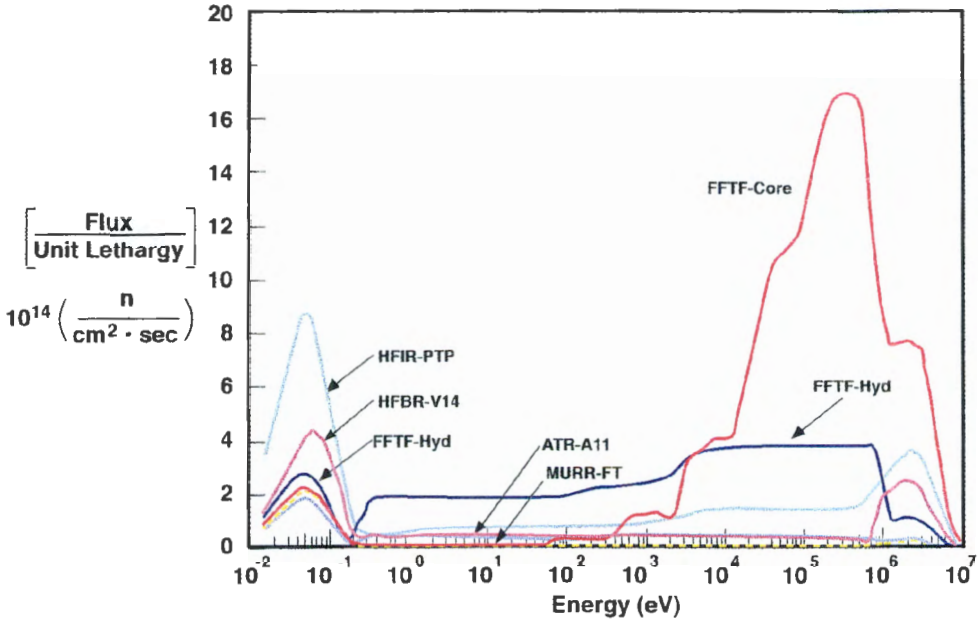

Figure 2-5. Comparison of FFTF neutron spectra with and without yttrium hydride (Hyd) moderator pins; also shown are neutron spectra from the core regions of the High Flux Isotope Reactor (HFIR, Oak Ridge National Laboratory), the High Flux Beam Reactor (HFBR, Brookhaven National Laboratory), the Advanced Test Reactor (ATR, Idaho National Environmental and Engineering Laboratory), and the Missouri University Research Reactor (MURR).

2.1.5 Associated Systems Description

As discussed in the section entitled "Production Vehicles," three positions will initially be reserved in the reactor core for medical isotope production assemblies. Two different types of assemblies will be used for production of these isotopes—one type for production of long half-life isotopes (using the Long-Term Irradiation Vehicle) and the other type for production of short half-life isotopes (Rapid Radio-isotope Retrieval system). Existing FFTF systems and equipment will be used for handling these isotope production assemblies and for preparing irradiated targets for shipment to the 325 Building.

2.1.5.1 Long-Term Irradiation Vehicle Operations

Conceptually, the assembly used for production of long half-life isotopes will consist of a bundle of target pins installed inside a nozzle, duct and handling socket assembly similar in appearance to an FFTF 12-foot long fuel assembly (Figure 2-6). This assembly will be installed in the reactor during normal refueling operations and will be handled similar to a fuel assembly using the standard FFTF fuel and component handling equipment. The Closed Loop Ex-Vessel Handling Machine (CLEM) (Figure 2-7) will be used to install the assembly at the reactor.

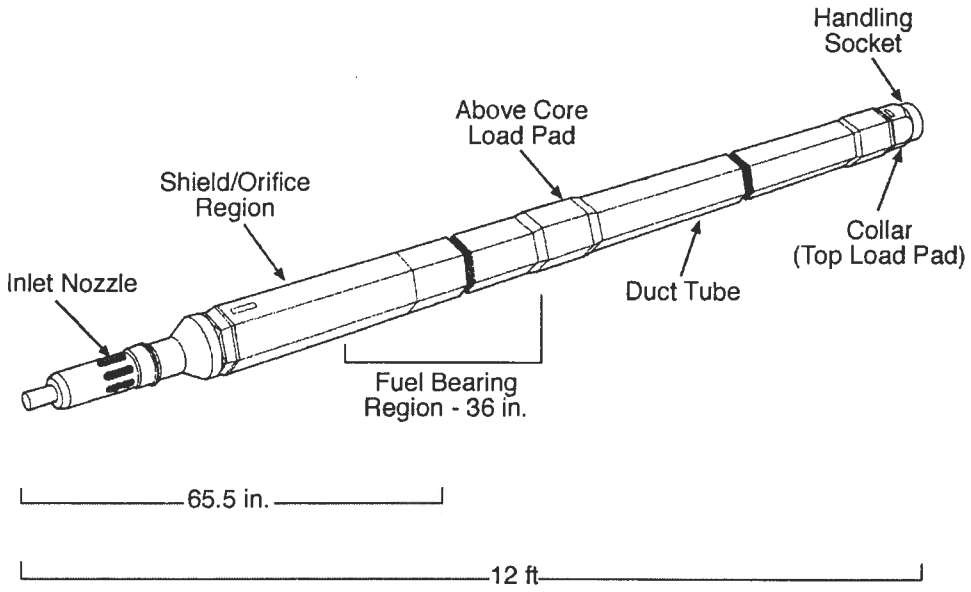

Figure 2-6. Schematic of FFTF fuel pin assembly.

Figure 2-7. Closed Loop Ex-Vessel Machine (CLEM) for installing target assemblies at FFTF.

On completion of irradiation (one or more 100 day irradiation cycles), the assembly will be removed from the reactor following shutdown for normal refueling. The irradiated assembly will be transferred from the reactor to the Interim Examination and Maintenance (IEM) Cell (see Figure 2-8) using the CLEM and associated refueling equipment.

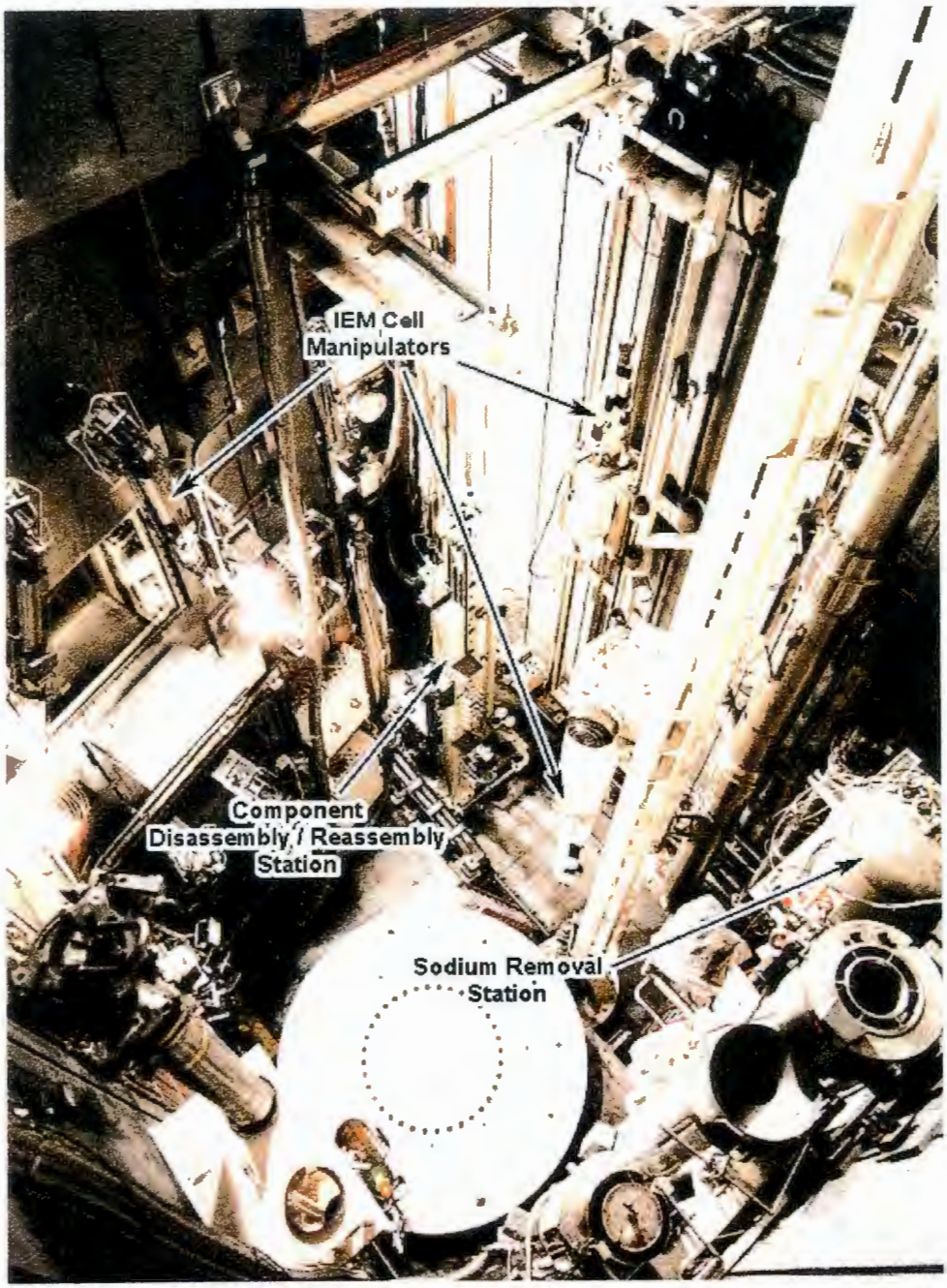

Figure 2-8. Interim Examination and Maintenance (IEM) Cell used to remove residual sodium from target assemblies and for removal and inspection of target pins.

In the IEM Cell, which is located inside the FFTF Containment Building, the long-term irradiation assembly will be washed and dried in the sodium removal system to remove residual sodium prior to disassembly. This sodium removal system has been used extensively to wash all fuel and experimental test assemblies processed in the IEM Cell in the past as well as to wash a large number of the FFTF spent fuel assemblies.

Following sodium removal and drying, the irradiated long half-life target pins will be remotely removed from the target assembly using existing IEM Cell manipulators, fixtures and tooling as appropriate. The irradiated target pins will be loaded into an appropriate pin container for transfer from the IEM Cell. The pins will be transferred from the IEM Cell to an existing intermediate holding cell using CLEM. The pins and pin container will then be transferred from the Containment Building to the Cask Loading Station in the Reactor Service Building using the Bottom Loading Transfer Cask (BLTC) shown in Figure 2-9. At the Cask Loading Station, the pins and pin container will be loaded into an appropriate transportation cask, such as the T-3 or other casks, for transfer to the processing facilities in the 325 Building.

2.1.5.2 Rapid Radioisotope Retrieval System Operations

The rapid retrieval system will be used for the production of short-lived isotopes at FFTF. As discussed in Section 2.3 ("Production Vehicles"), a preliminary concept for this system consists of three major components; a 40-foot-long in-reactor thimble assembly, a replaceable string or chain of isotope target carriers, and a target carrier insertion and retrieval system. The first of these components, the 40-foot-long in-reactor thimble assembly, will provide the greatest interface with existing FFTF systems and equipment.

The 40-foot-long in-reactor thimble assembly will be installed in the reactor, through a reactor head mounted spoolpiece, using the CLEM and associated Center Island refueling equipment similar to previous installations of Materials Open Test Assemblies (MOTA) at FFTF. This will be done as part of a normal refueling outage. Up to two in-reactor thimble assemblies can be installed in the reactor in separate spoolpieces at any given time. Purge or sweep gas lines, any instrumentation, confinement sleeves and temporary isolation valves will be installed to properly interface the in-reactor assembly with existing FFTF systems and a new target carrier insertion/retrieval system.

During reactor operation at full power, capsules containing target materials to be irradiated will be shuttled into and out of the core region by the target insertion and retrieval system. Ideally, the insertion and retrieval system will load irradiated target chains directly into a shielded cask. After transferring the shielded cask to the Reactor Service Building for installation of appropriate transportation overpacks, this assembly will be shipped to the processing laboratories in the 325 Building.

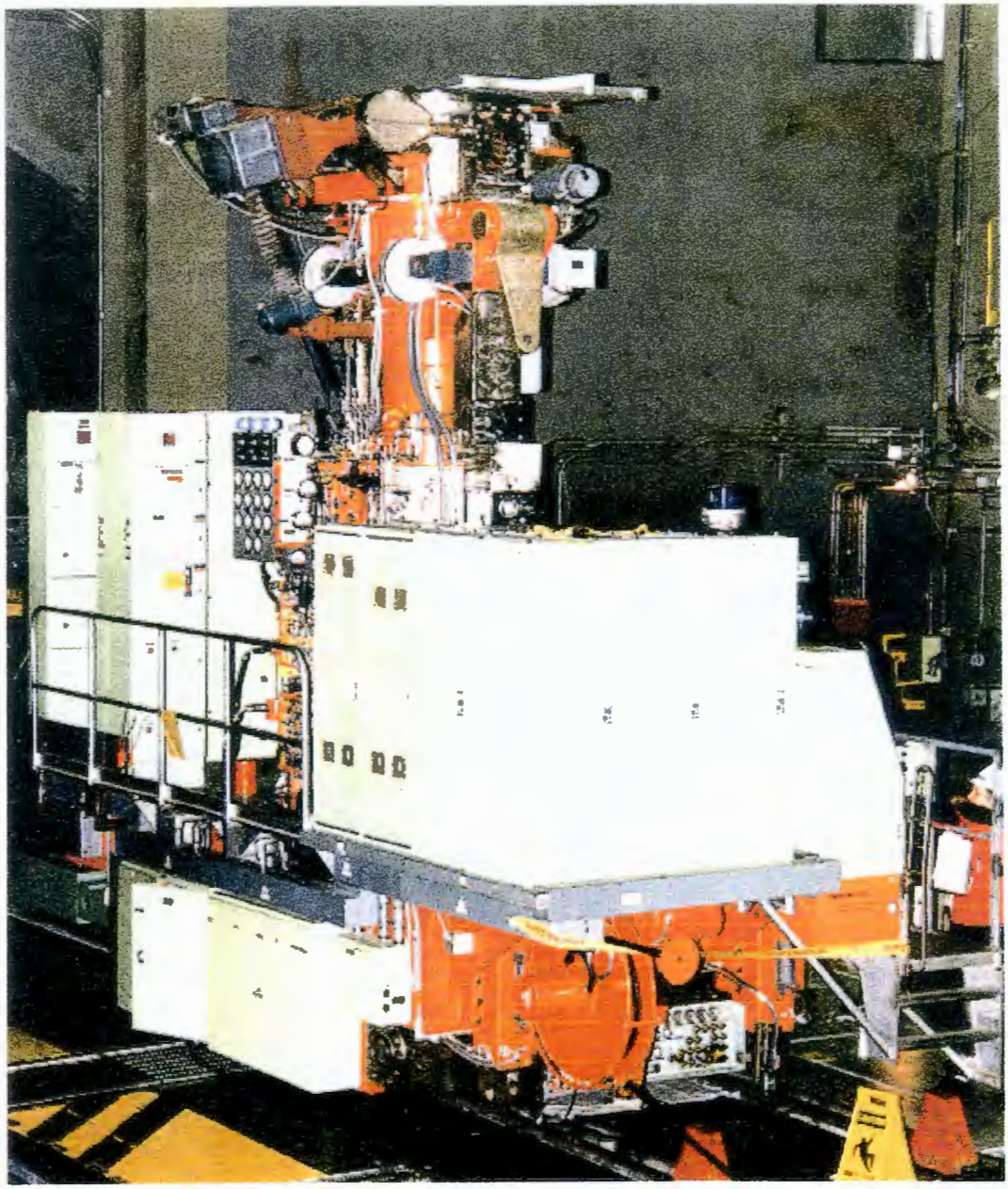

Figure 2-9. Bottom Loading Transfer Cask (BLTC) for loading target pins into a transportation cask.

The 40-foot-long in-reactor thimble assembly will remain in the reactor through a number of 100-day operating cycles. At the end of its lifetime, based on factors such as the lifetime of any moderator material used or on irradiation damage effects, the assembly will be removed from the reactor using CLEM and a new assembly will be installed. The irradiated in-reactor assembly will eventually be delivered to the IEM Cell with CLEM where it will be disassembled, cut into shorter pieces and be washed to remove sodium before disposal as radioactive waste.

2.2 Past History and Performance

During the period 1982-1992, multiple experiments were performed to test the quantity and quality of isotopes that can be produced at FFTF for medical, industrial, agricultural, and research applications. As illustrated in Figure 2-10, 39 radioisotopes were produced at FFTF during its decade of operation, 25 of which have applications in diagnostic and therapeutic medical procedures.

Product Isotope	Target Isotope	Half Life
√ * Ac-227	Ra-226	21.8 y
Ar-37	Ca-40	35 d
* Au-198	Au-197	2.69 d
√ C-14	N-14	5730 y
Ca-41	Ca-40	10^5 y
Ca-45	Ca-44	163 d
√ * Cd-109	Ag-107, Cd-108	462 d
Cd-115m	Cd-114	44.6 d
* Ce-141	Ce-140	32.5 d
√ * Cf-252	Cm-244	2.64 y
Cm-244	Am-243	18.1 y
√ Co-57	Ni-58	272 d
√ * Co-60	Co-59	5.27 y
* Cs-131	Ba-132	9.69 d
* Cu-64	Zn-64	12.7 h
√ * Cu-67	Zn-67	2.58 d
* Dy-165	Dy-164	2.33 h
√ Es-254	Cf-252	276 d
√ Eu-155	Sm-154	4.71 y
√ Fe-55	Fe-54	2.73 y
√ Fe-59	Fe-58	44.5 d
√ * Gd-153	Gd-152, Eu	242 d
√ H-3	Li-6	12.3 y
* Ho-166	Ho-165	1.12 d
√ * I-125	Xe-124	60.1 d
* I-131	Te-130	8.04 d
* In-111	Sn-112	2.81 d
√ * Ir-192	Ir-191	73.8 d
Kr-85	Kr-84	10.7 y
* Lu-177	Lu-176	6.68 d
* Mo-99	Mo-98	2.75 d
Na-22	Na-23	2.6 y
* Nb-95	Mo-95	35 d
√ Ni-63	Ni-62	100 y
√ * Os-191	Os-190	15.4 d

Product Isotope	Target Isotope	Half Life
√ * Os-194	Os-192	6 y
* P-32	S-32	14.3 d
√ * P-33	S-33, Cl-36	25.3 d
* Pd-103	Pd-102	17 d
* Pd-109	Pd-108	13.4 h
√ Pm-145	Sm-144	17.7 y
√ Pm-147	Nd-146	2.62 y
* Pt-195m	Pt-194, Pt-195	4.02 d
√ Pu-238	Np-237	87.7 y
√ * Re-186	Re-185	3.78 d
* Rh-105	Ru-104	35.4 h
* Ru-103	Ru-102	39.3 d
√ S-35	S-34	87.2 d
√ * Sc-46	Sc-45	83.8 d
√ * Sc-47	Ca-46, Ti-47	3.3 5 d
√ * Se-75	Se-74	120 d
√ * Sm-145	Sm-144	340 d
√ Sm-151	Sm-150	90 y
* Sm-153	Sm-152	1.93 d
Sn-113	Sn-112	115 d
√ * Sn-117m	Sn-117, Sn-116	13.6 d
√ * Sr-85	Sr-84	64.8 d
√ * Sr-89	Sr-88	50.5 d
√ * Ta-182	Ta-181	114 d
* Tb-161	Gd-160	6.91 d
√ * Th-228	Ra-226	1.91 y
√ * Th-229	Ra-226	7300 y
√ Tl-204	Tl-203	3.78 y
√ * Tm-170	Tm-169	129 d
Tm-171	Tm-169	1.92 y
U-232	Pa-231	70 y
√ * W-188	W-186	69.4 d
√ * Xe-127	Xe-126	36.4 d
* Y-91	Zn-91	58.5 d
* Yb-169	Yb-168	32 d

√ denotes isotopes previously produced in FFTF
* denotes isotopes for diagnostic and therapeutic medical applications

Figure 2-10. Seventy isotopes for which FFTF has production capability; check marks indicate 39 isotopes produced in FFTF tests conducted during the period 1982-1992, and asterisks indicate 44 isotopes that have diagnostic and therapeutic medical applications.

In addition to illustrating the capability for producing medical radioisotopes, the FFTF isotope production tests were focused on several experimental objectives. For example, specific operational performance features of FFTF were tested, including: 1) advantages of a high flux of fast neutrons (up to 7×10^{15} neutrons/cm^2/sec in the core region) and a large target volume (approximately 30,000 cm^3 at flux

levels above 10^{15} neutrons/cm^2/sec) were demonstrated; 2) it was shown that the neutron energy within target assemblies in both the reactor core and reflector regions can be moderated to match the optimum energy spectrum for producing various types of isotopes; 3) several different target vehicles were fabricated and shown to be functional for the production of multiple isotope species; and 4) cross-section data and calculational methods were verified for several types of isotopes, enabling close correspondence to be achieved between predicted and measured isotope production rates.

Some of the more noteworthy experimental tests that were carried out at FFTF included: 1) Multiple Open Test Assembly (MOTA) irradiations were performed, 2) a Co-60/Gd-153 target assembly was irradiated to test FFTF flux tailoring capabilities, and 3) a Multiple Isotope Production test was performed with an array of 30 isotope targets. The following is a brief description of the results of these experimental tests.

2.2.1 MOTA Irradiations

From 1983 to 1992 a total of nine MOTAs were irradiated at FFTF.[a] The design of a MOTA irradiation vehicle is shown in Figure 2-11. Each MOTA vehicle was irradiated for approximately one year, with the exception of one vehicle that was irradiated for only four months to obtain low fluence data on isotope production rates. Temperature data and information on radiation damage to the MOTA vehicle were obtained for numerous locations in the FFTF core and reflector regions. Very importantly, the MOTA tests demonstrated the ability to produce abundant quantities of nearly 40 different radioisotopes of commercial and research value. As an example, Table 2-1 lists 21 different isotopes produced in the MOTA-2B test conducted during FY 1993. The commercial value of these radioisotope products was demonstrated by the sale of all of the Cd-109 produced in MOTA-2B and much of the Gd-153 produced in MOTA-1E/1G for more than $1 million. Several other isotopes were sold in small quantities for medical research applications.

Table 2-1. MOTA-2B Isotope Products

Actinium-227	Iridium-192	Plutonium-238	Thulium-170
Cadmium-109	Iron-55	Promethium-147	Tungsten-188
Carbon-14	Nickel-63	Samarium-145	Xenon-127
Europium-155	Osmium-194	Sulfur-35	Thorium-228
Gadolinium-153	Phosphorus-33	Thallium-204	Thorium-229
Iodine-125			

(a) Schenter, R.E., Smith, S.G., and Whitten, B.D. "Disposition and analyses for FFTF MOTA-produced isotopes." Westinghouse Hanford Company report number 9455355, Richland, Washington (1994).

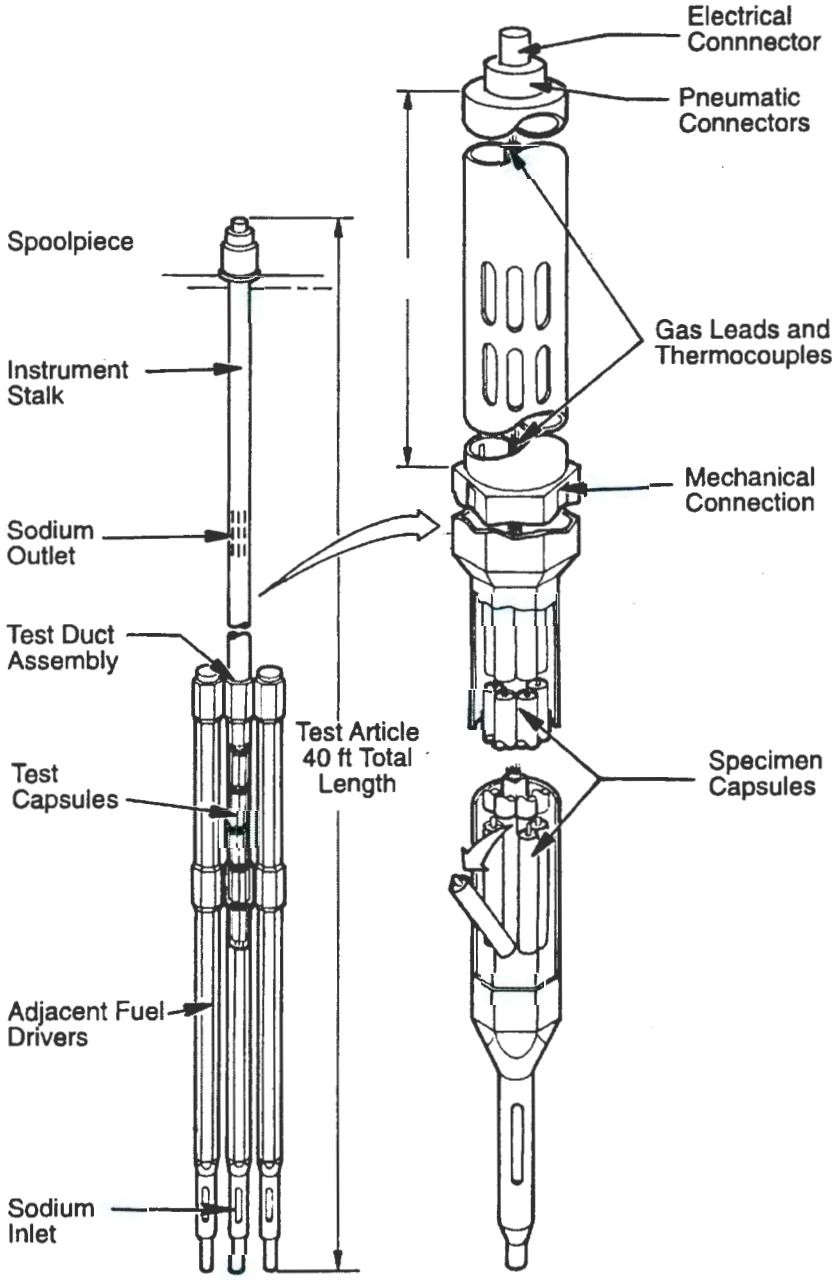

Figure 2-11. Diagram of Materials Open Test Assembly (MOTA) used at FFTF.

2.2.2 Co-60/Gd-153 Test Assembly

In 1986 a key experiment was performed which demonstrated the ability to enhance FFTF isotope production by inserting pins of moderator material that increased the total neutron flux in the epithermal and thermal energy ranges.[a] An assembly that contained 32 pins of Co-59, the target for Co-60 production, and 4 pins with natural Eu-151/153, the target for Gd-153 production, was constructed with numerous interspersed yttrium hydride pins for neutron energy moderation. The target assembly was irradiated for 138 days at a power level of 291 MW, and demonstrated a significant increase in the production of Co-60 and Gd-153 as a result of neutron flux tailoring by insertion of the yttrium hydride moderator material. This test also demonstrated the ability of FFTF to produce Gd-153 with a very high specific activity of greater than 100 curies per gram. In addition, the results of this experiment illustrated the high degree of accuracy achieved by the calculational methods used to predict the effect of neutron energy moderation on isotope production rates.

2.2.3 Multiple Isotope Production (MIP) Test

In this experiment, conducted during May 1988, multiple test assemblies containing 30 isotope targets were irradiated in the FFTF reflector region.[b] The primary purposes of the MIP test were: 1) to reduce uncertainties in the prediction of Pu-236 production rates and burnout associated with the production of Pu-238, and 2) to demonstrate the capability of FFTF to simultaneously produce multiple isotopes with beneficial applications. Of the isotopes produced in the MIP test, 20 had medical research applications. Although the MIP test was not designed to produce large quantities of isotopes, three isotopes—Os-191, Re-186 and Se-75—were produced in sufficient quantities to be sold for research applications.

As illustrated by the above discussion of FFTF experimental tests during its decade of operation, there is a firm scientific foundation upon which a future medical isotope production mission for this reactor can be built.

(a) Rawlins, J.A., Wootan, D.W., Carter, L.L., Brager, H.R., and Schenter, R.E. "FFTF Cobalt Test Assembly Results." Westinghouse Hanford Company report number WHC-SP-0108, Richland, Washington (1987).

(b) Wootan, D.W., Caggiano, J.A., Carter, L.L., Jordheim, D.P., Lu, A.H., Mann, F.M., Rawlins, J.A., Schenter, R.E., Schmittroth, F.A., Schwarz, R.A., and Simons, R.L. "Isotope Production Test in the Fast Flux Test Facility." Westinghouse Hanford Company report number WHC-SA-0869-FP, Richland, Washington (1990).

2.3 Production Vehicles

Three positions will be reserved in the core for medical isotope production assemblies. Both long-irradiation vehicles and/or rapid radioisotope retrieval systems can be used in these core positions. The new systems will be installed and tested before FFTF restart. A description of these systems is provided in the following sections.

2.3.1 Long-Term Irradiation Vehicle

Conceptually, the long-irradiation assembly used for production of long-lived isotopes consists of a bundle of target pins installed inside a nozzle, duct, and handling socket assembly similar in appearance to an FFTF 12-foot long fuel assembly (Figure 2-6). The bottom 4 feet (approximately) of the target pins contains target material to be irradiated to form isotopes. The pins will be seal-welded to prevent entry of sodium or escape of target materials or isotopes. The vertical center of this 4-foot section of the pin will be centered in the active region of the reactor core. Depending on the isotopes to be produced, the pin bundle can also contain moderator pins and neutron shield pins. The target assembly will be designed to ensure easy remote removal of the target pins from the assembly in the IEM Cell. A design that will allow reuse of the long-term irradiation assembly nozzle, duct, and handling socket hardware will be considered during the design process in an effort to reduce costs and the volume of radioactive waste.

The long-term irradiation assembly will be installed in the reactor during normal refueling operations and handled using the standard FFTF fuel and component handling equipment. On completion of irradiation, the assembly will be removed from the reactor following shutdown for refueling, and be transferred to the IEM Cell using existing FFTF equipment. Following sodium removal, the target pins will be remotely removed from the target assembly. If necessary for shipping and handling, the target pins will be designed to be remotely shortened to approximately 4 feet or less in the IEM Cell without breaching the pin pressure boundary. Consideration will be given to the use of sodium-compatible low-activation cladding materials (e.g., zirconium alloy) to facilitate shipping, handling, and processing operations. The irradiated pins will be shipped from the FFTF to the 325 Building using an appropriate transportation cask.

2.3.2 Rapid Radioisotope Retrieval System

Rapid radioisotope retrieval systems will be used for the production of short-lived isotopes at FFTF. This allows target materials to be inserted and withdrawn from the reactor core region with the reactor operating at full power. Systems for routinely inserting and removing irradiation targets, nuclear instrumentation, and research hardware at an operating reactor have been in use at various research reactors throughout the world for years. Most of these systems use either a pneumatic 'rabbit' type system or a mechanical cable type system for insertion and retrieval.

Initially, two rapid retrieval systems will be fabricated and installed at the FFTF. These systems will be installed at existing Closed Loop In-Reactor Assembly/Open Test Assembly positions in row 6 of the

reactor core that are located under spool pieces in the reactor head. A preliminary concept for the rapid retrieval system consists of three major components: a 40-foot-long in-reactor thimble assembly, a replaceable string or chain of isotope target carriers, and a target carrier insertion and retrieval system (Figure 2-12).

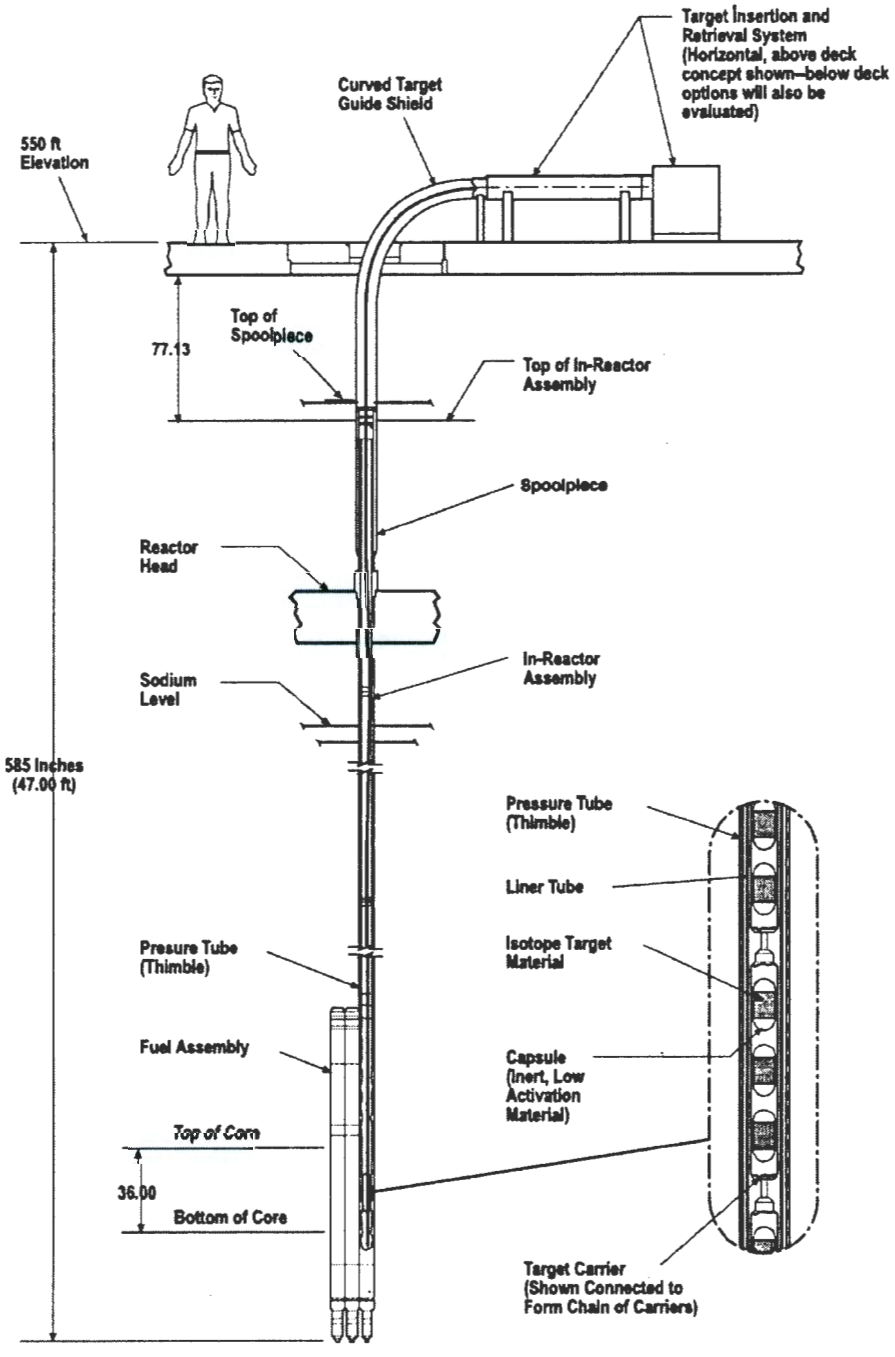

Figure 2-12. Major system components for rapid radioisotope retrieval system.

The in-reactor thimble assembly consists of an upper 28-foot-long stalk and a lower duct and inlet nozzle assembly. This assembly extends from the top of the spool piece on the reactor head, down through the core region, and is seated in the core basket, similar to previous long test assemblies irradiated in FFTF. A gas-filled pressure boundary tube or thimble, welded closed at the bottom end, extends along the radial center line of the assembly from near the top of the spool piece down through the active core to at least 6 inches below the core. A liner tube (or tubes) open at the top and bottom, and installed inside this pressure boundary tube, provides a guide for insertion and retrieval of isotope target carriers.

To preclude direct neutron streaming from the core region to the area above the reactor head, the pressure boundary tube can be offset from the assembly center line for some distance, or can contain a spiral section to provide axial shielding below the top of the spool piece. A curved shielded guide above the spool piece also might be required to minimize radiation streaming.

The pressure tube in the core region can be surrounded by yttrium hydride and shield material pins to moderate the neutron spectra within the thimble to enhance isotope production and to protect adjacent fuel assemblies. These pins and the outside of the gas filled pressure tube/thimble will be cooled by sodium flowing up through the in-reactor assembly. A helium sweep gas flowing through the annular regions inside the pressure tube will be monitored to detect any sodium leakage into the pressure tube.

The target materials will reach relatively high temperatures due to nuclear heating within the thimble. To adequately contain the isotope target material, to minimize formation of any eutectics, and to minimize cross contamination, it is likely that the target material will be placed in a short capsule made of a high-temperature, high-purity, inert, low-activation material. Fused silica or quartz and other materials will be evaluated for fabrication of these capsules. The capsules will need to pass through curved offset shielded sections to be transferred into and out of the core region. This can be achieved by placing one or more capsules into a closed target carrier. To reduce the weight and thickness of shielding required on the retrieval, shipping and irradiated target handling equipment, the target carriers will be made of a low-activation structural material such as a vanadium or zirconium alloy. Carriers will be linked to one another to make an articulated chain to allow for flexible insertion and retrieval from the reactor core (see Figure 2-13 for one concept for an insertion and retrieval chain).

Target carrier insertion and retrieval system(s) will be installed external to the reactor to shuttle a target carrier chain into and out of the core region. This system may use some form of mechanical cable insertion and retrieval mechanism. Ideally, the insertion and retrieval system will load irradiated target chains directly into the transportation cask. The IEM Cell can be used to separate the chain of target carriers shall separation of certain isotopes be desired before shipment to the 325 Building.

In addition to irradiating solid (and molten) targets in the rapid retrieval system carrier chains discussed previously, gas targets can also be irradiated to produce short-lived isotopes. Two options will be evaluated for producing the gas-based isotopes. One option will involve one or more small diameter, thin-wall tubes routed down through the in-reactor thimble assembly into the active core region. These tubes will be connected via preheated and shielded tubes to a shielded ex-reactor gaseous isotope

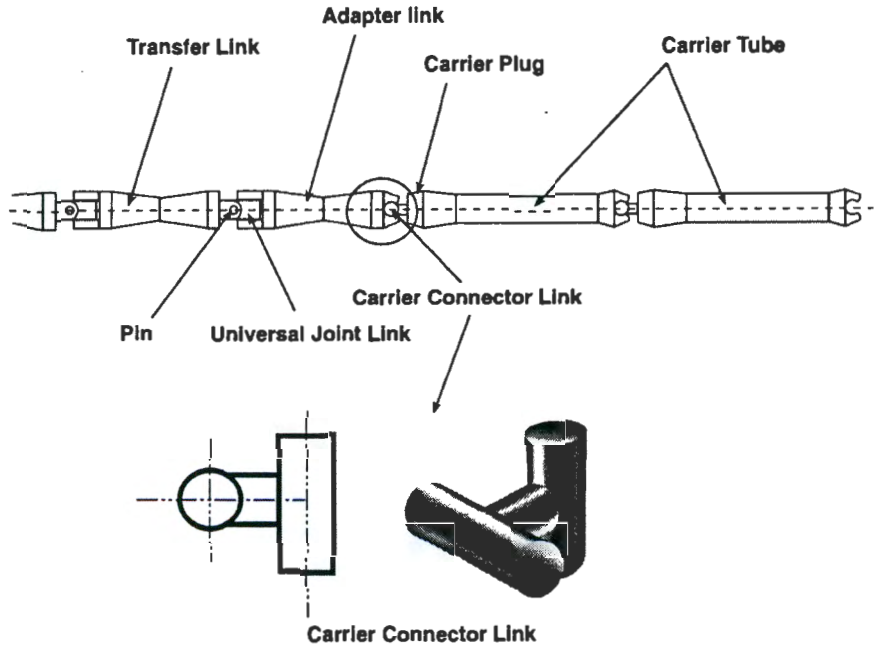

Figure 2-13. Components of target insertion and retrieval chain for rapid radioisotope retrieval system.

recovery system. The target gas will be introduced into the tubing under pressure and the gas circulated through the recovery system to extract the isotope produced. The practice of routing external gas lines down into the active core region is not new at FFTF, and has been used in several irradiation test assembly designs previously installed in the reactor. The Materials Open Test Assembly (MOTA) was a forty (40) foot long test assembly which used externally supplied gas mixtures to control material sample temperatures in the active core. The Fusion MOTA assembly, which irradiated several materials for international fusion material experiments, had this same gas line arrangement, plus additional gas lines that were routed from the assembly to a special glove box for tritium recovery and gas analysis (up to twelve gas lines were used). Additionally, studies were performed in late 1991 that showed it will be feasible to produce I-125 in flowing gas loops routed into the FFTF reactor core via a 40-foot long in-reactor assembly. The establishment of an efficient ex-reactor gas isotope extraction system will require additional design and development work for actual implementation at FFTF.

A second option for producing gas based isotopes involves irradiating capsules filled with a high pressure target gas. The gas-filled capsules are installed in a target carrier and become part of a typical target chain. Upon removal from the reactor, the irradiated gas is recovered in special recovery equipment installed in appropriately shielded enclosures.

To ensure the basic feasibility of the rapid radioisotope retrieval system concept described above, scoping calculations have been performed to evaluate key issues. Preliminary calculations have been done to evaluate nuclear heat deposition in candidate isotope target materials to be irradiated in the in-reactor thimble, to evaluate neutron streaming from the active core through an off-set thimble, and to

calculate activation of various isotope target, structural and encapsulation materials. Additionally, based on the above nuclear heat rate calculations, analyses have been done to evaluate the peak temperature that the various isotope target and surrounding materials will reach during irradiation. The heating and streaming calculations were based, in part, on computer modeling of a preliminary concept for the 40-foot long in-reactor thimble assembly, and these identified concept improvements. The scoping calculations performed to date indicate that the basic rapid retrieval system concept is viable for FFTF and identifies areas where more refined analysis is needed. Based on this work, no major problems have been identified that would not reasonably be expected to be resolved by additional study and more refined analysis such as by thermal finite element modeling.

2.4 Specific Isotopes and Production Levels

Calculations have been made to determine activity levels for a "Top 30" list of medical isotope candidates to be produced in the FFTF. Table 2-2 lists these 30 isotopes, along with a description of their medical applications. These applications primarily involve the diagnosis and treatment of three major medical aliments—cancer, arthritis and heart disease. Some of these product isotopes have numerous uses both for diagnostic and therapeutic applications (Iodine-131, Iodine-125, etc.). In addition, Table 2-2 presents the reaction process ("Reaction") used to transmute the target isotope through neutron irradiation to make the desired medial isotope product. As shown, three types of reaction processes are considered. Specifically, these are neutron capture reactions ((n,γ) or (n,p)) with the ejection of a gamma ray or proton, respectively, and inelastic excitation (n,n') which transforms the target isotope nucleus to an excited isomeric state.

Table 2-2. Top 30 FFTF Medical Isotopes Applications/Reactions

Medical Isotope	Medical Applications	Reactions
Actinium-227 (Ac-227)	Parent of Ra-223 (monoclonal antibody attachment used for cancer treatment by radioimmunotherapy (RIT))	Ra226(n,γ)Ra227/Ac227
Gold-198 (Au-198)	Mini-gun, treating ovarian cancer, prostate cancer, brain cancer, intracavity therapy, limits growth of ministatic disease	Au197(n,γ)Au198
Cadmium-109 (Cd-109)	Cancer detection, pediatric imaging	Cd108(n,γ)Cd109 or Ag107(n,γ)Cd108 Cd 108(n,γ)Cd109
Copper-64 (Cu-64)	PET scanning planar imaging, SPECT imaging, dosimetry studies, cerebral and myocardial blood flow, colorectal cancer therapy	Zn64(n,p)Cu64

Table 2-2. (contd)

Medical Isotope	Medical Applications	Reactions
Copper-67 (Cu 67)	Cancer treatment/diagnostics, radioimmunotherapy (RIT), planar imaging, SPECT or PET	Zn67(n,p)Cu67
Gadolinium-153 (Gd-153)	Dual photon source, osteoporosis detection, SPECT imaging	Eu (n,γ)Eu152? Gd152 Gd152 (n,γ)Gd153
Holmium-166 (Ho-166)	Treatment of rheumatoid arthritis, radiolabeling and monoclonal antibody techniques	Ho165(n,γ)Ho166
Iodine-125 (I-125)	Osteoporosis detection, diagnostic imaging, tracer drugs, monoclonal antibodies, brain cancer treatment (I-131 replacement), SPECT imaging, radiolabeling, tumor imaging, mapping of receptors in the brain, interstitial radiation therapy, brachytherapy for treatment of prostate cancer, determination of glomerular filtration rate (GFR), determination of plasma volume, detection of deep vein thrombosis of the legs	Xe124(n,γ)Xe125/I125
Iodine-131 (I-131)	Lymphoid tissue tumor/hyperthyroidism treatment, antibody labeling, brain biochemistry in mental illness, diagnosis of thyroid disorders by gamma camera imaging or counting, alternative to T1-201 radioimmunotherapy, imaging, cellular dosimetry, adrenal medulla scintigraphy, treatment of Grave's disease, treatment of goiters, SPECT imaging, treatment of prostate cancer, treatment of hepatocellular carcinoma, treatment of melanoma, locate metastatic lesions, treatment of neuroblastoma and malignant pheochromocytoma, internal (systemic) radiation therapy, treatment of thyroid carcinoma, study of kidney functions, construction of renogram, adrenal cortex imaging, investigations of hepatobillary function, determination of plasma volume	Te130(n,γ)I131

Table 2-2. (contd)

Medical Isotope	Medical Applications	Reactions
Iridium-192 (Ir-192)	Brachytherapy, brain and spinal cord tumor treatment, restenosis stents, seed implants for breast and prostrate tumors	Ir191(n,γ)Ir192
Lutetium-177 (Lu-177)	Heart disease treatment (restenosis therapy), cancer therapy (RIT)	Lu176(n,γ)Lu177
Molybdenum-99 (Mo-99)	Parent for Tc-99m generator used for brain, liver, lungs, heart imaging, PET imaging	Mo98(n,γ)Mo99
Osmium-194 (Os-194)	Monoclonal antibody attachment used for cancer treatment (RIT)	Os192(n,γ)Os193 Os193(n,γ)Os194
Phosphorus-32 (P-32)	Polycythemia rubra vera (blood cell disease) and leukemia treatment, bone disease diagnosis/treatment, SPECT imaging of tumors, pancreatic and liver cancer treatment, radiolabeling, labeling nucleic acids for in vitro research, diagnosis of superficial tumors, heart disease treatment (restenosis), intracavity therapy	S32(n,p)P32 or P32(n,γ)P33
Phosphorus-33 (P-33)	Leukemia treatment, bone disease diagnosis/treatment, SPECT imaging of tumors, radiolabeling, restenosis treatment	S33(n,p)P33
Palladium-103 (Pd-103)	Prostate cancer treatment	Pd102 (n,γ)Pd103
Platinum-195m (Pt-195m)	Noninvasive monitoring of drug biodistribution and metabolism, studies with intraarterial Pt-195m-cisplatin	Pt195(n,n')Pt195m or Pt194(n,γ)Pt195m
Rhenium-186 (Re-186)	Cancer treatment/diagnostics, monoclonal antibodies, bone cancer pain relief, treatment of rheumatoid arthritis, treatment of prostate cancer, bone cancer pain relief	Re185(n,γ)Re186
Scandium-47 (Sc-47)	Bone cancer pain relief, radioimmunotherapy (RIT)	Ti47(n,p)Sc47

Table 2-2. (contd)

Medical Isotope	Medical Applications	Reactions
Selenium-75 (Se-75)	Radiotracer used in brain studies imaging of adrenal cortex by gamma-scintigraphy, lateral locations of steroid secreting tumors, pancreatic scanning, detection of hyperactive parathyroid glands, measure rate of bile acid loss from the endogenous pool	Se74(n,γ)Se75
Samarium-145 (Sm-145)	Treatment of ocular cancer	Sm144(n,γ)Sm145
Samarium-153 (Sm-153)	Cancer treatment/diagnostics, bone cancer pain relief, treatment of leukemia	Sm152(n,γ)Sm153
Strontium-85 (Sr-85)	Detection of bone lesions, brain scans	Sr84(n,γ)Sr85
Strontium-89 (Sr-89)	Bone cancer pain relief, treatment of prostate cancer, treatment of multiple myeloma, osteoblastic therapy, potential agent for treatment of bone metastases from prostate and breast cancer	Sr88(n,γ)Sr 89
Thorium-228 (Th-228)	Cancer treatment (RIT), monoclonal antibodies, parent of Bi-212	Ra226(n,γ)Ra227/Ac227 Ac227(n,γ)Ac228/Th228
Thorium-229 (Th-229)	Grandparent of Bi-213 (alpha emitter used in cancer treatment (RIT)), parent of Ac-225	Ra226(n,γ)Ra227/Ac227 Ac227(n,γ)Ac228/Th228 Th228(n,γ)Th229
Tin-117m (Sn-117m)	Bone cancer pain relief	Sn117(n,n')Sn117m or Sn116(n,γ)Sn117m
Tungsten-188 (W-188)	Cancer treatment (RIT), parent for Re-188 generator	W186(n,γ)W187 W187(n,γ)W188
Xenon-127 (Xe-127)	Neuroimaging for brain disorders, research on variety of neuropsychiatric disorders, especially schizophrenia and dementia, higher resolution SPECT studies with lower patient dose, lung imaging evaluation of pulmonary ventilation, indicator for measurement of local cerebral blood flow	Xe126(n,γ)Xe127

Table 2-2. (contd)

Medical Isotope	Medical Applications	Reactions
Yttrium-91 (Y-91)	Cancer Treatment (RIT), cellular dosimetry	Zr91(n,p)Y91

Extensive and accurate production calculations were made using a series of previously verified computer codes. These codes have been used in reactor physics calculations of isotope production in the FFTF and other U.S. fission reactor systems for the past 12 years.[a][b][c] Experimental verification of these calculations has also been made in a number of previous FFTF test irradiations. The calculations involve combining neutron flux data with cross-section data obtained primarily from the BNL-325 data sources[d] and the ENDF/B[e] cross-section data files.

FFTF neutron flux data were obtained from calculations made with the MCNP[f] computer code executed by Wootan et al.[g] Figure 2-14 shows the flux spectra used to obtain the "Top 30" medical isotope production results. The two spectra used were for four different target assemblies placed in Row 6 of the FFTF:

1. Unperturbed in a Long-Term Irradiation Vehicle
2. Perturbed (Hydride) in a Long-Term Irradiation Vehicle
3. Unperturbed in a Rapid Radioisotope Retrieval (R3) System
4. Perturbed (Hydride) in a Rapid Radioisotope Retrieval (R3) System

Self-shielding effects were also included in these calculations using the C-factor approach described in Jordheim.[b]

(a) Mirzadeh, S., R. E. Schenter, A. P. Callahan, and F. F. (Russ) Knapp, Jr., *Production Capabilities in U.S. Nuclear Reactors for Medical Radioisotopes*, ORNL/TM-12010, Nov. 1992.

(b) Jordheim, D. P., R. E. Schenter, et al., *Computer Code for Calculation of Pu-238 Production, Quality, and Impurity*, Trans. Amer. Nucl. Soc., Vol. 423, pg. 63, 1991.

(c) Schenter, R. E., *Comparison of Medical Isotope Production in Fast and Thermal Reactor Systems*, Trans. Amer. Nucl. Soc., Vol. 148, pg. 62, 1990.

(d) Mughabghab, S. F., *Neutron Cross Sections Volume 1: Neutron Resonance Parameters and Thermal Cross Sections*, Academic Press, Inc., New York, 1984.

(e) McLane, V., et al., *ENDF-201 ENDF/B-VI Summary Documentation Supplement I; ENDF/HE-VI Summary Documentation*, BNL-NCS-17541, Dec. 1996.

(f) Briesmeister, J. F., Radiation Transport Group, Los Alamos National Laboratory, *Monte Carlo Neutron Particle Code (MCNP), A General Monte Carlo N-Particle Transport Code, Version 4A*, Nov. 1993.

(g) Wootan, D. W., et al., unpublished calculations, Nov. 1997.

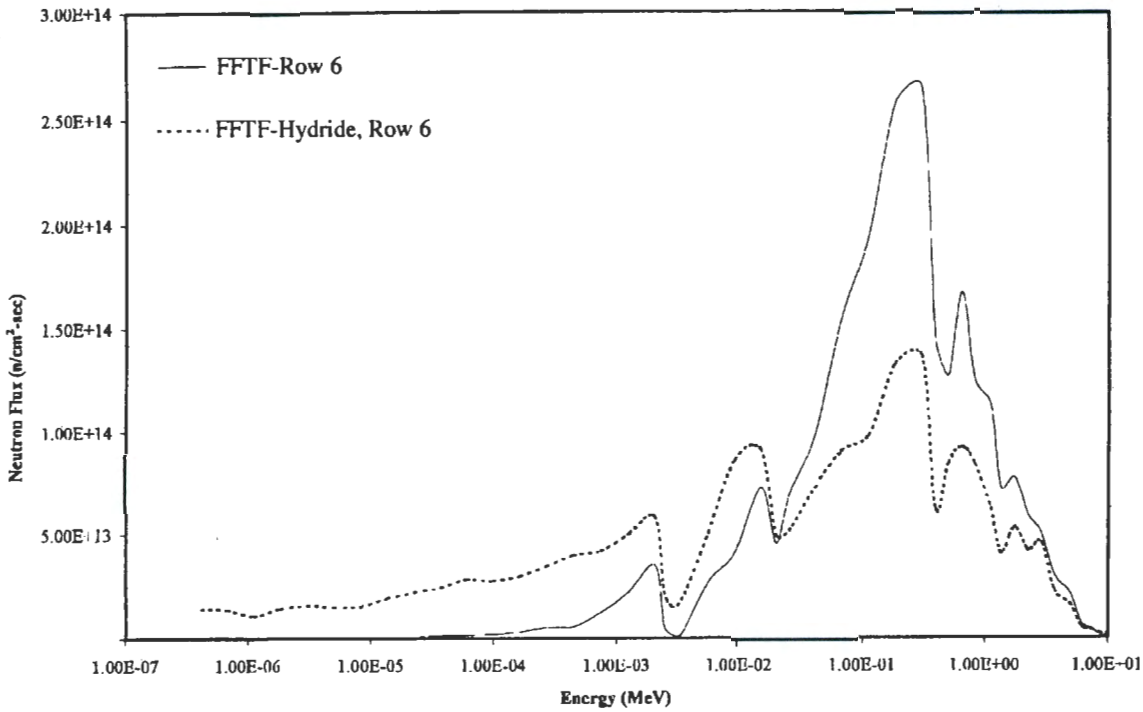

Figure 2-14. Neutron spectrum in Row 6 of the FFTF core region, with and without energy moderation by hydride pins.

Table 2-3 summarizes the results of these calculations for the product isotopes of interest. Additional results (not reported here) for associated "impurity" isotopes were also obtained in these calculations. Table 2-3 presents results for the isotope activity produced (last column) corresponding to the situation of putting a target amount ("Primary Target Isotope Mass (g)") that satisfies the following three conditions:

1. The full target volume of the irradiation vehicle is available.
2. The amount of product isotope generated will have a yearly sales projection consistent with its value.
3. The amount of target specified is available for purchase.

The "Reduction Factor" column quantitatively reflects the three conditions described above (see Section 7 for further discussion of the market demand and sales projection). The results presented in Table 2-3 are for five "Target Vehicle" types (LIV-H, LIV, R3-H, R3 and Gas Line), which are described in the table. The "Hydrided" case corresponds to using yttrium hydride pins as a moderating compound,

Table 2-3. Production Activities for "Top 30" FFTF Medical Isotopes

	Product Isotope	Half Life	Primary Target Isotope	Target Vehicle	Irradiation Time (days)	Reduction Factor	Primary Target Isotope Mass (g)	Product Isotope Specific Activity (Ci/g)	Product Isotope Activity Produced (Ci)
1	Ac-227	21.8 years	Ra-226	LIV-H	200	2.2E-03	3.3E+01	7.2E+01	2.0E+02
2	Au-198	2.69 days	Au-197	R3-H	10	3.1E-04	1.4E-01	1.3E+03	1.8E+02
3	Cd-109	462.0 days	Cd-108	LIV	200	2.0E-02	1.0E+03	2.1E+00	4.0E+03
4	Cu-64	12.7 hours	Zn-64	R3	10	6.8E-02	1.1E+01	3.8E+06	2.2E+01
5	Cu-67	2.58 days	Zn-67	R3	10	6.0E-01	9.3E+01	7.5E+05	8.4E+00
6	Gd-153	242 days	Natural Eu	LIV-H	200	1.7E-01	1.7E+03	3.4E+01	9.8E+01
7	Ho-166	1.117 days	Ho-165	R3-H	10	6.1E-04	1.3E-01	3.1E+02	4.0E+01
8	I-125	60.1 days	Xe-124	Gas Line	200	8.1E-01	4.3E+00	1.7E+04	1.4E+04
9	I-131	8.04 days	Te-130	R3-H	25	9.7E-01	1.4E+02	5.5E+04	6.0E+02
10	Ir-192	73.8 days	Ir-191	LIV	200	6.4E-02	1.5E+04	1.4E+02	1.3E+03
11	Lu-177	6.68 days	Lu-175	R3-H	25	1.6E-05	2.7E-03	2.8E+03	1.0E+01
12	Mo-99	2.75 days	Mo-98	R3-H	10	9.1E-01	2.1E+00	5.5E+01	1.2E+04
13	Os-194	6.0 years	Os-192	LIV	200	1.0E+00	2.3E+05	5.6E-05	1.3E+01
14	P-32	14.3 days	S-32	R3	25	4.1E-01	2.0E+01	2.8E+05	8.0E+01
15	P-33	25.3 days	S-33	LIV	200	3.7E-04	7.1E+00	1.5E+05	4.0E+02
16	Pd-103	17.0 days	Pd-102	R3-H	25	2.7E-01	5.4E+01	1.5E+03	2.7E+03
17	Pt-195m	4.02 days	Pt-195	R3-H	25	1.0E+00	5.0E+02	3.1E-02	2.3E+00
18	Re-186	3.78 days	Re-185	R3-H	25	3.2E-02	1.5E+01	4.5E+01	7.0E+03
19	Sc-47	3.35 days	Ti-47	R3	10	7.1E-01	7.2E+01	8.2E+05	4.0E+01
20	Se-75	120.0 days	Se-74	LIV-H	200	2.0E-05	3.0E-01	5.9E+02	1.0E+02
21	Sm-145	340 days	Sm-144	LIV-H	200	1.6E-04	1.1E+01	9.4E+00	6.7E+01
22	Sm-153	1.93 days	Sm-152	R3-H	10	4.7E-05	8.3E-03	4.6E+02	8.0E+01

Table 2-3. (contd)

	Product Isotope	Half Life	Primary Target Isotope	Target Vehicle	Irradiation Time (days)	Reduction Factor	Primary Target Isotope Mass (g)	Product Isotope Specific Activity (Ci/g)	Product Isotope Activity Produced (Ci)
23	Sn-117m	13.6 days	Sn-116	R3-H	25	5.4E-03	2.7E+00	3.6E+01	1.0E+02
24	Sr-85	64.8 days	Sr-84	LIV-H	200	3.5E-04	3.4E-03	1.2E+02	5.0E+02
25	Sr-89	50.5 days	Sr88	LIV-H	200	2.1E-02	2.5E+02	7.2E-01	8.0E+02
26	Th-228	1.91 years	Ra-226	LIV-H	200	2.2E-03	3.3E+01	6.4E+02	2.1E+03
27	Th-229	7300 years	Ra-226	LIV-H	200	2.2E-03	3.3E+01	4.8E-02	1.6E-01
28	W-188	69.4 days	W-186	LIV-H	200	5.3E-01	3.0E+04	1.1E+00	3.3E+04
29	Xe-127	36.4 days	Xe-126	LIV	200	2.2E-01	1.2E+00	3.4E+02	4.0E+02
30	Y-91	58.5 days	Zr-91	LIV	200	1.5E-01	9.5E+03	2.5E+04	1.0E+02

LIV-H: Long Irradiation Vehicle, Hydrided with 3000 cc Target Volume
LIV: Long Irradiation Vehicle, with 10,000 cc Target Volume
R3: Rapid Radioisotope Retrieval System with 24 cc Target Volume
R3-H: Rapid Radioisotope Retrieval System, Hydrided with 24 cc Target

Gas Line 5000 cc Target Volume

which has been used successfully in the past to produce high activity levels of product isotopes when the target isotopes have high epithermal cross sections.[a][b]

The choice of target irradiation time is based on the product isotope's half-life, on calculations of the irradiation time that maximizes isotope production, and on operational factors such as avoiding interference with the tritium production mission. For purposes of illustrating the production yields of the 30 isotopes being evaluated in this report, irradiation cycles of 10, 25, and 200 days were used to obtain the results shown in Table 2-3.

Table 2-3 also provides specific activity results ("Product Isotope Specific Activity (Ci/g)") for the 30 product isotopes. Even though these results do not account for "optimization" of target configurations, very high levels of specific activity are achieved relative to "thermal" reactor systems.

An excellent check on the reaction rate parameters used in these calculations was made by a comparison with calculations performed by Wootan et al.[c] using the MCNP computer code. These comparisons are shown in Table 2-4, where our values ("BW Reaction Rates") are directly compared to the MCNP values for several isotopes. The five cases shown are not identical (the spectra used were not identical), but they are close enough to show good agreement with both the perturbed spectrum (hydride) and the unperturbed spectrum results (non-hydride).

(a) Mirzadeh, S., R. E. Schenter, A. P. Callahan, and F. F. (Russ) Knapp, Jr., *Production Capabilities in U.S. Nuclear Reactors for Medical Radioisotopes*, ORNL/TM-12010, Nov. 1992.

(b) Jordheim, D. P., R. E. Schenter, et al., *Computer Code for Calculation of Pu-238 Production, Quality, and Impurity*, Trans. Amer. Nuc. Soc., Vol. 423, pg. 63, 1991.

(c) Wootan, D. W., et al., unpublished calculations, Nov. 1997.

Table 2-4. Reaction Rates in Medical Isotope Target Region (Average over 49.4 Inches)

	MCNP Calculated Reaction Rates			BW Reactions Rates	
Reaction	**Case M1 w/inc/yh**	**Case M2 natli/yh/yh**	**Case M3 inc/inc/inc**	**FFTF-Row 6 hydride**	**FFTF-Row 6 non-hydride**
Total Flux	2.39E+15	2.48E+15	2.36E+15	2.06E+15	2.32E+15
Os192 (n,g)	5.71E+14	7.10E+14	2.86E+14	4.81E+14	2.50E+14
Pd102 (n,g)	1.27E+15	1.57E+15	4.49E+14	1.11E+15	3.07E+14
Pt195 (n,g)	1.73E+16	3.08E+16	4.08E+15	1.73E+16	9.05E+14
Se74 (n,g)	2.07E+16	3.83E+16	3.03E+15	3.04E+16	1.91E+15
Sr88 (n,g)	2.02E+12	2.21E+12	2.41E+12	8.18E+12	6.61E+12
Sn116 (n,g)	7.80E+14	1.16E+15	3.01E+14	8.06E+14	1.92E+14
Xe126 (n,g)	1.96E+15	3.46E+15	5.46E+14	2.51E+15	1.60E+15
Eu151 (n,g)	3.03E+17	7.33E+17	1.28E+16	5.02E+17	1.03E+16
Eu153 (n,g)	5.39E+16	8.84E+16	7.67E+15	6.39E+16	6.15E+15
Zn67 (n,p)	1.03E+12	1.13E+12	1.21E+12	4.66E+11	4.10E+11
S32 (n,p)	1.40E+13	1.66E+13	1.49E+13	1.54E+13	1.75E+13
Re185 (n,g)	4.77E+16	9.24E+16	6.27E+15	6.75E+16	3.70E+15
W186 (n,g)	2.11E+16	3.46E+16	1.38E+15	2.24E+16	1.02E+15
Sm152 (n,g)	1.02E+17	1.64E+17	4.49E+15	1.03E+17	2.88E+15
Mo98 (n,g)	5.27E+14	6.20E+14	2.89E+14	7.06E+14	3.42E+14
Zn64 (n,p)	6.73E+12	8.00E+12	7.22E+12	7.93E+12	8.51E+12
Cd108 (n,g)	2.55E+15	3.18E+15	1.08E+15	1.52E+15	5.28E+14
Xe124 (n,g)	5.31E+16	1.07E+17	8.33E+14	1.10E+17	5.94E+15
Te130 (n,g)	4.01E+13	5.28E+13	2.58E+13	4.20E+13	2.37E+13
Lu176 (n,g)	1.31E+17	3.81E+17	5.65E+15	3.14E+17	3.10E+15

2.5 Primary Medical Isotope Candidates

Of the 30 medical isotopes for which production yields and radiochemical processing procedures have been evaluated, a subset of 20 isotopes has been selected as the primary candidates for production at the onset of FFTF operations in 2002. The basis for this selection was the expected demand for these isotopes based on the results of recent surveys of the market for radiopharmaceuticals during the first two decades of the 21st century (described in Section 7 of this report). Estimates of facility requirements and operating costs described in Sections 4, 5, and 6 of this report are based on the assumption that medical isotope production at FFTF would be centered on the 20 isotopes described below. It is expected, however, that other isotopes from the "Top 30" list will be produced at FFTF from the onset of operations in 2002, but only in limited quantities for research applications.

The following is a list of the 20 primary medical isotope candidates, along with a summary of their applications and the capability of FFTF to produce significant quantities of these isotopes.

Actinium-227

Radium-223, the daughter of actinium-227, is an alpha emitter that can be used in a number of medical applications, and could be the isotope of choice in cell-directed radiation therapy for numerous types of cancers. The FFTF is ideally suited for the production of this isotope. Production would use an in-core hydrided target assembly.

Cadmium-109

Cadmium-109 has both medical and environmental applications. In the medical area it is used as a diagnostic agent for cancer detection and pediatric imaging. It has previously been produced in the FFTF, and after processing was sold commercially and shipped to Dupont/Merck in Billerica, Massachusetts. It was made in FFTF in two different ways using enriched targets of Cd-108 and Ag-107. Though it also is produced in charged-particle accelerators, production is superior in the FFTF via these two different methods because they provide the flexibility and options to obtain inexpensive and high-specific-activity Cd-109.

Copper-67

This isotope was achieving excellent success in treating lymphoma patients, but the clinical trial had to be stopped because of lack of availability. It is also under consideration for use in treating arthritis, breast cancer, and colorectal cancer. It can be made in a reactor or an accelerator. Both methods are difficult because of the small production cross-section and the high energy particles that are required. But the FFTF has a clear advantage in its ability to produce this isotope because of its high neutron flux level, large target volume, and the fact that its average neutron energy is several orders of magnitude higher than in a thermal reactor.

Gadolinium-153

This isotope was, in the past, primarily used as a source for the detection of osteoporosis by Dual Photon Absorptiometry (DPA). In 1987, Hologic introduced a new method for bone density measurements using a dual-energy x-ray absorptiometry system. This new system has began to replace DPA systems, thereby reducing the need for Gd-153 in this area. Recently, Gd-153 has been used as a calibration source for SPECT cameras because it has a much longer half-life than previous calibration sources. Gd-153 could replace Tc-99m in many hospitals in the U.S. for SPECT diagnosis. The FFTF has already shown its capability for producing this isotope, averting a world shortage in 1988 by supplying large quantities of the highest purity Gd-153 ever made.

Holmium-166

Although this isotope is not being widely used in clinical trials at the present time, it has several desirable qualities that might eventually make it a market leader. It is made via neutron capture in Ho-165 which, as a target material, has some excellent properties including low cost, purity (naturally

occurring holmium is 100% Ho-165), and a high absorption cross-section. Ho-166 has a 26.8 hr half-life and emits several beta particles.

Iodine-125

This isotope is primarily used as a diagnostic tool, but is also being evaluated for its therapeutic value. It will be made at the FFTF via neutron capture of Xe-124 in a gas loop. This method will produce very pure I-125. It has numerous medical applications.

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% among otherwise terminal lymphoma patients, while another trial showed similar success in treating myeloid leukemia patients. Iodine-131 is also currently used to treat thyroid cancers, hyperthyroidism, and Grave's disease. Current supplies of this isotope are limited and shortages are already starting to impact patient care. Once the FDA approves its routine use, the FFTF will be needed for production of I-131. The FFTF would also make I-131 via neutron capture in tellurium-130, as contrasted with the currently available fission product iodine. This production pathway will allow the FFTF to provide extremely high specific activities (~1.24E+5 Ci/g or 99.87% hot atoms) for this isotope. This, in turn, will increase its effectiveness dramatically over current fission product I-131 (generally <0.1% hot atoms).

Iridium-192

This isotope has both important medical and industrial applications. Medically it is already being used in brachytherapy procedures using Ir-192 needles that are placed next to the cancer for effective treatment. It is a high-energy gamma emitter that has also been used in research trials for the treatment of heart disease (restenosis). In FFTF Ir-192 can be produced at very high specific-activity levels, which are required for effective medical applications. By optimizing target design to reduce self-shielding effects, product quality can be maximized to a level not previously achieved in Ir-192 produced in other reactors.

Lutetium-177

Lutetium-177 is expected to be an important isotope in the treatment of two major health problems—heart disease and cancer. It is a high-energy beta emitter with properties that are ideal for use in restenosis stents. It has a very large thermal and epithermal neutron cross-section. Consequently, large quantities of this isotope can easily be produced in the FFTF using enriched targets of Lu-176.

Palladium-103

Patients suffering from prostate cancer are being denied therapy because of the short supply of this isotope. It is also undergoing clinical trials for a number of other cancers. The FFTF has vast production potential for this isotope (~ 1.0E+05 Ci in just one irradiation target assembly/yr).

Phosphorus-32

Phosphorus-32 is used for a number of applications, including the treatment of cancer-induced bone pain and Polycythemia rubra vera, and most recently, for infusional brachytherapy treatment of various cancers. At this time, the high cost of P-32 (~$48 dollars/mCi) is tending to reduce its use. Because of flux tailoring capabilities, the FFTF can produce P-32 in large quantities at a relatively low cost.

Rhenium-186

This isotope requires a very high specific-activity for several applications. It is 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. The FFTF can produce large quantities of this isotope with a high specific-activity not readily achievable in other reactors. Unfortunately, some radiopharmaceutical development companies (NeoRx) have had to discontinue their research with Re-186 because, without the FFTF, they could not obtain this isotope at the required high specific-activity from other sources.

Rhenium-188

Rhenium-188 is a candidate for several therapeutic medical applications. It can be used in the treatment of heart disease (restenosis), bone pain from metastatic cancer, breast cancer, lung cancer, colorectal cancer, and ovarian cancer. It is the daughter of tungsten-188, which is a direct FFTF product obtained by double neutron capture using a tungsten-186 target. Because of its large epithermal flux capability, FFTF can produce an order-of-magnitude higher specific activity of W-188 relative to typical thermal reactors. Re-188 generators have been developed at Oak Ridge National Laboratory for both cancer and heart disease applications.

Samarium-145

Extensive research has been performed at Brookhaven National Laboratory on the use of Sm-145 in conjunction with I-127 to produce auger electrons for the treatment of brain cancer. In addition, new uses for this isotope have been identified in the treatment of eye cancer. One approach to Sm-145 production is to make the isotope in a stainless steel seed using a highly enriched Sm-144 target.

Samarium-153

This isotope, along with strontium-89, tin-177m, and rhenium-186, is used for the palliation of cancer-induced bone pain, treating brain cancer, and is also being considered for use in treating leukemia. Since this isotope (under the brand name Quadramet) was just recently approved by the FDA for bone pain relief, it currently has a growing market demand.

Scandium-47

Sc-47 is another beta-emitting isotope that has attractive properties for radioimmunotherapy. It has a coordination chemistry that favors chelation attachment to antibodies, decays via two mid-range beta particles, and emits a photon (159 keV) for imaging. Sc-47 is made by a high energy (n,p) reaction on Ti-47, making the FFTF an ideal source of this isotope.

Strontium-85

This diagnostic isotope is used in medical applications associated with detection of bone lesions and for brain scans. It can be very effectively produced in FFTF using highly enriched Sr-84 targets.

Strontium-89

This isotope is used for bone cancer pain relief. It has been approved for use by the FDA (under the brand name Metastron), and the market demand should eventually be strong but is currently somewhat low due to the high cost (~$2,000/4mCi dose). The U.S. supply of Sr-89 for this application comes from foreign reactors (in Belgium).

Thorium-229

Bismuth-213, the granddaughter of thorium-229, is currently being used in Phase 1 human cancer trials. These radioimmunotherapy trials are being performed at the Memorial Sloan Kettering Cancer Center for the treatment of Acute Mylogenous Leukemia (AML), and preliminary results indicate excellent therapeutic effectiveness of this alpha emitter. Production of Th-229 involves a triple neutron capture process using radium-226 as a target isotope. It should be noted that there are a number of organizations that are trying to dispose of their Ra-226 sources, which could be used as target material for producing the major alpha emitters Ac-227, Th-228, and Th-229.

Yttrium-91

This isotope is a relatively long-lived beta emitter (half-life of 58.5 days). It is an excellent candidate for cancer treatments using radioimmunotherapy. Carrier-free Y-91 can be produced by an (n,p) reaction using a Zr-91 enriched target. FFTF is well-suited for producing large amounts of Y-91 by this production pathway.

2.6 Integration with the Tritium Mission

The FFTF has an extensive background in coordinating multiple missions. Past operating experience has demonstrated that the facility's design is very flexible and that the engineering, physics, and operations staff are fully capable of supporting multiple tasks.

The FFTF tritium production core model has been established, and includes three in-core positions for medical isotope production. Studies show that using these in-core positions for medical isotope production will have a minor impact on tritium production. As other tritium sources come on line and/or the amount of tritium required is reduced, more and more reactor positions will be available for medical isotope production.

2.6.1 Cycle and Refueling Equipment Compatability

Factors other than calculated isitope production rates must be evaluated to ensure the compatibility of the tritium and medical isotope missions. First of all, the medical isotope mission will be designed to minimize interference with tritium production, yet still satisfy medical customer requirements.

As stated in Section 2.4, long-lived isotopes will be produced in a 12 ft. LIV. This assembly will run on compatible cycles with the tritium mission. Initial studies indicate that the LIV should be changed out every other cycle (200 days). It will be handled by the normal refueling equipment such as the In-Vessel Handling Machine (IVHM) and the CLEM. Initial disassembly of the LIV will be in the IEM Cell where pins will be removed from the assembly, placed in a pin container, and shipped to the 325 Building in a shielded cask. Since this process will occur only about once a year, impact on tritium target handling activities will be minimal.

Short-lived isotopes will be produced in the rapid radioisotope retrieval (R3) assemblies. These isotopes will be handled during full-power operation of the reactor, and thus will have almost no impact on the tritium and fuel handling activities that will occur during reactor outages. The 40 ft. assembly that houses the R3 system will need to be changed out by the CLEM approximately every three years due to burn-out of the yttrium hydride moderator. Considering its infrequent nature, this process will have a very minor impact on other reactor outage activities.

2.6.2 Staffing and Operational Impacts

Operations staff at the FFTF will not need to be increased significantly to support the medical isotope mission. Overall staffing of the medical isotopes program will increase considerably, as discussed in Section 5.1, but staffing at the FFTF will remain nearly constant. Tritium mission staffing levels at the FFTF will be able to support much of the additional workload that will be required to handle medical isotope assemblies and target trains. As stated previously, isotope assembly (LIV) transfers and disassembly will be very infrequent and will have a minor impact on IEM Cell usage. Change out of the

R3 target trains, which will occur on 10 and 25 day cycles, will only require a few hours. This procedure will be done during non-peak staffing periods, and will thus have a minor impact on overall operations at FFTF.

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3.0 Radiochemical Processing

3.1 General Requirements

Processing of FFTF irradiated targets to recover medical grade medical isotopes produced under current Good Manufacturing Practices (cGMP) can be broken down into distinct steps: receipt of irradiated targets into a chemical separations facility (325 Building), chemical processing of the targets (using hot cells, shielded glove boxes and appropriate open faced hoods), waste handling, analysis of the products, recycle of some of the target materials, and shipment of the isotope products to customers (Figure 3-1). Facility requirements for cGMP will be discussed in Section 4 of this document.

Each of the 30 medical isotope products evaluated for production at FFTF is unique (see Table 3-1). Eighteen (18) of the targets produce an isotope of the same element and will not be separated, i.e., Cd-109 produced from a Cd-108 target. Twelve (12) target materials will produce different elements, i.e., Cu-67 produced from a Zn-67 target; and will require chemical separation, both for separation of the target material and unwanted impurities.

3.1.1 Same Target/Products Requiring No Separation

Thirteen (13) of the same target element/products do not require extensive chemical separation (Table 3-2). However with experience, target purity and/or customer requirements may change, requiring additional separation/purification.

A typical example of a product requiring no separation is Ho-165/Ho-166 (Figure 3-2). Medical isotope target carriers will be unloaded from the cask into A-Cell where they will be separated and prepared for transport from A-Cell to isotope processing stations. The target material will be removed from the carrier and dissolved using $HN0_3$, HCl or a combination of acids. The dissolved material will be evaporated to near dryness to remove the acid. The resulting salt will be redissolved in dilute acid. The product solution will be analyzed for chemical and radionuclide purity, and aliquots of the analyzed product will be placed in appropriate containers and shipped to customers. Analytical techniques available at the 325 Building where the radiochemical processing will be performed include: 1) inductively coupled plasma/atomic emission spectroscopy (ICP-AES), 2) gamma energy analysis (GEA), 3) alpha energy analysis (AEA), and 4) counting equipment.

All liquid waste will be neutralized and captured on a solid absorbent as solid waste. Solid waste for each product will range from 1 to 5 ft^3/yr/product (excluding cladding hardware).

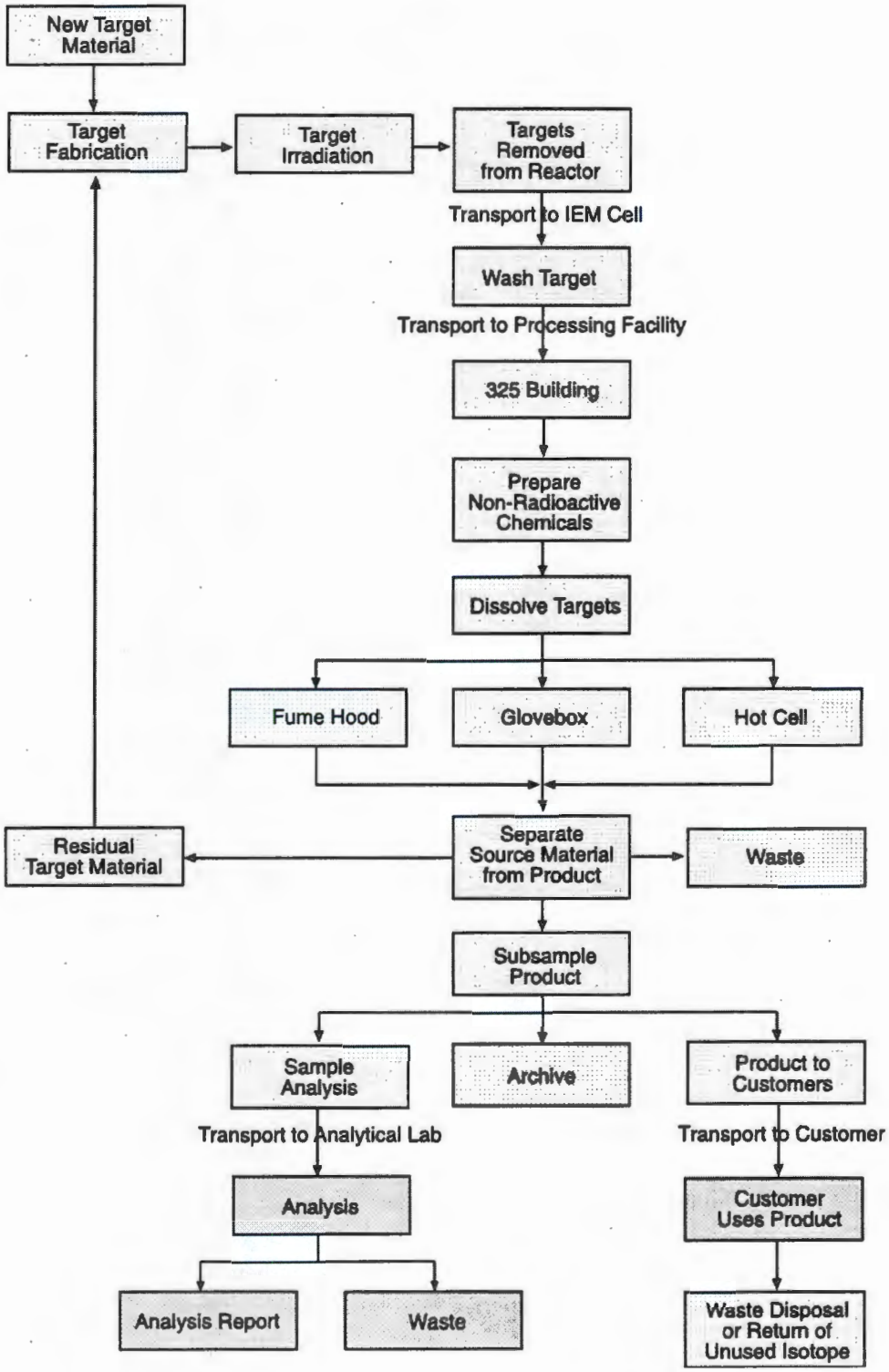


Figure 3-1. Flow chart representation of production and radiochemical processing steps in the preparation of FFTF medical isotope products.

Table 3-1. Radiochemical Processing of 30 Medical Isotopes

#	Same Product (Target)	Product Half-Life	Product Daughter	Impurties	Separations Required(2)	Target(3)	Separation Method	Isotope Ci/Yr 2005	Irrad. Time, d	Process camp./ yr(1)	Ci Processed per campaign	Minumum Facilities Required 325 Bldg 500 Labs								Per Year, Vol. Waste, ft3 (Liq./ Solid) (4)
												325A	325B	Rm 30A	Hot C	GBox	Hood	325A PbGB	Hood	
3	Cd-109 (Cd-108)	462 d	Ag-109	Ag	Yes	O (P)	AgCl precipitation	4,000	400	1	4,000		x		x	x	x			0/1
11	Lu-177 (Lu-176)	6.68 d	Hf-177	Yb, Hf, Eu	Yes	O	Difficult Separation	100	25	10	10		x						x	0/1
12	Mo-99 (Mo-98)	2.75 d	Tc-99	Tc	No	M/O	--	300,000	10	25	12,000				x	x	x			0/10
13	Os-194 (Os-192)	6 yr	Ir-194	Ir, Pt	Yes	M	Method not identified	26	400	1	26				x	x	x			0/1
16	Pd-103 (Pd-102)	17 d	Rh-103	Rh, Ag	No	M/O	--	27,000	25	5	5,400				x	x	x			0/1
17	Pt-195m (Pt-195)	4.02 d	Pt-195	Ir, Au	No	M	--	50	25	25	2				x	x	x			0/5
18	Re-186 (Re-185)	3.78 d	Os/W-186	W, Os	No	M/O	--	70,000	25	25	2,800				x	x	x			0/5
20	Se-75 (Se-74)	120 d	As-75	As	No	M/O	--	100	200	1	100				x	x	x			0/1
22	Sm-153 (Sm-152)	1.93 d	Eu-153	Eu	No	O	--	2,000	10	25	80		x							0/5
23	Sn-117m (Sn-116)	13.6 d	Sn-117	None	No	M/O	--	1,000	25	25	40				x	x	x			0/5
25	Sr-89 (Sr-88)	50.5 d	Y-89	Rb, Y	Yes	C	Dissolution & IX or SX	1,000	100	25	40				x	x	x			0/5
28	W-188 (W-186)	69.4 d	Re-188	Ta, Os	No	M	--	33,000	200	6	5,500	x			x	x	x			0/5
29	Xe-127 (Xe-126)	36.4 d	I-127	I	Yes	Gas	Gas Capsule	500	100	25	20				x	x	x			0/1
7	Ho-166 (Ho-165)	26.8 h	Er-166	--	No	M/O	Dissolve HNO3/HCl; evaporate, take up 0.1M HCl	1,000	10	25	40		x		x	x	x			0/1
10	Ir-192 (Ir-193)	73.8 d	Pt-192	Os-192	No	M	HNO3/HCl Dissolution	2.E+06	300	6	330,000		x						x	0/5
2	Au-198 (Au-197)	2.7 d	Hg-198	--	No	M	--	4,500	10	25	180	x			x	x	x			0/1
21	Sm-145 (Sm-144)	340 d	Pm-145	Pm, Nd	No	C/O	--	100	300	1	100		x		x	x	x			0/1
24	Sr-85 (Sr-84)	64.8 d	Rb-85	Kr-85	No	C	--	500	200	25	20		x		x	x	x			0/5

Table 3-1. (contd)

#	Different Product(Target)	Product Half-Life	Product Daughter	Impurities	Separations Required	Target(3)	Separation Method(2)	Isotope Ci/Yr 2005	Irrad. Time, d	Process camp./ yr(1)	Ci Processed per campaign	Minumum Facilities Required 325 Bldg 500 Labs								Per Year, Vol. Waste, ft3 (Liq./ Solid) (4)
												325A	325B	Rm 30A	Hot C	GBox	Hood	325A PbGB	Hood	
4	Cu-64 (Zn-64) (R)	12.7 h	Zn/Ni-64	Zn	Yes	O	Diss/Elec Depo/IX	540	10	25	22				x	x	x			0/10
5	Cu-67 (Zn-67) (R)	2.58 d	Zn-67	Zn	Yes	O	Diss/Elec Depo/IX	210	10	25	8.5				x	x	x			0/10
14	P-32 (S-32) (R)	14.3 d	S-32	S	Yes	S	Distil and IX	800	25	5	160				x	x	x			0/5
8	I-125 (Xe-124)	60.1 d	Te-125	Xe	Yes	Gas	Gas flow-loop	14,000	200	17	824		At FFTF(gas loop)							0/1
9	I-131 (Te-130) (R)	8.04 d	Xe-131	Te	Yes	M/O	Gas Trap	6,000	25	10	600		x		x	x	x			0/5
1	Ac-227 (Ra-226)(R)	21.8 y	Th-227	Ra, Th	Yes	C (P)	Ion Exchange	200	200	1	200			x						0/5
26	Th-228 (Ra-226) (R)	1.91 y	Ra224	Ra, Ac	Yes	C (P)	Ion Exchange	1,000	200	1	1,000			x						0/5
27	Th-229 (Ra-226)(R)	7.3E3 y	Ra-225	Ra, Ac	Yes	C (P)	Ion Exchange	0.04	200	1	0.04			x						0/0
6	Gd-153 (Eu)	241.6 d	Eu-153	Eu, Sm	Yes	D (P)	Prec, IX band displa.	6,000	300	1	6,000	x						x	x	10-100/10
15	P-33 (S-33) (R)	25.3 d	S-33	S	Yes	S	Dist/IX	500	100	2.5	200		x		x	x	x	x	x	0/5
19	Sc-47 (Ti-91) (R)	3.34 d	Ti-47	Ca, Ti	Yes	O	IX/Sol Extra.	1,000	10	25	40				x	x	x			0/1
30	Y-91 (Zr-91) (R)	58.5 d	Zr-91	Zr	Yes	O	IX/Sol Extra.	100	200	25	4				x	x	x			0/1

(1) Processing campaigns per year are based on ½ t and irradiation time required.
(2) Excluding dissolution of target. No = not identified based on initial investigation.
(3) Assumed target composition
C = Carbonate M/O = Metal or Oxide
O = Oxide R = Possible recycle of target.
M = Metal P = pellet
(4) Cladding not included.

Table 3-2. Products Requiring No Separation

Product	Curies per Target Campaign	Irradiation		Campaigns per Year
		Material	Time	
Mo-99	12,000	Mo-98	10 d	25
Pd-103	5,400	Pd-102	25 d	5
Pt-195m	2	Pt-195	25 d	25
Re-186	2,800	Re-185	25 d	25
Se-75	100	Se-74	200 d	1
Sm-153	80	Sm-152	10 d	25
Sn-117m	40	Sn-116	25 d	25
W-188	5,500	W-186	200 d	6
Ho-166	40	Ho-165	10 d	25
Ir-192	3.3E5	Ir-193	300 d	6
Au-198	180	Au-197	10 d	25
Sm-145	100	Sm-144	300 d	1
Sr-85	20	Sr-84	200 d	25

3.2 Same Target/Product Requiring Separation

Approximately five target materials producing other isotopes of the same element will require further processing; Cd-109, Lu,-177 Os-194, Sr-89 and Xe-127. A typical example of a product requiring separation is Cd-109 from Cd-108. The Cd-109 produced from enriched Cd-108 will contain small amounts of Co-60, Zn-65 and Ag-110m, along with Cd-109 and Cd-115m. Medical isotope target carriers will be unloaded from the cask into A-Cell where they will be prepared for transport from A-Cell to the appropriate isotope processing stations. The cadmium oxide will be removed from the target carrier, dissolved in HCl and diluted with H_20 to 0.1M HCl. The impurities and cadmium are adsorbed on a Dowex 50-X8 cation exchange column. The cadmium is then selectively eluted with 0.2M HCl. The eluate is analyzed (ICP, GEA) and aliquots of the product solution placed in appropriate containers and shipped to the customers.

All liquid waste will be neutralized and captured on a solid absorbent as solid waste. Solid waste for each same product/target will be ~1 to 5 ft^3/yr/product (excluding cladding hardware).

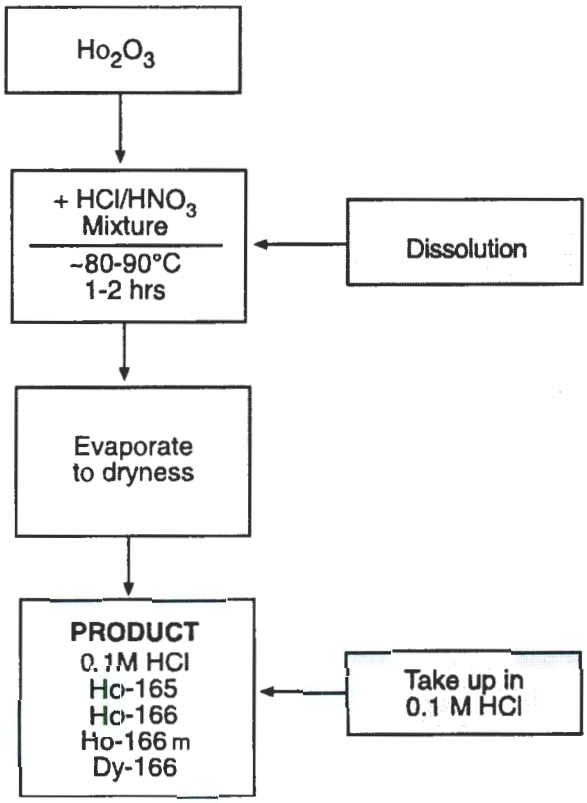


Figure 3-2. Processing of target material where the isotope product (Ho-166) is chemically identical to the target isotope (Ho-165).

3.3 Processing Target Materials Containing New Elements

Twelve (12) target materials will produce different product elements and will each require unique chemical separations as shown in Table 3-1. The steps will include: separation/purification of the product isotope, retrieval of the original target material for possible reutilization, and disposal of the residual wastes. Four examples of process separation will be discussed to show the diversity of the separation methods. These examples are described below.

3.3.1 Ac-227 and Th-228/229 from Ra-226

Radium-226 is the only target that is radioactive before being irradiated in FFTF and is used to produce two products: Ac-227 and Th-228/Th-229. Room 30A in the 325 Building will be used to process the radium targets. The room will contain a high-level radiochemical cell, a leaded glove box, and an open face hood, all connected to a radon capture facility. The radon capture facility (temperature controlled charcoal filter) is required to prevent release of radon gas from the 325 Building while storing the original target material and processing the irradiated targets.

The capsule containing the irradiated target ($RaC0_3$) material will be transported from the 325A Building's A-Cell to the Room 30A hot cell in a shielded pig and opened for removal of the target material by cutting the cladding. The carbonate salt will be dissolved with acid (Figure 3-3). The radium will then be separated by nitrate precipitation and filtration. The remaining Th, Ac and Ra in the filtrate solution will be purified using ion exchange separation.

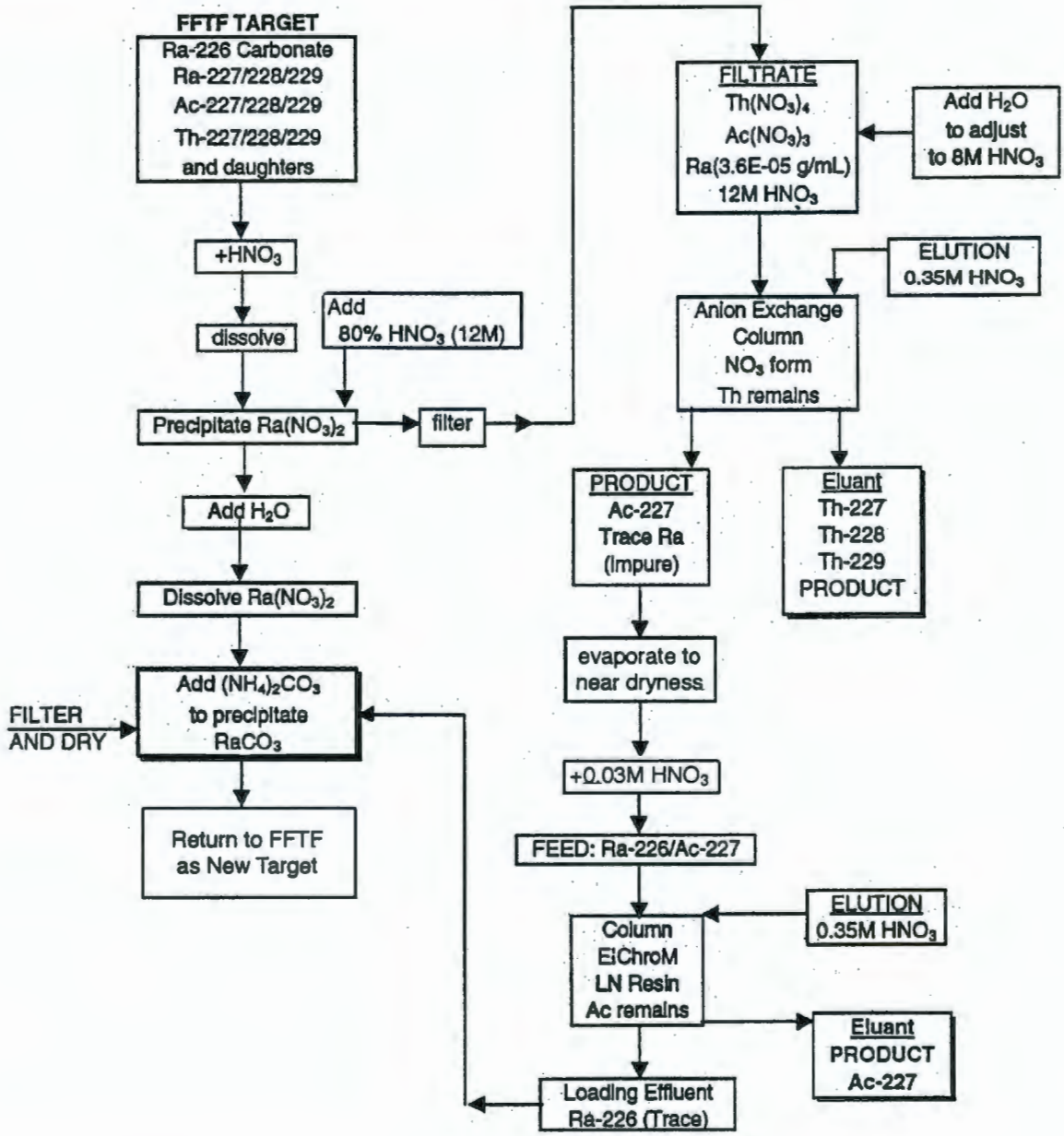


Figure 3-3. Processing procedures for removal of Ac-227, Th-228, and Th-229 products from irradiated Ra-226 targets.

Detailed steps in processing the Ra-226 includes removal of the radium carbonate solid from the metal capsule for dissolution in dilute nitric acid. An addition of 80% $HN0_3$ to the mixture is then performed to precipitate the radium as $Ra(N0_3)_2$, followed by filtration. The precipitated Ra will be retrieved by the addition of H_20 to redissolve the radium nitrate precipitate. $(NH_4)_2C0_3$ is then added to the dissolved radium nitrate solution to precipitate $RaC0_3$. The carbonate precipitate will be filtered, dried, and can be reutilized as target material for return to FFTF.

The 12M $HN0_3$ acid filtrate from the $Ra(N0_3)_2$ precipitation, containing thorium, actinium and traces of radium, will be adjusted with H_20 to 8M acid and loaded on to an anion exchange column. The thorium is held on the column allowing the Ac, Ra and other impurities to be captured in the effluent. The purified thorium is eluted from the anion exchange column with 0.35M $HN0_3$. The Th-228/229 product solution will be analyzed (ICP, GEA, and AEA), and aliquots of the analyzed product will be placed in appropriate containers and shipped to customers.

The Ac-227 and traces of radium, found in the effluent solution from the anion exchange purification of thorium, will be evaporated to dryness and redissolved in 0.03M $HN0_3$. This solution is loaded on to an EiChroM resin column and the effluent containing the radium retrieved via carbonate precipitation. The resin column containing purified Ac-227 will be eluted with 0.35M $HN0_3$. The Ac-227 product solution will be analyzed (ICP, GEA, and AEA), and aliquots of the analyzed product will be placed in appropriate containers and shipped. The Ac-227 can also be used "on-site" as the "Ac-227 cow" for recovery and shipment of Ra-223.

All liquid wastes will be neutralized and captured on a solid absorbent. Solid waste is estimated at 10 ft^3/yr (excluding cladding hardware and radon holdup charcoal).

3.3.2 Cu-64 and Cu-67 from Zn-64 and Zn-67

The capsule containing the irradiated Zn0 target will be transported to the 325A Building receiving hot cell (the A-Cell). Irradiated targets/carriers will be transported in shielded pigs from the A-Cell to an isotope processing station containing a hot cell, a lead-shielded glove box, a fume hood, and a laminar flow hood. The target material will be removed from the carrier by cutting the capsule containing the zinc oxide. The oxide will be dissolved with sulfuric acid. The sulfuric acid solution will be placed in an electrochemical cell and the copper deposited on to a Pt electrode (Figure 3-4). The Pt electrode will be removed from the electrochemical cell and Cu-64 or Cu-67 dissolved from the surface by immersing the Pt electrode in $HN0_3$. The zinc can be retrieved by converting it to the oxide form to be utilized as target material at FFTF.

Detailed steps in processing the copper isotopes include removal of the zinc oxide from the metal capsule for dissolution in 1M H_2S0_4 and transfer to the electrochemical cell. After 30 minutes, the Cu has been completely deposited on the Pt electrode. The target solution still containing the zinc will be removed and replaced with fresh acid and Cu deposition continued for an additional 30 minutes. This step will be repeated for a second time to assure purification. The deposited Cu on the Pt electrode will then be removed from the cell and dissolved by immersing the electrode in concentrated $HN0_3$ for

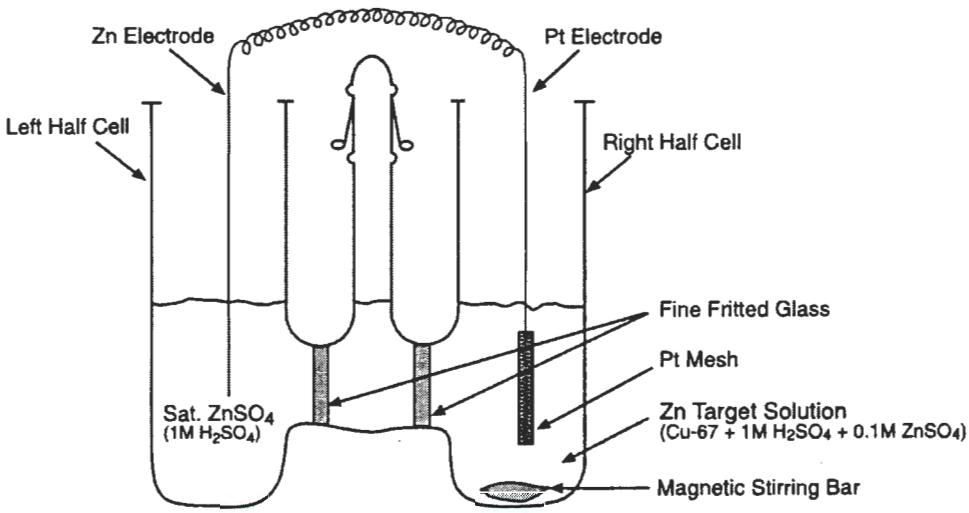


Figure 3-4. Electrochemical separation of Cu-67 product from Zn-67 target material.

1-2 minutes. This solution will be evaporated to near dryness to remove the strong acid. The dried product will then be redissolved in an appropriate acid. The solution will be analyzed for chemical and radionuclide purity, and aliquots of the final product placed in containers and shipped to customers.

The Zn^{+2} contained in the spent electrochemical solution can be retrieved, converted back to zinc oxide, and returned to FFTF for re-irradiation. If other unwanted metal ions are found in this solution, the Zn^{+2} will be purified by ion exchange prior to oxalate precipitation and calcination to the oxide.

All liquid wastes will be neutralized and captured on a solid absorbent as solid waste. Solid waste is estimated at 10 ft^3/yr (excluding cladding hardware).

3.3.3 Gd-153 from Eu and Sm

The capsule containing the irradiated Eu_2O_3 target pellets will be transferred to "C" cell in the 325A Building's radiochemical hot cells for dissolution and europium removal, followed by ion exchange band displacement in a heavily shielded glove box in Room 603 at the 325A Building. The pellets are removed by cutting open the capsule containing the irradiated europium oxide. The Eu_2O_3 pellets are dissolved with acid, greater than 99.9% of the Eu isotopes are removed by sulfate precipitation of Eu(II), and ion exchange band displacement is used to separate 0.1% of the remaining Eu, along with the Sm and Gd, into fractional purified bands (Figure 3-5). The final Gd-153 product will be precipitated, dried, and heated to a high temperature to form Gd_2O_3.

Detailed steps in processing the Gd-153 include removal of the oxide pellets from the metal capsule for dissolution in acetic acid. With argon sparging to prevent air oxidation, the solution will be contacted with amalgamated zinc (Jones reductor) to reduce the Eu(III) to Eu(II). A sulfate salt will be added to precipitate the Eu(II), separating it from Sm(III) and Gd(III).

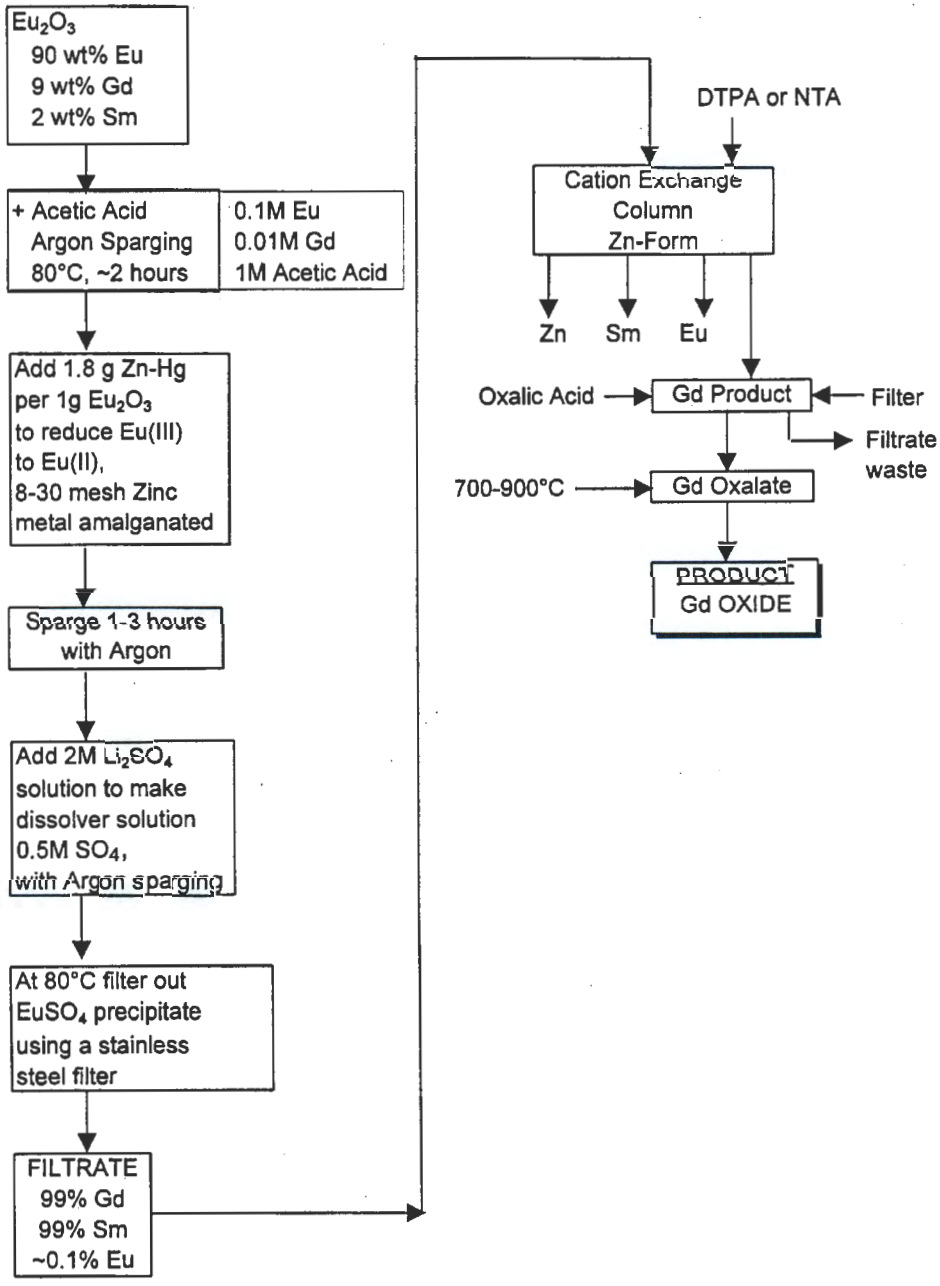


Figure 3-5. Procedure for separation of Gd-153 product from europium target isotopes.

The resulting filtrate solution contains Gd, Sm and <0.1% of the Eu. This solution will be transferred to a shielded glove box to separate/purify the Gd-153 using band-displacement cation exchange chromatography. Ammonium-buffered chelating agents such as nitrilotriacetic acid (NTA) or diethylenetriamine-pentaacetic acid (DTPA) are used to fractionate Gd/Sm/Eu using a zinc-loaded cation exchange column.

The purified Gd-153 product solution will be transferred into a second shielded glove box for oxalate precipitation, filtration, and calcination to the oxide, and then pressed into pellets for shipment to customers.

Very high-level liquid wastes will contain Zn, acetic acid, 45 Ci of Eu per Ci of Gd product separated, and NH_4DTPA organic complexant (0.05 - 0.5 L of liquid waste per Ci of Gd recovered). Solid waste is estimated at 10 ft^3/yr including the Jones reductor [excluding cladding and hardware (ion exchange columns, sulfate precipitation equipment, and the pellet press will be reused and only becomes solid waste at the termination of the project, 10-100 ft^3)].

3.3.4 I-125 from Xe-124 Gas Target

The method of production and separation is based on the irradiation of 5 liters of enriched Xe-126 for ~2.5 hrs, trapping the irradiated gas, letting the Xe-125 gas decay to I-125 for ~2 days, distilling off the inert gases, chemically reacting to remove I-125 from the wall of the cryotrap, followed by final processing, packaging and shipping of the product.

The production, separation, and shipping facilities for I-125 will be at FFTF. The conceptual system is shown in Figure 3-6. The system consists of several cold traps (Cryotrap), flow restrictors, the MOTA gas canister, and a processing system (glove box and cryopump).

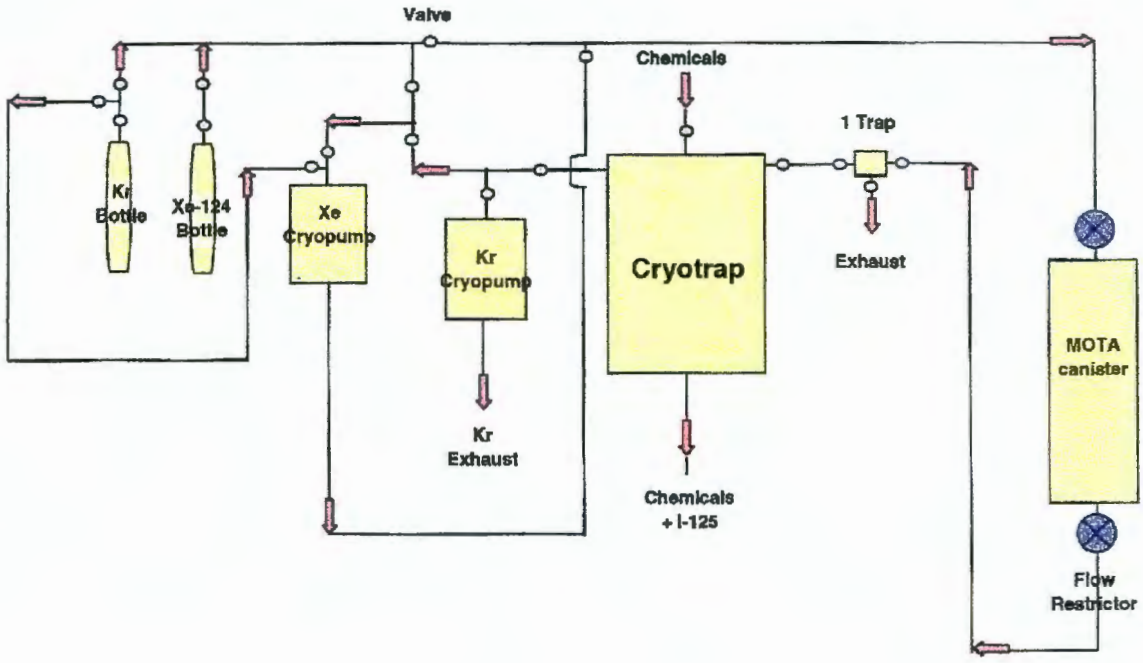


Figure 3-6. Gas trapping procedure for separation of I-125 product from Xe-124 gas target.

Detailed procedures for producing I-125 at FFTF are only at the conceptual stage. Once the system is ready, the Xe-124 gas bottle valve will be opened. The rate of flow will be controlled by the flow restrictors located downstream and upstream of the MOTA canister. Once the Xe-124 bottle is empty, Kr gas will be valved in and used to push the Xe-124 first through the gas line and next through the MOTA canister. Once the gas has been pushed through the downstream MOTA flow restrictor, the gas flows through the Iodine Trap to the Cryotrap which will be maintained at a low temperature and result in a low pressure ($<10^{-6}$ torr). The Xe-124, transmuted Xe-125 and some Kr "pusher" gas will be absorbed on the Cryotrap cold surface. The Cryotrap inlet valve is then closed and the Kr in the gas lines will be evacuated to the Kr Cryopump.

After about 2 days with the Xe-125 (17 hrs t ½) decaying to I-125 (60 d t ½), the Cryotrap downstream valve will be opened and the Cryotrap warmed to first distill off the Xe-124 to the Xe Cryopump, and then any Kr to the Kr Cryopump. The product I-125 remaining in the Cryotrap will then be chemically reacted (caustic) and the product analyzed, processed, packaged and shipped.

No liquid wastes are expected. Any liquid wastes will be neutralized and captured on a solid absorbent as solid waste. Solid waste is estimated at 10 ft^3/yr of silver-loaded zeolite (excluding hardware remaining as solid waste at the termination of the project, 10-100 ft^3).

4.0 Facilities and Equipment for Isotope Production and Processing

This section describes facilities and equipment required to produce medical isotopes at FFTF. Scope includes receipt of target materials, fabrication of isotope targets, handling of isotope target/carriers and processing to recover isotope products.

Facilities, equipment and procedures will be designed to meet current Good Manufacturing Practices (cGMP) for production of pharmaceutical-grade radioisotopes for clinical use as required in 21 CFR 210 and 211. This will require establishment of quality control procedures and methods to assure traceability, product quality and purity from receipt of raw materials to shipment of final products. Facilities and equipment will be designed and selected to provide microbiological control of air, components containers, utensils and dilutions. Processing equipment will provide Class 100 chambers inside of processing enclosures as required. Quality Control procedures will be established for product sampling and testing to verify that all products meet sterility, pyrogen, chemical, and radionuclide requirements, as well as release specifications and labeling. Procedures will include meeting appropriate record documentation requirements to assure compliance with cGMP.

The following sections describe Target Fabrication and Isotope Processing facilities and equipment that will be established to produce medical isotopes. Cold targets will be fabricated in the 306E Building. Radioactive and recycled targets will be fabricated in 325 Building. Isotope processing will be performed in the 325 Building.

4.1 Target Fabrication

Both radioactive (hot) and non-radioactive (cold) target material will be used for the selected list of radioisotopes to be produced at FFTF. In addition, capability will be needed to recycle some of the target material due to its high procurement cost. Cold targets will be fabricated at the 306E Building and hot and recycled targets will be fabricated at the 325 Building. The following sections describe locations and infrastructure requirements for target fabrication.

4.1.1 Cold Target Fabrication - 306E

Cold (non-radioactive) targets will be fabricated in the 306E Building. This building has been used to fabricate a variety of reactor components, fuel assemblies and radioisotope target assemblies in prior years. Some of the fabrication equipment and Non Destructive Examination (NDE) equipment still exist in this facility. Adequate space and secured storage is available. Figure 4-1 shows the planned utilization of 306E for fabrication of cold isotope targets and gas tag capsules for this project.

Target materials will be fabricated into Long-Term Irradiation Vehicles (LIVs) and Short-Term Irradiation Carrier Trains (see Section 2.3 for additional information). It is assumed that the LIV targets will be fabricated as pencils for installation in standard 8 ft. long pins. Pencils will contain the target

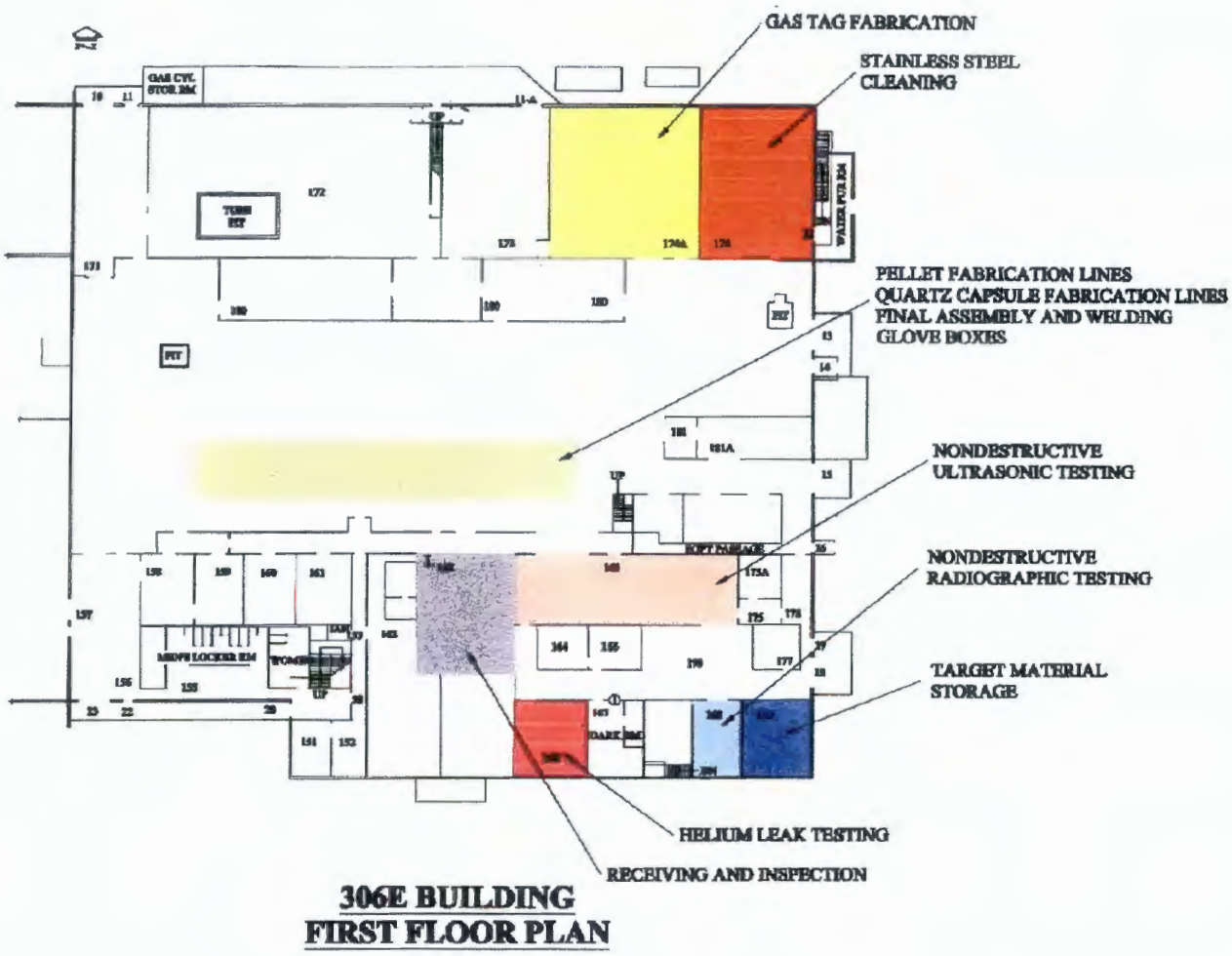


Figure 4-1. First floor of 306E Building, where cold targets will be fabricated.

material and will be seal-welded prior to installation inside the pins. Pin assemblies will include target pencils, spacers and springs. The LIV pins will be fabricated in 306E and shipped to FMEF for installation in the LIV bundle.

Short-Term Irradiation Carriers will contain high temperature, radiation resistant and chemically inert capsules that hold the target material. Capsules will be filled with target material, sealed and inserted in the carriers. Carriers will either be mechanically closed or seal-welded, assembled into carrier trains and shipped to FFTF for insertion in the reactor using the Rapid Radioisotope Retrieval system (see Section 2.3.2 for a description of this system).

4.1.1.1 Stainless and Metallic Material Receipt and Cleaning

Stainless steel (SST) and metallic parts to fabricate isotope pencils, pins and carriers that are received at 306E, will be moved to Room 162 for receipt inspection and quality control inventory. As

part of receipt inspection, target metallic pencils, pins and carriers will undergo Ultrasonic Test (UT) examinations in Room 163. New UT examination equipment will be purchased for this inspection. Prior to use, all metallic parts will be cleaned in the SST Cleaning Room (Rm. 174).

4.1.1.2 Target Material Receipt

Target material received at the 306E Building will be moved to Room 162 for receipt inspection and quality control inventory. Due to the value of target materials, they will be kept in locked storage in Room 169 until they are ready to be used for target fabrication.

4.1.1.3 Target Material Forms

Target material will be received in the following forms: metal, oxide, carbonate and gas. Samples will be obtained for analysis prior to fabrication of targets. After inventory and sample analysis, metal, oxide and carbonate target materials will be stored in Room 169 until needed for target fabrication. Gas target materials will either be loaded into capsules or sent to FFTF for use in the in-reactor gas loop.

4.1.1.4 Target Material Processing

Metal Target Material: It is assumed that metal target material will require no processing. Metal target material will be procured in a form that can be installed directly into target capsules or pencils.

Oxide and Carbonate Target Material: It is assumed that all but two of the oxide/carbonate target materials will be purchased in a form that can be loaded directly into capsules or pencils without additional processing or conditioning. The following two target materials will be pelletized: Cd-108 (target for Cd-109 production) and natural Eu-151/153 (target for Gd-153 production). Two pellet fabrication lines will be set up in the south bay area of the 306E Building. The following equipment will be required for each pellet fabrication line:

A. Pellet Fabrication Line Equipment:

1. Receipt Glovebox - 4 ft, unshielded

   This enclosure will be used for target material sampling, weighing and packaging in containers for transport to other target fabrication stations. The following summarizes equipment and process steps performed in this glovebox:

   a. Sampling equipment
   b. Weighing equipment
   c. Package target material for transport to next step

2. Powder Conditioning Glovebox - 6 ft, unshielded

   This enclosure will be used to blend, bind and sieve target material for pelletizing. The following summarizes equipment and process steps performed in this glovebox:

   a. V-Blender
   b. Granulating Sieve
   c. Add binder
   d. Package target material for transport to next step

3. Pelletizing Glovebox - 6 ft, unshielded

   This enclosure will be used to pelletize and sinter the target material. The following summarizes equipment and process steps performed in this glovebox:

   a. Pelletizer
   b. Centaur Furnace for sintering
   c. Package pellets for transport to next step

4. Grinding Glovebox - 6 ft, unshielded

   This enclosure will be used for final grinding of pellets. The following summarizes equipment and process steps performed in this glovebox:

   a. Centerless grinder
   b. Grind pellets to final dimensions for installation in target carriers
   c. Package pellets for transport to final assembly enclosures

4.1.1.5 Target Assembly Fabrication

As stated above, targets will be assembled in pencils for the LIV assemblies and in capsule/carriers for use in the Rapid Radioisotope Retrieval system. Enclosures and equipment required for each type of target assembly are as follows:

A. LIV Pencil/Pin Target Assembly

1. Pencil Loading Glovebox - 4 ft, unshielded

   This enclosure will be used to load pellets from the pellet fabrication lines, metal target material or oxide/carbonate target material into pencils. The following summarizes equipment and process steps performed in this glovebox:

a. Target material loaded into pencils
b. Pencils capped with temporary plug/cap
c. Pencils cleaned and prepared for move to LIV Pin Assembly and Closure Glovebox

2. LIV Pin Assembly and Closure Glovebox - 15 ft Glovebox, unshielded, He Atm

This enclosure will be used to perform final weld closures on pencils, install pencils in pins and perform final weld closures on pins. It is assumed that this common glovebox can be used for final assembly and closure of all LIV targets. This glovebox is existing and must be relocated from its current location in the 308 Building to the 306E Building. The following summarizes equipment and process steps performed in this glovebox:

a. Pencil closure welding station, Gas Tungsten Arc Welding (GTAW) and power supply
b. LIV pins assembled (pencils, spacers, springs, etc.)
c. LIV pin closure welding station, GTAW and power supply
d. Pins cleaned prior to removal from glovebox

B. Capsule/Carrier Target Assembly

1. Capsule Fabrication Glovebox - 4 ft, unshielded

This enclosure will be used to load metal target material, oxide/carbonate target material and gas target material into capsules and seal the capsules. It is assumed this common glovebox can be used to fill capsules for all types target materials. This will be accomplished either by thorough clean-up between target fabrication campaigns or by replacement of fixtures and filling equipment used inside the glovebox. The following summarizes equipment and process steps performed in this glovebox:

a. Target material loaded into capsules
b. Capsules evacuated, backfilled with He and sealed
c. Capsule loaded into carriers
d. Carriers capped with temporary plug/cap
e. Carriers cleaned and prepared for move to Capsule/Carrier Assembly and Closure Glovebox

2. Capsule/Carrier Assembly and Closure Glovebox - 4 ft, unshielded, He Atm

This enclosure will be used to perform final closures on Capsule/Carriers. It is assumed that this common glovebox can be used for final assembly and closure of all Capsule/Carrier targets. This glovebox is existing and must be relocated from its current location in the 308 Building to the 306E Building. The following summarizes equipment and process steps performed in this glovebox:

a. Capsule/Carriers with mechanical seals will be closed
b. Capsule/Carrier welding closure station, GTAW and power supply
c. Carriers cleaned prior to removal from glovebox

4.1.1.6 NDE and Leak Test Area and Equipment

Following completion of welding closures, pencils, pins and carriers will undergo Radiographic Testing (RT) and leak testing. The following new equipment will be purchased and added to the compliment of existing NDE equipment in the 306E Building:

A. New in-motion RT System
B. Portable He Leak Detectors (2 ea)

4.1.1.7 Target Storage

Completed targets will be stored in Room 169 until shipment to FMEF. This room is a secured vault.

4.1.1.8 Target Shipping

LIV Targets will be shipped to FMEF where they will be assembled into bundles. See Section 4.1.3 for LIV target assembly at FMEF. Capsule/Carrier Trains will be assembled and shipped to FFTF for insertion into the reactor using the Rapid Radioisotope Retrieval System.

4.1.1.9 General Equipment

In addition to the above, the following general equipment will be needed: Pin boxes, Carts, etc.

4.1.1.10 Gas Tag Fab Station

A gas tag fabrication station will be set up in Room 174-A. Gas tags were previously made in 306E for use in FFTF when the reactor was operating. Enclosures used for gas tag fabrication are existing and must be relocated from the 308 Building to the 306E Building. These enclosures will be refurbished and installed in Room 174-A. The following process equipment will be installed in the gas tag fabrication room and enclosures:

A. New Laser Beam Weld System
B. Upgrade Electron Beam Welder
C. New Fixtures
D. New Gas Tag Rupture Fab Station

4.1.2 Hot and Recycled Target Fabrication - 325 Building

Radioactive (hot) targets and recycled targets will be fabricated in the 325 Building. Ra-226 is the only hot target material that will be received for initial target fabrication. Ra-226 and several other targets will be recycled due to the value of the target material. This section describes how hot and recycled targets will be fabricated.

4.1.2.1 Material Receipt

Stainless steel (SST) and metallic parts required to fabricate hot and recycled isotope targets will be received at 306E, inspected, inventoried and cleaned prior to being moved to the 325 Building for use in fabrication of hot and recycled targets. It is assumed that carriers, pencils and pins for hot and recycled targets will undergo UT examination at the 306E Building prior to use at the 325 Building to assemble hot and recycled targets. Therefore, additional UT examination equipment will not be purchased for use in the 325 Building.

Ra-226 target material will be received at the 325 Building and moved to Room 30A, which contains a radon gas capture system, for receipt inspection and quality control inventory (see Figure 4-2). Recycled target material will be recovered from isotope processing operations as described in Section 4.2.2. Due to the value of the hot and recycled target materials, they will be kept in locked storage in Room 40C until they are ready to be used for hot and recycled target fabrication.

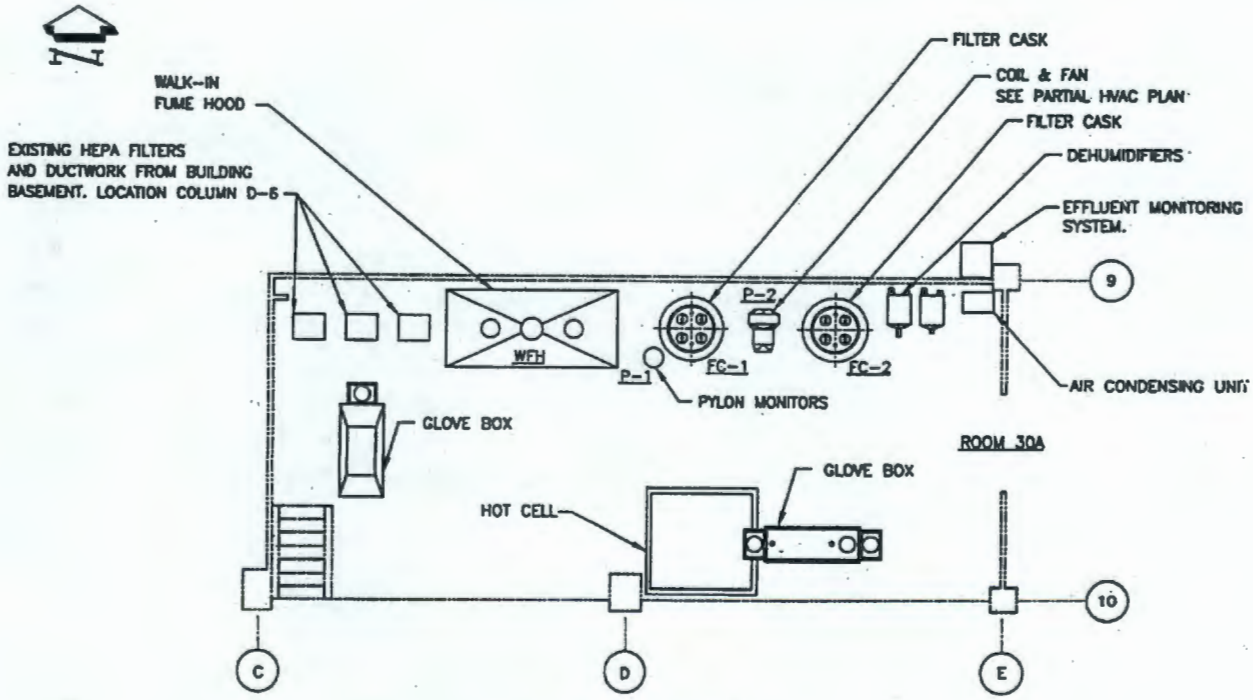
4.1.2.2 Hot Target Material Form

Ra-226 will be received in the form of a carbonate powder.

4.1.2.3 Recycled Target Material Forms and Assembly Forms

It is assumed the following isotopes will be recycled in the target forms identified:

Isotope (Target)	Short/Long Irrad	Target Material Form	Target Assembly Form
Cu-64 (Zn-64)	Short	Oxide Powder	Capsule/Carrier
Cu-67 (Zn-67)	Short	Oxide Powder	Capsule/Carrier
P-32 (S-32)	Short	Sulfur	Capsule/Carrier
I-131 (Te-130)	Short	Gas	Capsule/Carrier
Ac-227 (Ra-226)	Long	Pellets	Pencils
Th-228/229 (Ra-226)	Long	Pellets	Pencils
P-33 (S-33)	Long	Sulfur	Pencils
Sc-47 (Ti-91)	Short	Oxide Powder	Quartz Capsule
Y-91 (Zr-91)	Long	Oxide Powder	Pencils



325 BUILDING
BASEMENT, ROOM 30A

Figure 4-2. Floor plan for 1500 sq. ft. laboratory in the 325 Building where Ra-226 and other isotopes that decay through a radioactive radon gas intermediate species will be processed and stored. The primary components of the radon gas capture system, to which all of the fume hoods, glove boxes, and the hot cell are connected by ductwork, are shown in this drawing.

4.1.2.4 Ra-226 and Recycled Ra-226 Target Material Processing

Ra-226 and recycled Ra-226 will be processed into pellets for installation in pencil/pin LIV targets. It is assumed that the initial Ra-226 target material received from offsite will be loaded into the Room 30A Hot Cell where the material will be sampled for analysis and fabricated into pellets. Pellets will be transferred into the Room 30A shielded glovebox for insertion into target pencils. Following cleaning, the pencils will be moved in shielded pigs to the Hot and Recycled Target Assembly and Closure Glovebox in Rooms 31/31A. The following equipment will be installed in Room 30A enclosures to allow hot and recycled target processing:

A. Pellet Fabrication

1. Hot Cell, Room 30A

This enclosure will be used for fabrication of initial Ra-226 and recycled Ra-226 target pellets. The following summarizes equipment and process steps performed in this hot cell:

a. Sampling Equipment
b. Weighing Equipment.
c. Muffle Furnace
d. Binder/Blend/Sieve
e. Small Pellet Press
f. Small Grinder to machine pellets to final dimensions
g. Pellets moved to Shielded glovebox through transfer port

B. Pencil Assembly and Cleaning

1. Shielded Glovebox, Room 30A

This enclosure will be used to install pellets in pencils, provide temporary caps, and clean pencils prior to transfer to the Hot and Recycled Target Assembly and Closure Glovebox. The following summarizes equipment and process steps performed in this glovebox:

a. Equipment to install pellets into pencils and install temporary caps
b. Pencil cleaning equipment
c. Pencils loaded out to shielded pigs for transfer to the Hot and Recycled Target Assembly and Closure Glovebox located in Rooms 31/31A.

4.1.2.5 Recycled Target Material Processing

It is assumed that all processing required for recycled targets will be performed in the isotope processing enclosures. Following processing, the recycle target material will be loaded into either capsules or pencils. Capsules will be evacuated, backfilled with He and sealed in the isotope processing enclosures, loaded into carriers and provided with temporary caps. Pencils will be filled and provided with temporary caps. Capsule/carriers and pencils will be cleaned and loaded out into shielded containers and moved to the Hot and Recycled Target Assembly and Closure Glovebox located in Rooms 31/31A.

4.1.2.6 Hot and Recycled Target Assembly Fabrication, Rooms 31/31A

A. LIV Pencil/Pin and Capsule/Carrier Target Assembly

1. Hot and Recycled Target Assembly and Closure Glovebox - 12 ft, shielded, He Atmosphere

   It is assumed that one shielded final assembly and closure glovebox can be used to perform final closures for hot and recycled capsule/carriers, pencils and pins. This enclosure will be installed in Rooms 31/31A in the basement of 325 Building. Complete renovation of these rooms will be required. The following summarizes equipment and process steps performed in this glovebox:

   a. Capsule/Carriers with mechanical seals will be closed
   b. Capsule/Carrier welding closure station, GTAW and power supply
   c. Pencil closure welding station, GTAW and power supply
   d. LIV pins assembled (pencils, spacers, springs, etc.)
   e. LIV pin closure welding station - assume same station as used for pencils
   f. Capsule/carriers assembled into carrier trains
   g. Carrier trains and LIV pins cleaned prior to transfer to NDE glovebox

4.1.2.7 NDE and Leak Test Enclosure and Equipment

It is assumed that hot and recycled targets that are to be re-inserted in the reactor for irradiation will require the same level of Quality Control as cold targets fabricated in 306E. Therefore, the following equipment will be required in Rooms 31/31A for final examination and acceptance of hot and recycled targets:

A. Hot and Recycled Target NDE Glovebox - 12 ft, shielded

A separate shielded glovebox will be installed in-line with the Hot and Recycled Target Assembly and Closure Glovebox. Separate transfer ports will be provided to allow fabricated components to be moved from the Closure Glovebox to the NDE Glovebox for either leak testing or RT examination. The following summarizes equipment and process steps performed in this glovebox:

1. Vacuum chamber for leak testing
2. Radiography System
3. He Leak Detectors
4. Following NDE, pins and carrier trains are loaded into shielded shipping containers.

4.1.2.8 Hot and Recycled Target Storage

It is assumed completed Ra-226 and recycled targets will be stored in 325, Room 40C.

4.1.2.9 Hot and Recycled Target Shipping

Hot and recycled LIV pins will be shipped in shielded casks to FMEF or to the FFTF IEM Cell where they will be inserted into a duct, nozzle and handling socket assembly. Hot and recycled capsule/carrier trains will be loaded into a shielded isotope insertion/retrieval device that will be used to transport capsule/carrier trains. This device will be designed to interface with the Rapid Radioisotope Retrieval system.

4.1.3 Target Assembly in FMEF

Final assembly of the LIV targets will take place in the FMEF. The FMEF is an existing structure adjacent to the FFTF which was specifically designed and constructed for reactor fuel element construction and post-irradiation processing of spent driver fuel elements and test experiments. There are six main levels from 35 feet below grade to 70 feet above grade. Much of the FMEF houses hot cells intended for post-irradiation fuel and material examination work, but was never used based on programmatic considerations. The FMEF provides space for fuel fabrication and storage activities; tritium target and test pin fabrication and assembly; LIV target assembly; mechanical equipment for heating ventilation and air conditioning; a battery and switchgear room; and a fully enclosed shipping and receiving area. Both FFTF fuel fabrication and tritium target fabrication will occur in the FMEF.

The LIV and the tritium targets will have very similar requirements for the final assembly process of combining the target pins into a complete FFTF core assembly. All the assembly steps and inspections essentially will be the same as used previously for fabricating FFTF driver fuel assemblies and test article assemblies. Since only one to two LIV assemblies per year will be fabricated, the process stations established for tritium target assembly will be utilized to as great an extent as possible. The specific location for the assembly area has not yet been determined, but the FMEF has several suitable areas.

Some target pins handled will be radioactively hot, due either to the Radium-226 target material, or from radioactive recycled target materials. Shielded gloveboxes will be provided for assembly of hot LIV bundles.

4.1.3.1 LIV Pin Receipt

Target pins will be received in the FMEF truck and rail car handling area. The pins will be moved to the target assembly area and placed on pin storage racks. Hot pins will be stored on separate racks in an appropriately shielded area.

4.1.3.2 Wire Wrap

Cold target pins will be transported by a pin cart to the wire wrap station, where a small diameter wire is spirally wound around the target pin and secured to each end cap with a weld. The wire wrap machine for tritium target pins will be used for cold medical isotope target pins.

A 12 ft shielded glovebox will be provided for wire wrapping hot pins. The following equipment will be provided in the Hot Target Wire Wrap Glovebox:

A. Wire-wrap machine
B. GTAW welding equipment and power supplies
C. Miscellaneous fixtures
D. Shielded transfer port to mate up to Final Assembly Glovebox

4.1.3.3 Pin Wire Wrap Inspection

Prior to wire wrapping, the pins will be inspected for straightness. After wire wrapping is completed, pins will be visually inspected to assure wire-wrap welds are acceptable and gaps between the wire-wrap and the clad tube are within specifications. These inspections will be performed on a granite table for cold pins and inside the shielded Wire Wrap Glovebox for hot pins. Special fixtures will be provided inside the shielded Wire Wrap Glovebox to permit inspection of hot pins for straightness prior to wire-wrapping.

Following wire wrapping, cold target pins will be transported to the tritium and medical isotope target final assembly area. Hot target pins will be moved to the shielded Hot LIV Final Assembly Glovebox through the shielded transfer port connected to the Wire Wrap Glovebox.

4.1.3.4 Final Assembly

Final assembly is a multi-step process where target pins are 'strip layered' (assembled onto pin rails to establish their proper geometric configuration), bundled and installed into the assembly duct. The duct is then welded to the shield inlet assembly. Final inspections complete the process. Individual steps of the process are summarized as follows:

A. Receipt Inspection
B. Weld duct to handling socket
C. Weld Inspection
D. Assemble pins into strip layers
E. Bundle pin assembly
F. Install assembly duct onto pin bundle
G. Weld duct to the shielded inlet nozzle
H. Inspect weld
I. Final Inspection/Release

Assembly of cold LIV targets will utilize the same equipment being used for tritium target assembly.

A 15 ft shielded glovebox will be provided for final assembly of hot target pin bundles. The following equipment will be provided in the shielded Hot LIV Final Assembly Glovebox:

A. Pin assembly fixtures
B. Welding System, GTAW and power supply
C. Transfer ports to insert shroud and end connections.
D. RT examination equipment
E. Following fabrication and inspection, bundles will be transferred into shielded casks and moved to storage.

4.1.3.5 Storage and Shipping

Completed targets will be stored in the FMEF until shipment to the FFTF for insertion into the reactor.

4.2 Isotope Processing

Irradiated medical isotope targets will be transported from FFTF to the 325 Building for processing, packaging, and shipment of the product isotopes to one of three designated medical isotope distribution centers. Existing Hot Cells in 325A and 325B will be used and a group of ten laboratories in the 500 Corridor of 325 Building will be remodeled for isotope processing. Facility modifications will also be made in the basement of 325 Building to accommodate radioactive target fabrication and processing of isotopes obtained by irradiation of Ra-226. The following sections describe receipt of irradiated targets, isotope processing, radioactive target fabrication, and final product quality control and distribution facilities. Figure 4-3 shows the areas of the first floor of the 325 Building and 325A and 325B annexes that will be utilized for medical isotope processing and Figure 4-4 shows the areas of the 325 basement that will be used.

4.2.1 Irradiated Target Receipt

Following irradiation in the reactor, isotope targets/carriers will be transported to the 325 Building for processing in approved shielded devices or casks. Devices or casks will be off-loaded in the 325A Truck Lock. An existing crane will be used to move the devices or casks into the cask handling area where they will be mated to A-Cell for removal of targets/carriers. Medical isotope targets/carriers will be unloaded from the cask into A-Cell where they will be separated and prepared for transport from A-Cell to isotope processing stations.

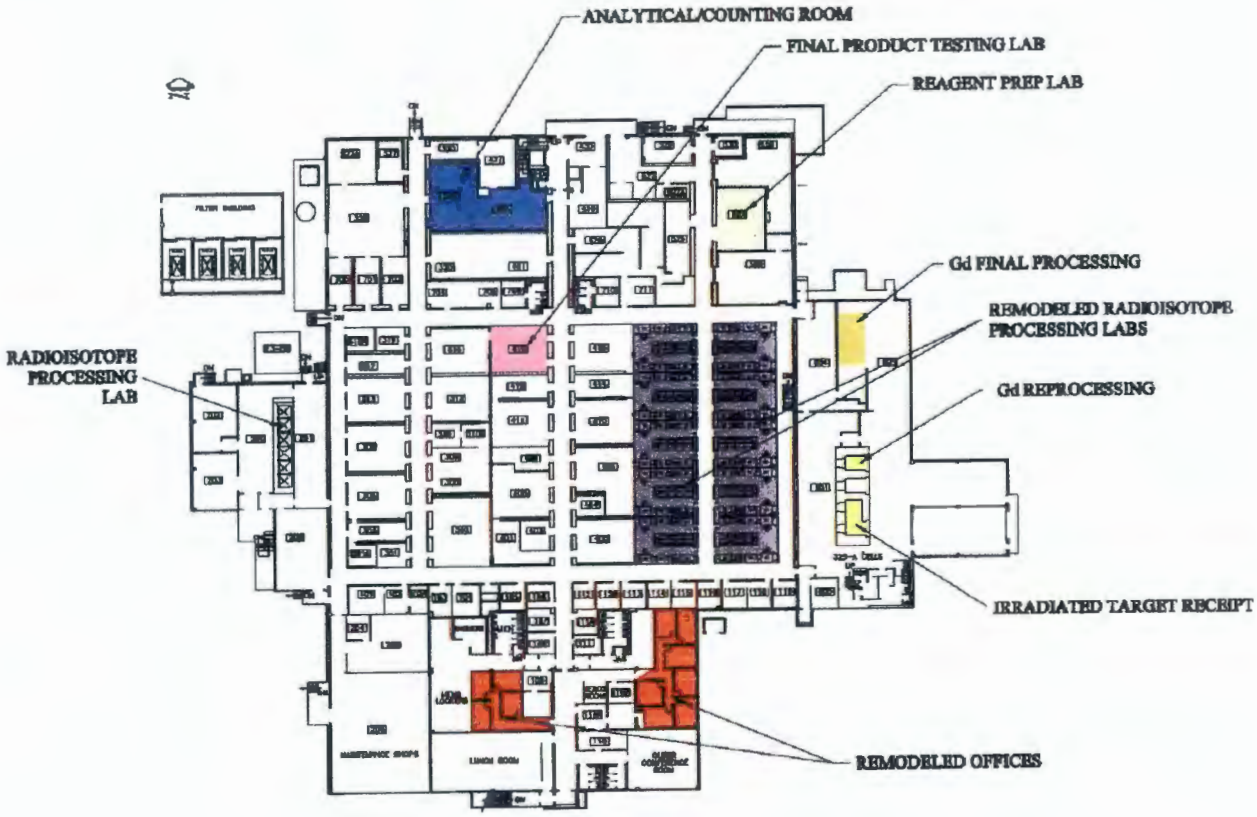
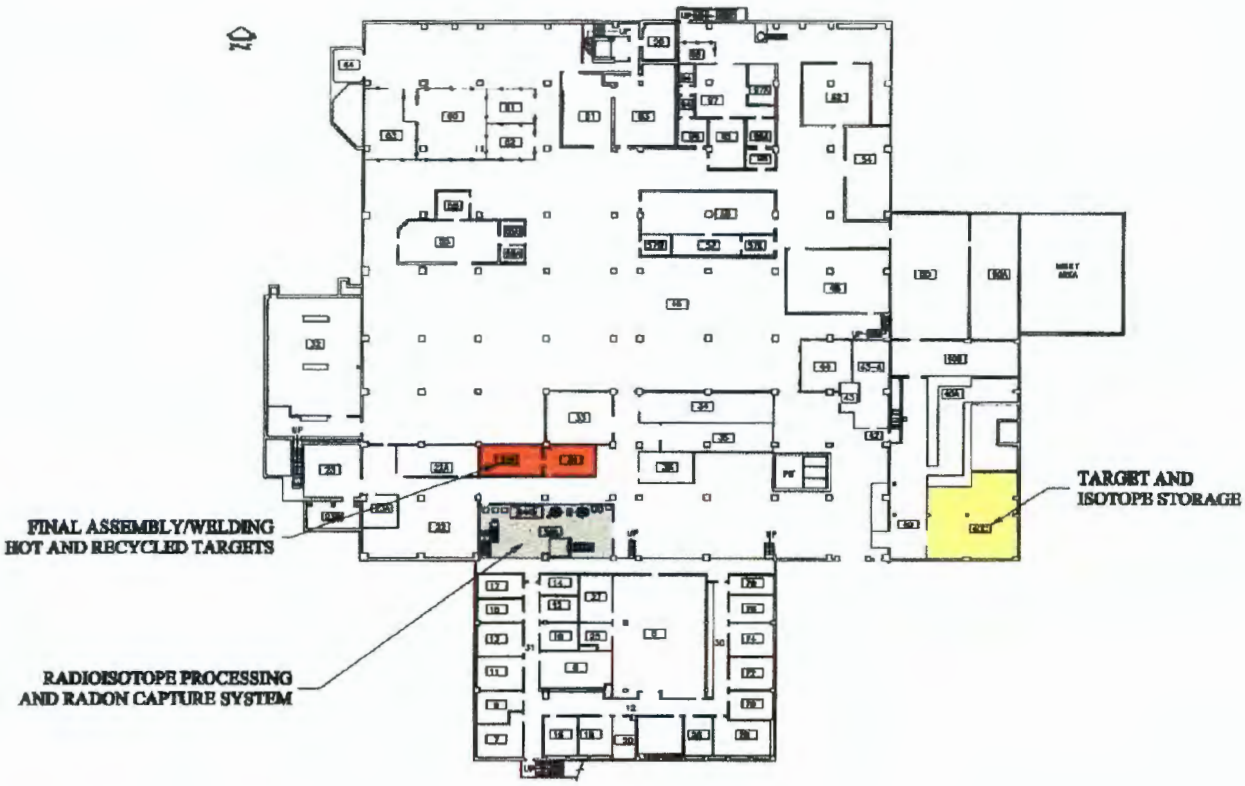


Figure 4-3. First floor of the 325 Building, showing locations of the radiochemical processing laboratories, the heavily shielded hot cell for receipt of targets, the heavily shielded hot cell and laboratory for processing of Gd-153 targets and products, and laboratories for reagent preparation, chemical and radionuclide analysis of isotope products, and final product sterility and pyrogen testing. Office areas are available on the first and second floors of the 325 Building.

4.2.2 Isotope Processing Facilities

Separate radioisotope processing stations will be set up to process specific isotopes in the following areas of the 325 Building, 325A Annex and 325B Annex:

- **325A, C-Cell:** Irradiated Eu targets will be transferred from A-Cell to C-Cell through existing transfer ports between hot cells. Equipment will be provided in C-Cell to cut up, dissolve and process Gd-153. Gd product, contaminated with Eu and Sm will be transferred from C-Cell to a shielded glovebox in Room 603 provided with equipment required for final product purification.



325 BUILDING
BASEMENT FLOOR PLAN

Figure 4-4. Basement of the 325 Building, showing locations of the laboratory with a radon capture system (see Figure 4-2) and the laboratories for assembly of "hot" targets and targets containing recycled material with residual radioactivity.

- **325B, Hot Cells:** The following isotopes will be processed in existing hot cells in 325B; Lu-177, Sm-153 and Ir-192. A separate hot cell will be used for each product. Three existing hot cells will be refurbished and provided with process equipment required for each product.

- **325, Rooms 500 - 517:** These laboratories will be remodeled to provide ten (10) isotope processing laboratories as shown in Figure 4-5. Each laboratory will include two separate isotope processing stations. Each isotope processing station will include a 5 ft. hot cell, a 4 ft. Shielded Glovebox, a 4 ft. Fume Hood and a 5 ft. Vertical Laminar Flow Hood. A sufficient number of processing stations are being provided to avoid cross-contamination of different products by working with only one isotope product in each processing station. Irradiated targets/carriers will be transported from 325A, A-Cell to isotope processing stations in shielded pigs. Targets/carriers will be transferred into processing hot cells where they will be opened and the irradiated target material will be removed. Equipment required for processing each isotope will be installed in the enclosures. Air-lock transfer ports will be provided between enclosures to allow movement of the product through required

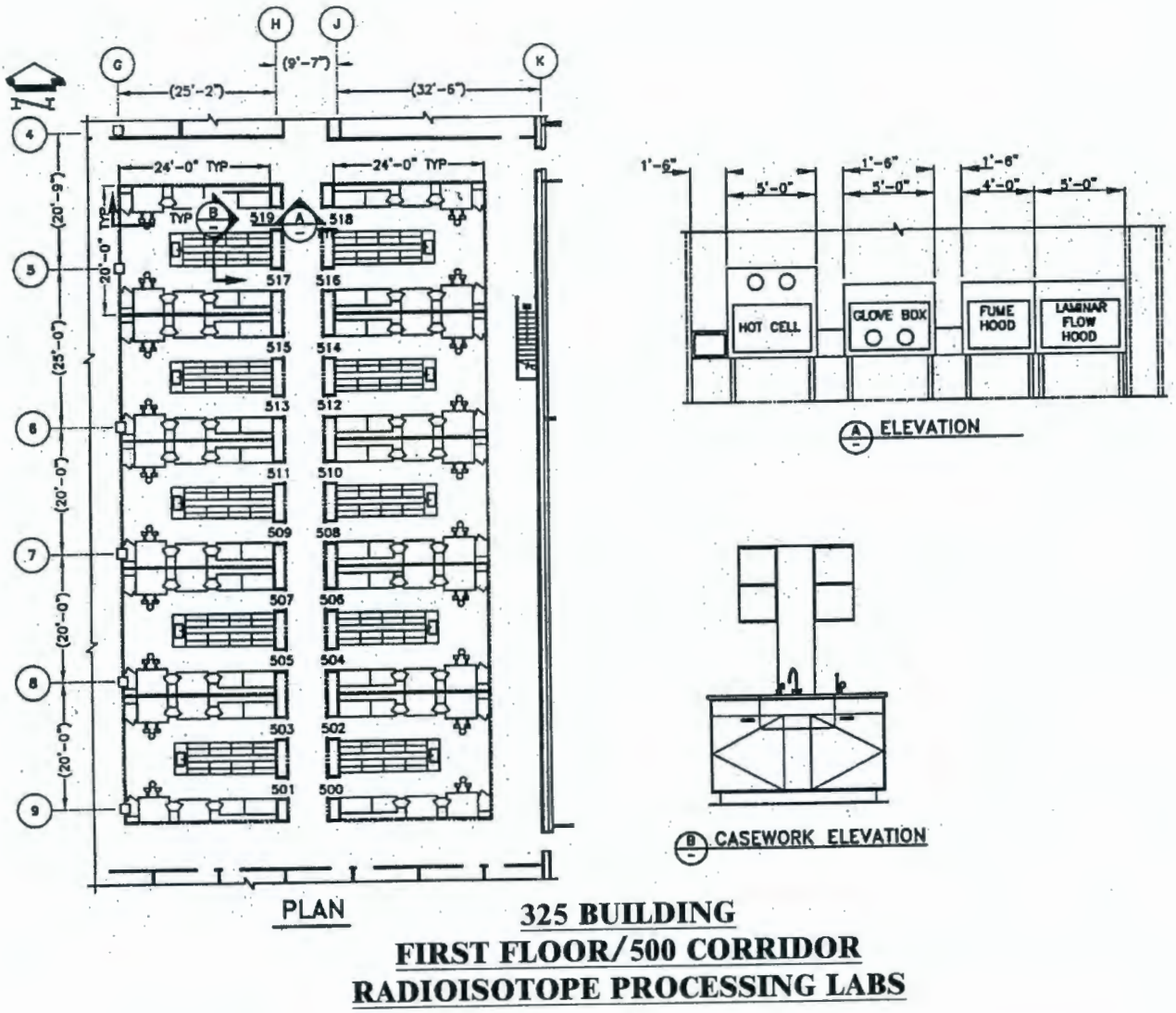


Figure 4-5. Diagram of 10 radiochemical laboratories on the first floor of the 325 Building, each of which will have two separate isotope processing lines containing the equipment shown at the upper right in the figure.

processing steps. Final products will be prepared and packaged in vertical laminar flow hoods at the end of each processing line. Structural support for hot cells and shielded gloveboxes located on the first floor will be provided by constructing structural steel support towers resting on the floor in the basement.

- **325 Basement, Room 30A:** The following isotopes will be processed in Room 30A: Ac-227, Th-228, and Th-229. Room 30A is currently being remodeled to provide a new radium repository. An existing hot cell (clean) will be relocated from Room 203 to Room 30A to provide capability to process the above isotopes. Figure 4-2 shows the layout of enclosures and equipment required in

Room 30A. This project is relocating and installing the existing hot cell, existing radon storage casks and existing gloveboxes, and providing all isotope processing equipment. Equipment will also be installed in the Room 30A hot cell to make radioactive Ra-226 target material pellets. See the Target Fabrication section for additional description of facilities to fabricate radioactive and recycled targets.

- **325 Basement, Rooms 31/31A:** These rooms will be remodeled for fabrication of radioactive and recycled targets. See the Target Fabrication section for additional description of facilities to fabricate radioactive and recycled targets.

- **325, Room 524:** Room 524 will be remodeled to become the Reagent Prep Laboratory. All "cold" aqueous solutions required for isotope processing will be prepared in this lab under controlled and sterile conditions. Equipment will include fume hoods, biohazard laminar flow hoods, autoclaves and depyrogenation ovens.

- **325 Building Office Mods:** Existing change rooms will be modified to provide additional office space for operating staff. The location for these modifications is shown in Figure 4-3 in the south end of the building on the first floor. Other office space is available on the second floor of the 325 Building.

4.2.3 Isotope Packaging and Shipping

Prior to release for shipment to customers, all isotope products will undergo rigorous analytical and quality control examination. Quality control implementation will begin with target material receipt and continue through target fabrication and isotope processing. Final quality control measures will verify product radionuclide and chemical purity and assure the product is sterile and pyrogen free.

- **325, Room 419:** Room 419 will be remodeled to become the Final Product Testing Laboratory. Final isotope products will flow through this laboratory for sterility and pyrogen testing and for final quality control inspection prior to shipment to customers. Equipment in this laboratory will include fume hoods, biohazard laminar flow hoods, incubators, pyrogen test kits, particle counters and microbial testing materials.

The following additional existing equipment and facilities will also be utilized for quality control:

- **325, Room 324:** Existing chemical and radionuclide analytical equipment located in this room will be used to characterize isotope products and assure product quality control.

- **325B, Room 201:** An existing glovebox and existing analytical equipment will be used in this room to characterize isotope products and assure product quality control.

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5.0 Operations Support

5.1 Staffing Requirements

An increase in the number of personnel will be required to support a medical isotope production mission. Each step of the process, medical isotope target fabrication, target insertion and retrieval in the FFTF, and target processing, along with program administration and marketing functions, will require qualified, trained and motivated staff members to ensure success. Estimates are provided below of the numbers of personnel required for these functions, and how their duties might interrelate with other job functions in support of a tritium production mission.

5.1.1 Target Fabrication and Assembly

5.1.1.1 Long-Term Irradiation Vehicle

Two designs of target insertion and retrieval systems will be fabricated for medical isotope production: the Long-Term Irradiation Vehicle (LIV) system and the Rapid Radioisotope Retrieval (R3) system. The LIV design is similar to that of the tritium production target in that it is a 12-foot long assembly, consisting of target pins placed inside a stainless steel duct assembly. It is anticipated that fabrication of the LIV will take place at the FMEF, since that is where the tritium targets and fuel will be fabricated. Some assembly equipment can be used for fabrication of both the tritium targets and the medical isotope targets. Likewise, it is anticipated that the staff available for tritium target fabrication will also be used for LIV fabrication since only two to three LIV assemblies per year need to be built. This additional work scope will require that two full-time-equivalent (FTE) employees are added to the FMEF staff.

5.1.1.2 Rapid Radioisotope Retrieval (R3) Assembly

The R3 targets will be fabricated either in the 306E Building or the 325 Building. It is anticipated that two reactor core assembly positions will be outfitted with the R3 system, and that one R3 target will operate on a 10-day irradiation cycle, with the other target on a 25-day irradiation cycle. This will require a fabrication rate of about thirty-five R3 target vehicles per year. Each target vehicle will consist of 30 to 40 capsules linked together to form a string about four feet long.

All R3 targets during their initial irradiation cycle will use stable isotope materials, simplifying their handling requirements. However, the high cost of the stable isotope materials will necessitate that the target material that does not get transmutated into the product isotope during irradiation, be separated during chemical processing and recycled back into target material. This involves handling the target materials in a manner appropriate to radioactive materials.

If it is decided that pellets are to be loaded into the R3 capsules (e.g., Ra-226 pellets), the pellet would be formed using a mixing, binding and pressing process similar to the fuel production process. If the target material is loaded as a powder, the process is simplified further. Regardless of pellet or powder form, fume hoods or glove boxes will be used to manually load the materials into the capsules. The capsules will be sealed, leak tested and inspected before use. It is estimated that fabrication of the R3 targets will require a staff of 12 FTE employees.

5.1.2 Target Insertion and Removal

5.1.2.1 Long Irradiation Vehicle

Removal of the LIV target from the reactor will occur during reactor outages, using the same handling equipment and personnel as will be used for fuel and tritium target handling. The LIV assembly will be transferred from the reactor to the IEM cell using existing fuel handling equipment. The assembly will be washed and dried in the IEM cell's sodium removal system. Also within the IEM cell, the assembly will be dismantled, and the target pins loaded into a pin container. The pin container will then be transferred from the IEM cell into a shipping container and transported by tractor trailer to the 325 Building. These tasks are all similar in job scope to those presently done by the FFTF staff for fuel off-loading activities, and those previously carried out during FFTF full-power operations for processing fuels and materials test assemblies. Based on this experience, approximately 100 person shifts will be required for each LIV assembly (crews of five people, two shifts per day for ten days). Assuming two LIVs per year are irradiated, approximately one additional FTE will be required.

5.1.2.2 Rapid Radioisotope Retrieval (R3) Assembly

Insertion and removal of the R3 will occur while the reactor is running. This process will entail positioning a shielded handling cask up to the R3 retrieval location at the top of the reactor head. The cask will be mated, the irradiated R3 target mechanically retrieved into the cask, and a fresh target inserted into the reactor. The cask will be transferred to the Reactor Service Building for installation of transportation overpacks, and then loaded onto a tractor trailer truck for transport to the 325 Building for target processing.

Insertion and removal of the R3 targets will be done on cycles of either 10 or 25 days, depending upon the half lives of the isotopes being produced. Due to the short half lives of these isotopes, the insertion and removal process will be optimized to minimize their decay. The insertion and removal cycle will be scheduled such that the products can be processed, packaged and loaded onto the air carriers that provide the fastest service to the customers. These activities will probably need to be staffed on a round-the-clock basis. However, due to the periodic nature of the tasks (every 10 or 25 days), the same FFTF staff can be used that will be doing fuel and tritium target handling. Each insertion and removal cycle will require a team of approximately seven people for about eight hours. Assuming 35 target strings per year are irradiated, the FFTF staff will require one additional FTE above the staff level required for fuel and tritium target handling.

5.1.3 Target Processing

5.1.3.1 LIV Processing

The LIV target pins will be received at the 325 Building loaded in a pin container inside a shipping cask. The shipping cask will be removed by overhead crane from the tractor-trailer transport vehicle, and mated up to the back of a hot cell. The target pins will be removed from the cask and pin container by use of a remote manipulator. The target materials will then be removed from the cladding. It has not yet been determined what means will be necessary to separate the target material from the cladding. In experience with Gadolinium-153, Cobalt-60 and various other isotopes produced in FFTF assemblies, the target pins readily dropped out of the cladding when they were opened. This may not always be the case due to the differing physical properties of the various isotopes expected to be produced. Regardless, the task will be performed by either mechanical or chemical means in a single hot cell involving the use of a remote manipulator. Since processing time is not critical for these long-lived product isotopes, it is expected that each target pin (approximately 19 target pins per LIV assembly) will be individually disassembled and the product isotope removed and placed in a shielded container for transfer to the location of the next processing step. The 325 Building currently has personnel who perform duties similar to these. For each LIV assembly processed, a staff of four people for about two hours will be required to off-load the cask and mate it to the hot cell. A staff of three people for five shifts will be required to open the transfer cask and portion the product isotopes into containers.

The containers of product isotopes will then be transferred within the 325 Building to the appropriate processing station. Each product isotope will have a separate processing station to preclude cross-contamination. The station will be either a hot cell with manipulator, shielded glove box or a fume hood depending upon the radiation level of the batch of isotope to be processed. Chemical processing will require two to three shifts per batch of isotope being processed, depending upon the complexity of the process. Isotopes processed by ion-exchange procedures require a staff of five for four shifts, while other isotopes require a staff of five for three shifts.

Preliminary estimates based on market analysis show that the LIV target can economically produce 10 different isotopes. These isotopes are used as a baseline to estimate staffing requirements, and are outlined in Table 5-1. It is also anticipated that small quantities of 'exotic' isotopes with a small market demand will be produced to support medical and scientific research. While each isotope is not specifically analyzed, it is assumed that twenty processing campaigns per year of the 'exotic' isotopes will be derived from LIV targets.

5.1.3.2 R3 Processing

The R3 targets will be received in the 325 Building in a manner similar to the LIV receipt. The shipping cask will be removed by overhead crane from the tractor-trailer transport vehicle, and mated to the back of a hot cell. The target capsule string will be removed from the cask by use of a remote manipulator. Using a manipulator, the target capsules will then be opened and each product isotope will be transferred into a separate container for transfer to the location of the next processing step.

Table 5-1. LIV Chemical Processing

Isotope	Ion Exchange Processing	Shifts per process	People per process	Campaigns per year	Person-Shifts per year
Ac-227	Yes	4	5	1	20
Cd-109	No	3	5	1	15
Gd-153	Yes	4	5	1	20
Ir-192	No	3	5	6	90
Sm-145	No	3	5	1	15
Sr-85	No	3	5	6	90
Sr-89	No	3	5	6	90
Th-229	Yes[a]	-	-	-	*
W-188	No	3	5	6	90
Y-91	Yes	4	5	6	75
Various Research Isotopes		4	5	20	75
			Totals	54	580
			LIV Chemical Processing FTEs:		2.5

(a) Th-229 and Ac-227 are processed from the same target material, therefore Th-229 processing resource requirements are included with Ac-227.

Preliminary market analysis and economic studies show that one of the R3 vehicles will be irradiated on 10-day cycles, yielding a throughput of about 25 target strings per year. The other R3 vehicle will be irradiated on a 25-day cycle, yielding a throughput of about 10 target strings per year.

For each R3 target string processed, a staff of four people for about two hours will be required to off-load the cask and mate it to the hot cell. A staff of four for five shifts will be required to open the transfer cask and place the product isotopes into containers. Assuming 35 target strings per year, approximately three FTEs will be required for this work.

The containers of product isotopes will then be transferred within the 325 Building to the appropriate processing station. Each product isotope will have a separate processing station to preclude cross-contamination. The station will be either a hot cell with manipulator, shielded glove box or a fume hood depending upon the radiation level of the batch of the isotope to be produced. Chemical processing will take between three to four shifts per batch of isotope being processed, depending upon the complexity of the process. Isotopes processed by ion-exchange procedures require a staff of five for four shifts, while other isotopes require a staff of five for three shifts.

Preliminary market analysis and economic studies indicate that one of the R3 vehicles will be operated on a 10-day irradiation cycle yielding a throughput of about 25 target strings per year. Cu-67, Ho-166, Re-186, and Sc-47 are the leading candidates for the 10-day R3. The other R3 vehicle will be operated on a 25-day irradiation cycle with a throughput of about 10 target strings per year. I-131, Lu-177, P-32 and Pd-103 are the leading candidates for the 25-day R3. Additionally, I-125 will by produced in a system that will most likely be a gas line with a cryogenic trap that is separate from the carrier capsule chain. The 10 R3 isotopes are used as a baseline to estimate staffing requirements, and are outlined in Table 5-2. It is also anticipated that very small quantities of short-lived 'exotic' isotopes will be produced to support medical and scientific research. While each of these isotopes is not specifically analyzed, it is assumed that 20 campaigns per year will be carried out with the 'exotic' isotopes produced in R3 targets.

Table 5-2. R3 Chemical Processing

Isotope	Ion Exchange	Shifts per Process	People per Process	Campaigns Per Year	Person Shifts Per Year
Cu-67	Yes	4	5	25	500
Ho-166	No	3	5	25	375
I-125	Yes	4	5	6	120
I-131	No	3	5	10	150
Lu-177	No	3	5	10	150
P-32	Yes	4	5	10	200
Pd-103	No	3	5	10	150
Re-186	No	3	5	25	375
Sc-47	Yes	4	5	25	500
Sm-153	No	3	5	25	375
Various Research Isotopes	Yes	4	5	20	400
			Totals	191	3295
			R3 Chemical Processing FTEs:		14.5

5.1.4 Packaging and Shipping

Each isotope must be properly packaged and the appropriate protocol prepared prior to shipment. The staffing estimates in Table 5-3 are based on experience gained by medical isotope production at the 325 Building by staff at the Pacific Northwest National Laboratory.

Table 5-3. Packaging and Shipping

Isotope	Campaigns per Year	Person Shifts Per Campaign	Person Shifts Per Year
Ac-227	1	7	7
Cd-109	1	7	7
Cu-67	25	7	175
Gd-153	1	7	7
Ho-166	25	7	175
I-125	6	7	42
I-131	10	7	70
Ir-192	6	7	42
Lu-177	10	7	70
P-32	10	7	70
Pd-103	10	7	70
Re-186	25	7	175
Sc-47	25	7	175
Sm-145	1	7	7
Sm-153	25	7	175
Sr-85	6	7	42
Sr-89	6	7	42
Th-229	1	7	7
W-188	6	7	42
Y-91	6	7	42
Various Research Isotopes	40	7	280
Totals	246		1722
Packaging and Shipping FTEs:			7.5

5.1.5 Marketing and Administration

Marketing and administrative staffing estimates shown in Table 5-4 are based on current medical isotope production by the Pacific Northwest National Laboratory. An average of five person-shifts are required per campaign. For 246 campaigns, a total of 1230 person shifts will be required, or 5.5 FTEs.

Table 5-4. Marketing and Administration

Isotope	Ion Exchange	Shifts per Process	People Per Process
Ac-227	1	5	5
Cd-109	1	5	5
Cu-67	25	5	125
Gd-153	1	5	5
Ho-166	25	5	125
I-125	6	5	30
I-131	10	5	50
Ir-192	6	5	30
Lu-177	10	5	50
P-32	10	5	50
Pd-103	10	5	50
Re-186	25	5	125
Sc-47	25	5	125
Sm-145	1	5	5
Sm-153	25	5	125
Sr-85	6	5	30
Sr-89	6	5	30
Th-229	1	5	5
W-188	6	5	30
Y-91	6	5	30
Various Research Isotopes	40	5	200
Totals	246		1230
Marketing and Administration FTEs:			5.5

5.1.6 Staffing Summary

Table 5-5 summarizes the staffing costs required to support the medical isotope production mission, assuming an average rate of $100/hr.

Table 5-5. Summary of Staffing Requirements and Costs.

FTE's Required	LIV	R3	FTE Total	Cost @ $100/hr
Target Fabrication	2	12	14	$2,564,800.00
Target Insertion and Removal	1	1	2	$366,400.00
Target Processing: Handling	1	3	4	$732,800.00
Target Processing: Chemistry	2.5	14.5	17	$3,114,400.00
Packaging and Shipping	N/A	N/A	7.5	$1,374,000.00
Marketing and Administration	N/A	N/A	5.5	$1,007,600.00
Total			50	$9,160,100.00

5.2 Laboratory Analysis

Radionuclide and analytical chemical analysis must be performed for each processing campaign. These analyses will either be performed within the 325 Building or at the 222S Laboratory at the Hanford Site. Analysis costs shown in Table 5-6 are based on those previously incurred for the medical isotope production program by the Pacific Northwest National Laboratory.

Table 5-6. Laboratory Analysis Costs

Number of Processing Campaigns	Analysis Cost per Campaign ($)	Annual Analysis Cost ($)
246	$2,000	$492,000

5.3 Waste Handling

Wastes products will be generated during the production of medical isotopes. Radioactive waste will be generated by activation of the target pin cladding and assembly duct in the LIV, and by activation of the carrier capsules in the R3. These wastes will be minimized by designing the assembly ducts and, if

possible, the R3 carrier capsules to be recycled. However, for the purpose of this document it is assumed that none of the LIV assembly or R3 carrier capsule components are recycled. Chemical processing of the medical isotopes will produce a mixed waste stream of low-level radioactive and chemical wastes consisting of impurities extracted from the product isotope, residual acids used for the processing, and laboratory glassware.

All wastes generated will be sent to existing radioactive waste disposal facilities on the Hanford Site. Tables 5-7 and 5-8 show estimates of the annual waste volume and disposal costs for processing the prototypical target loadings (based on market survey results and economic analysis) for two R3 reactor core locations and a single LIV core location.

5.3.1 Chemical Processing Disposal

Chemical processing will result in acid solutions and other chemicals which would become radioactive waste after processing is complete. Various plastics, paper products and laboratory glassware would also be disposed as radioactive waste. The chemical wastes generated per year and the cost of disposal are summarized in Tables 5-7 and 5-8.

Table 5-7. LIV Chemical Processing Waste Costs

Isotope	Target Vehicle	Chemical Processing Campaigns Per Year	Chemical Processing Waste Cu Ft/Year	Mixed Waste Storage Rate $/Cu Ft	Waste Staff Support per Campaign ($) @$100/hr	Disposal Cost $/Year
Ac-227	LIV	1	10	106	300	1360
Cd-109	LIV	1	2	106	300	512
Gd-153	LIV	1	20	106	300	2420
Ir-192	LIV	6	5	106	300	2330
Sm-145	LIV	1	1	106	300	406
Sr-85	LIV	6	5	106	300	2330
Sr-89	LIV	6	5	106	300	2330
Th-229	LIV	1	0	106	300	300
W-188	LIV	6	5	106	300	2330
Y-91	LIV	6	1	106	300	1906
Various Research Isotopes	LIV	20	5	106	300	6530
Total		55	54			$22,754

Table 5-8. R3 Chemical Processing Waste Costs

Isotope	Target Vehicle	Chemical Processing Campaigns Per Year	Chemical Processing Waste Cu Ft/Year	Mixed Waste Storage Rate $/Cu Ft	Staff Support per Campaign ($) @$100/hr	Disposal Cost $/Year
Cu-67	R3 #1	25	10	106	300	8560
Ho-166	R3#1	25	1	106	300	7606
I-125	Gas Line	6	1	106	300	1906
I-131	R3 #2	10	5	106	300	3530
Lu-177	R3#2	10	1	106	300	3106
P-32	R3 #2	10	10	106	300	4060
Pd-103	R3 #2	10	2	106	300	3212
Re-186	R3 #1	25	5	106	300	8030
Sc-47	R3#1	25	1	106	300	7606
Sm-153	R3#1	25	5	106	300	8030
Various Research Isotopes	R3 #1 & #2	20	5	106	300	6530
Total		191	46			$62,176

5.3.2 Hardware Disposal Costs

The LIV hardware disposal will occur through two separate waste streams, one from the FFTF and another from the 325 Building. The target pins will be removed from the assembly duct in the IEM cell in the FFTF. The pins will be shipped to the 325 Building for processing, while the assembly duct will be placed in a waste container in the IEM cell for disposal.

5.3.2.1 IEM Cell Hardware Waste Stream

When the waste container is full it is transferred from the IEM cell into the Disposable Solid Waste Cask (DSWC) for burial on the Hanford Site. The waste containers currently used can hold the hardware from six target assemblies. It is assumed that two LIV assemblies will be processed per year, so the volume of one DSWC will be filled over a three-year period.

There are no RCRA designated hazardous materials in the LIV duct assembly hardware, so the DSWC is not considered mixed radioactive waste. Since the DSWC provides shielding within a secured container, the disposal cost is equivalent to that for low-level contact handled radioactive waste. The IEM cell hardware disposal costs are summarized in Table 5-9.

Table 5-9. IEM Cell Hardware Disposal Costs

DSWC Volume Cu Ft	Disposal Rate $/Cu Ft	DSWC Assembly Capacity	LIV Waste Throughput Assemblies/Yr	DSWC Procurement Cost $/Cask	Annual Disposal Cost $/Yr
561	$12.00	6	2	$100,000	$35,577

5.3.2.2 325 Building Hardware Waste Stream

The LIV pin cladding and the R3 carrier capsule will both be disposed of from the 325 Building. These components will be loaded into shielded waste containers and disposed of as low-level radioactive waste. The amount of waste materials and the annual cost of disposal are shown in Table 5-10.

Table 5-10. 325 Building Hardware Disposal Costs

LIV Pin Clad Volume per Assembly (Cu Ft)	LIV's Per year	R3 Carrier Capsule Volume per String (Cu Ft)	R3 Assembly Strings per year	Disposal Rate ($/Cu Ft)	Staff support Per assembly $(@ $100/hr)	Annual Disposal Cost ($/Year)
0.83	2	0.022	35	68	300	$11,208.8

5.3.3 Waste Disposal Summary

Table 5-11 summarizes the total costs associated with waste disposal.

Table 5-11. Waste Disposal Summary

LIV Chemical Processing Cost	R3 Chemical Processing Cost	IEM Cell Hardware Disposal Cost	325 Building Hardware Disposal Cost	Total Disposal Cost/year
$41,814	$56,724	$35,577	$11,208	$145,323

5.4 Transportation

Transportation costs will be incurred during the production and processing of medical isotopes. The irradiated targets will be transported within a shielded transport cask by tractor trailer from the FFTF to the 325 Building. After processing, the product isotopes will be transported from the 325 Building to a local airport for Air Express shipping. The customers will be responsible for shipping costs once the product isotopes are delivered to Air Express.

Both the LIV and the R3 irradiated targets will be loaded into approved shipping casks for transport to the 325 Building. For the LIV targets, the T-3 shipping cask will be used since it is compatible with both FFTF and the 325 Buildings, and is also compatible with the pin containers presently utilized in the IEM cell. Two T-3 casks are currently available for use. It has not yet been determined if the current license, written for irradiated fuel assembly transport, will be applicable for medical isotope target transport. Therefore, it is conservatively assumed, from a cost standpoint, that road closures would be utilized for on-site transport between FFTF and the 325 Building.

The R3 target strings will also be transported in an approved shipping cask. Most likely, the cask will be an integral part of the R3 system design, and its design and procurement cost will be included with the R3 system. Again, it is assumed that road closures will be utilized for transport of this cask from FFTF to the 325 Building.

Costs for transportation from the 325 Building to the Air Express loading dock are based on transportation costs presently being incurred in the Pacific Northwest National Laboratory's medical isotope production program. The total annual transportation cost estimates are shown in Table 5-12.

Table 5-12. Transportation Cost Summary

		Number of Transports per Year	**Cost per Transport ($)**	**Annual Transportation Cost ($)**
FFTF to 325 Building:	LIV	2	$5,000	$10,000
	R3	35	$5,000	$175,000
	I-125 carbon trap	6	$5,000	$30,000
325 Building to Air Express		246	$1,750	$430,500
			Total	$645,500

6.0 Cost and Schedule

6.1 Facilities and Equipment Costs

Detailed cost estimates of procurement and construction items required to initiate FFTF medical isotope production are summarized in 11 tables contained in the Appendix. The following is a high-level summary of the costs associated with laboratory facilities and equipment, descriptions of which are given in Sections 2.3 and 4 of this report:

• Procurement	$15,293,800
• Construction	7,449,300
• Engineering Design and Inspection	5,200,100
• Task Management	2,883,700
• Construction Management	893,900
• Permits	135,000
• Reactor Hardware and Fabrication	19,012,300
• Operational Readiness Review	337,500

The total cost estimated in 1996 dollars is therefore $51,205,600. A 35% contingency has been included in this cost estimate.

Prior to initiation of medical isotope production at FFTF, target materials for the isotopes that will be produced at the onset of operations must be purchased for the fabrication and functional testing of targets and radiation vehicles. Initial costs to purchase these materials are difficult to estimate because the price of many of the materials that will be used as targets varies considerably with the isotopic purity and the quantity that is purchased. Assuming a market penetration of at least 20% for the isotopes that are expected to be produced at the onset of FFTF operations, the initial procurement costs for target materials are expected to be in the range of $5 to $15 million (1996 dollars). Subsequent annual procurement costs for FFTF target materials (described in Section 6.2) are expected to be lower because many of the target materials will be retrieved during radiochemical processing of the radiation products and reutilized as targets for subsequent irradiations.

6.2 Production and Operating Costs

Annual production and operating costs are estimated using the amounts determined for Operations and Support from Chapter 5, together with costs estimated for target isotope materials and target assembly hardware, as detailed below.

6.2.1 Target Isotope Materials

Annual costs for target isotope materials are estimated based on the supply needed to make targets for the 'prototypical' target loading of the 20 product isotopes described in Section 2.5. It must be stressed that these cost figures are based on a bounding estimate that assumes a 100 % market penetration. Clearly, this will not be the case. A more realistic case would be to assume 20% of the total costs (about $3 million) shown in Table 6-1.

Some of the target materials are needed in multi-gram quantities. For these materials, costs were estimated assuming price discounts could be acquired from the currently advertised prices given in the DOE Isotope Production Program catalog. Discussions with various suppliers of the target materials indicated that substantial discounts, around 50%, could be offered provided that material purchase was assured by contractual obligation.

While not considered for these cost estimates, it is likely that the application of new technology, such as the plasma separation process, will reduce the cost of target isotope materials. This process distinguishes between different particle masses by their cyclotron frequency in a magnetic field. Because of the mass dependence of the cyclotron frequency, particles of different isotopic mass can be selectively separated. This process will allow isotopic separation at a cost about ten times less than those currently achieved with a calutron. Oak Ridge National Laboratory is planning operation of a plasma separator in the near future.

Several curies of Radium-226, the target material for producing Actinium-227 and Thorium-228/229, are expected to be available from DOE stockpiles for the cost of packaging and transportation. The transportation cost, including rental of an appropriate shipping cask, is estimated to be $175,000. This is a one-time charge and is included with capital costs.

Product isotopes that are formed by an (n,p) reaction, in which the product isotope is a different chemical element, are candidates for recycling the target material. The amount of target material available for recycling depends upon the 'burn-up' (atom %) of the target during irradiation. Of the product isotopes in the prototypical core loading, Actinium-227/Thorium-229, Copper-67, Iodine-131, Phosphorous-32, Scandium-47, Thorium-229 and Yttrium-91 show potential for economically recycling the target isotope. For these isotopes, it is assumed that 95% of the available target material, determined by burn-up rate and irradiation time, is recovered during chemical processing. The annual demand for the recycled isotopes represents the amount that would be purchased to supplement recycling.

6.2.2 Target Assembly Hardware

Material and fabrication costs for the LIV target hardware (assembly duct, inlet nozzle, handling socket, pin cladding and assembly hardware) are estimated to be $150,000 per assembly, based on previous experience in fabricating fuel and test assemblies during FFTF operation. Assuming two LIVs per year are fabricated, the cost would be $300,000 per year.

Table 6-1. Target Isotope Material Cost Summary

Product Isotope	Target Isotope	Annual Demand gm/yr	Cost $/gm	Annual Cost $
Ac-227/Th-229	Ra-226[a]	0	N/A	$0
Cd-109	Cd-108	5.1	$89,000	$457,460
Cu-67	Zn-67[a]	1.2	$23,845	$29,282
Gd-153	Natural Eu	166	$10	$1,657
Ho-166	Ho-165	0.1	$10	$1
I-125	Xe-124 (gas)[a]	.0073 Liter/Yr.	$83,162/Liter	$609
I-131	Te-130[a]	10.4	$2,180	$22,751
Ir-192	Ir-191	556.2	$50	$27,808
Lu-177	Lu-175	0.0027	$10,430	$28
P-32	S-32	5.9	$207	$1,221
Pd-103	Pd-102	25.2	$433,885	$10,943,294
Re-186	Re-185	13.2	$10,340	$136,272
Sc-47	Ti-47[a]	17.6	$10,764	$189,144
Sm-145	Sm-144	11.0	$22,050	$242,411
Sm-153	Sm-153	0.00614	$3,100	$19
Sr-85	Sr-84	0.0034	$2,500	$8
Sr-89	Sr-88	2.6	$1,250	$3,241
W-188	W-186	1601.7	$830	$1,329,399
Y-91	Zr-91[a]	100.3	$11,561	$1,159,701
TOTAL			(Assuming 100% Market Penetration) (Assuming 20% Market Penetration)	$14,544,299 $2,908,859

(a) It is assumed that recycling of this target isotope will occur. Annual demand is the amount of isotope required to make up for irradiation burn-up of the target, as well as a 5% loss of the remaining available target isotope during the recycling process.

Material and fabrication costs for the R3 capsule chain is estimated to be $6,200 per target chain. Assuming that 35 irradiation cycles per year are run on the two R3 vehicles, the cost would be $217,000 per year.

6.2.3 Total Production and Operating Cost

The annual production and operating costs summarized in Table 6-2 are based on the prototypical target loading of two R3 assemblies and one LIV assembly, and assume a 100% market penetration for each of the 20 primary isotope products that will be produced at the onset of FFTF operations. It is clear that the total cost is driven primarily by that for the target isotope materials. For a smaller market demand, the annual operating cost will be reduced accordingly.

Table 6-2. Annual Production and Operating Cost

	Annual Cost ($)
Staffing	$9,160,100
Lab Analysis	$492,000
Transportation	$645,500
Waste Handling	$145,323
Target Isotope Materials	$14,544,271
LIV Assembly Materials	$300,000
R3 Assembly Materials	$217,000
Total	$25,472,905

6.3 Schedule

The overall schedule for implementing the medical isotopes production task at FFTF is consistent with that for the primary tritium mission. All planning documents, engineering designs, and other deliverables requested by DOE are expected to be completed in time for key decisions to be made on the development of facilities and equipment required to initiate medical isotopes production at FFTF during FY 2002. Figure 6-1 shows the time line for major activities leading to a capital construction project in FY 2000 - FY 2001 and a startup of reactor operations in FY 2002.

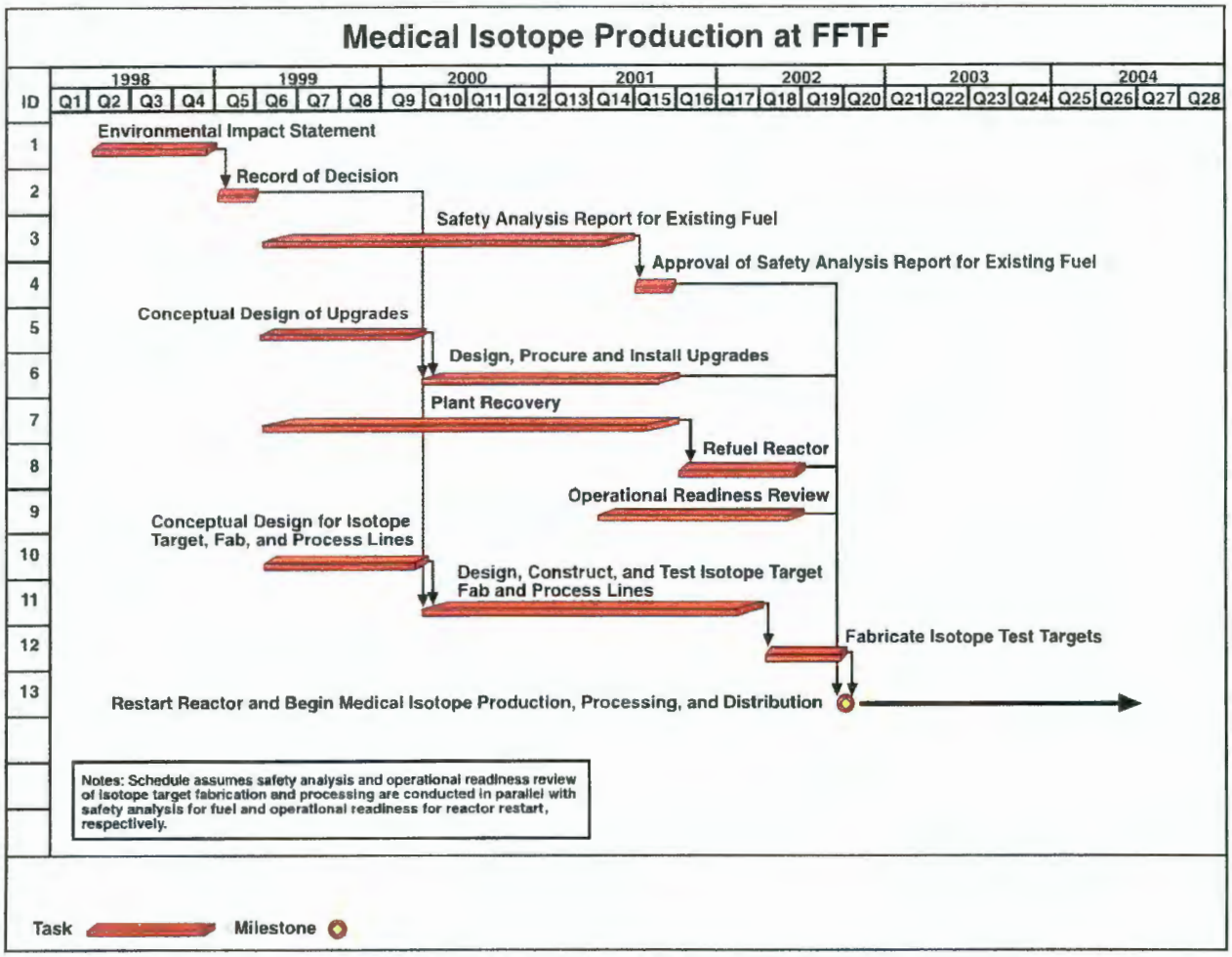

Figure 6-1. Time line showing major activities leading to a medical isotopes production mission at FFTF.

Three main elements of work leading to initiation of medical isotopes production during FY 1002 are the following:

- Following a DOE Record of Decision, anticipated by the first quarter of FY 1999, final conceptual designs will be completed for facilities and equipment required to fabricate and process medical isotope targets. These activities include the final engineering design of two rapid radioisotope retrieval (R3) systems for production of short-lived isotopes during full-power reactor operations (described in Section 2.3). In addition, final engineering designs will be completed for the upgrade of laboratory facilities in FMEF (target assembly), the 306E Building (target assembly), and the 325 Building (target assembly and processing). These facility requirements are described in Section 4 and the costs are summarized in Section 6.1.

- The construction and testing of equipment, including the two R3 systems, and the upgrades of laboratory facilities, will be carried out in FY 2000 and FY 2001 (work is scheduled to begin in the second quarter of FY 2000 with completion by the end of the first quarter of FY 2002).

- Fabrication of isotope targets and verification of operational readiness for medical isotope production will occur during the second and third quarters of FY 2002.

7.0 Market Forecast

There have been various market studies performed over the last decade. In general, the medical isotope market has not experienced a rapid growth due primarily to the fact that key isotopes needed for research, clinical trials, and eventual widespread medical applications are simply not available to the medical community. This problem extends to 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. Development of the market for medical isotopes depends upon their availability in smaller quantities to perform necessary clinical trials. Only when these trials are completed, and the isotope is approved by the FDA for routine clinical use, can the market grow.

7.1 Recent Studies

Table 7-1 provides a brief comparison of recent studies on medical isotope needs that were conducted by various groups. All of the studies predict growth of this industry in the upcoming years. There is some variation in the predicted growth rates, which is the result of different modeling assumptions, but there is clearly a consensus for growth. As more and more radiopharmaceuticals clear through pre-clinical and human trials and eventually obtain FDA approval, growth rate predictions will become better defined. The availability of the FFTF is essential for providing as many isotopes as possible during these early clinical trials.

Frost and Sullivan has just completed the most detailed medical isotopes market study performed to date. They have unmatched experience in performing analysis of health care markets and have completed numerous studies related to radiopharmaceuticals during the last few years. Considering their vast experience, their unique ability to draw on secondary resources, and the timeliness of their recent study, the Frost and Sullivan data should be the most accurate representation available.

Frost and Sullivan estimate that the sales of diagnostic radiopharmaceutical agents is expected to grow from $530 million in 1996 to about $17 billion in 2020. For therapeutic agents, which has a much smaller share of the pharmaceutical market, the growth in demand was projected to grow at an even faster pace. For therapeutic radiopharmaceuticals, sales revenues are expected to grow from $48 million in 1996 to about $6 billion in 2020. Frost and Sullivan's assumptions on the therapeutic market growth are extremely conservative and assume that even in the year 2020, less than 0.5% of available patients in the U.S. will receive therapeutic radiopharmaceuticals.

Table 7-1. Studies of Medical Isotope Production

Study	Market Information and Study Conclusions
FFTF Medical Isotope Market Study (Frost and Sullivan 1997)	Most recent and detailed study available. Current radioisotope market growth is at 5-8% per year. The study predicts the market growth rate to increase to at least 15% as new radiopharmaceutical agents for oncology applications come to market. Diagnostic and therapeutic retail market value is estimated to reach $17 billion and $6 billion, respectively, by the year 2020. The study also clearly defines a need for increased production capacity to not only meet the demand in the therapeutic market but also to help stimulate this demand by providing a reliable, long term supply to researchers and radiopharmaceutical companies.
Scoping Assessment on Medical Isotope Production at the FFTF (Scott 1996)	This study clearly states the case for increased production capacity in the U.S. This need is based on reducing overall costs of the health care system by utilizing medical isotopes in therapy and by keeping high-tech industry in the U.S. The study estimates FFTF radioisotope production revenues in excess of $100 million per year based on capturing 50% of the U.S. market for seven different isotopes. This figure is based on current pricing structure for these isotopes, patient numbers to be treated, and dosage of the radiopharmaceutical.
Isotopes for Medicine and the Life Sciences (Institute of Medicine 1995)	References studies by Tulane University, Landis, and Arthur Anderson. This study leans towards the conservative side of market estimates. According to this study, current production demands are being handled by existing reactors and accelerators. No market projections are provided, but the conclusions state that if therapeutic isotopes become successful, current North American production facilities will be inadequate to meet the demand.
U.S. DOE Isotope Production and Distribution Program Market Analysis Update (Arthur Anderson 1994)	Predicts growth rates of 5-10% per year. This study placed the worldwide wholesale market for radioisotopes at $92-$112 million in 1994 with a growth rate of approximately 8% per year. This growth rate does not take into account the emergent therapeutic market, but the study notes that this is the fastest growing segment of the isotope market and could surpass the diagnostic market.
Evaluation of the FFTF as a Multi-mission Reactor (John Landis et al. 1993)	This study evaluates the FFTF in a multi-mission capacity and contends that revenues of $20-$40 million per year certainly seem possible by 2003. The study assumed that the FFTF could not reach its full market potential in medical isotopes due to conflicts with other missions while serving as a multi-mission reactor.
The FFTF Business Plan (A.B. Freeman School of Business and Tulane University 1993)	Predicts a growth rate curve (averaging 14.1%) that was modeled on the growth of similar industries. This study assumes FFTF wholesale market share of up to 22% (after 25 years of operation) with a value of $515 million/yr (2017). This study also assumes a multi-mission role for the FFTF which results in a slow market penetration during the first 5-10 years of operation.

7.2 FFTF Market Potential

Challenges in estimating the exact size of the market potential for FFTF medical isotopes 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.

Frost and Sullivan estimated therapeutic market demand based on derived patient populations for 19 disease indications. When these disease indications and patient populations are matched with possible isotopes for treatment along with their associated therapeutic doses, the demand forecast for each isotope can be estimated. A summary of these data, along with the annual isotope delivery capacity for three in-core positions in the FFTF, is shown in Table 7-2.

Total costs and revenues for 20 isotopes are given in Table 7-3. This table provides summary calculations based on capturing 20%, 50%, and 100% of the U.S. market (2002) for these isotopes. It is assumed that operations costs will remain the same regardless of the production levels for these 20 isotopes, which is an assumption that requires further evaluation. Because of this assumption, the annual net earnings shown in Table 7-3 should be regarded as conservative estimates.

The FFTF has certain production advantages (Section 2.1.4) that will help to leverage it into the market mainstream. Considering these advantages, an initial market share of 20% of the 20 isotopes listed in Table 7-2 is certainly achievable. The demand forecasts for any one particular isotope are difficult to calculate, but there is a high confidence in the overall market profile portrayed by the summary data.

The above data are based solely on using the FFTF to make medical isotopes which, with the exception of Gd-153 and some percentage of I-125, are therapeutic isotopes. The analysis does not take into account possible earnings generated by diagnostic, research, or commercial isotopes. Part of the strategic recommendations in the recent Frost and Sullivan report were that the FFTF should not focus solely on medical isotope production, but should also consider producing radioisotopes for other applications. Frost and Sullivan indicated that there is significant potential for the FFTF to enter the market as a supplier of non-medical radioisotopes. The intent of this specific report, however, has been to look at the technical and economic feasibility of producing medical isotopes at FFTF. Production of non-medical radioisotopes would clearly improve the overall earning potential, but further studies are required to evaluate the feasibility of producing these isotopes at FFTF.

Several anti-nuclear groups have argued that the FFTF is not needed for medical isotope production. In general, it can be said that there is currently not a strong need for medical isotope production at FFTF. However, there are clear instances in which there is a current shortage of medical isotopes. Clinical trials treating lymphoma with Cu-67 at the University of California's Davis Medical Center had to be stopped because of the short supply of this isotope. Prostate cancer patients across the U.S. have been unable to get badly needed therapy using Pd-103 because it is in critically short supply. Currently, the

Table 7-2. FFTF Annual Delivery Capacity for Three In-Core Positions

Product Isotope	Annual Patient Delivery Capacity	Predicted Annual U.S. Demand in 2002	Vehicle Percentage Used to Meet Demand Figures**
Ac-227	9.0E+04	1.7E+02	0.19%
Cd-109	2.0E+05	4.0E+01*	0.02%
Cu-67**	1.1E+01	1.0E+03	45.00%
Gd-153	1.9E+05	6.0E+02*	0.32%
Ho-166	4.7E+05	4.3E+01	0.01%
I-125	1.7E+04	2.2E+03	13.27%
I-131**	4.2E+03	5.6E+03	80.00%
Ir-192	2.3E+07	7.7E+04	0.33%
Lu-177	5.0E+06	7.1E-02	<0.01%
P-32	1.8E+03	4.7E+01	2.66%
Pd-103	9.3E+04	2.5E+03	2.72%
Re-186	1.5E+06	6.0E+03	0.39%
Sc-47	9.3E+02	5.0E+02*	54.02%
Sm-145	4.2E+05	1.0E+02*	0.02%
Sm-153	2.1E+07	5.9E+01	<0.01%
Sr-85	1.4E+06	5.0E+02*	0.04%
Sr-89	3.7E+04	4.1E+00	0.01%
Th-229**	4.8E-01	3.7E+02	0.66%
W-188	6.1E+04	1.8E+03	2.90%
Y-91	6.4E+02	1.0E+02*	15.54%
Totals		LIV	20.04%
		R3 (2 Assemblies)	92.41%
		Gas Line	13.27%

* Figures are estimated high due to limited forecast data for these isotopes.

** Cu-67 and I-131 production rates cannot meet the anticipated U.S. demand with two R3 target assemblies, so their production numbers have been reduced to allow space in the R3 assemblies for producing other short-lived isotopes. Th-229 production has been limited due to limited target (Ra-226) material constraints.

Table 7-3. Estimated Annual Net Earnings Versus Market Penetration

Market Penetration	Annual Operating Costs	Annual Target Costs	Annual Revenue	Annual Net Earnings
20%	$10,929,000	$2,909,000	$18,819,000	$4,981,000
50%	$10,929,000	$7,272,000	$47,046,000	$28,845,000
100%	$10,929,000	$14,544,000	$94,093,000	$68,620,000

use of therapeutic radioisotopes is in its infancy. As this area grows, it will require a very large supply of a variety of medical isotopes. In the long term, if short-lived reactor-produced radionuclides become important for treating major diseases such as cancer, the present number and condition of isotope production reactors in North America will be inadequate.[a]

(a) Adelstein, S. J., et al., National Institute of Medicine report on "Isotopes for Medicine and the Life Sciences." National Academy Press, Washington, D.C. (1995).

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8.0 Conclusions

The analysis of technical and economic factors associated with the production of medical isotopes at FFTF, coupled with independent projections by Frost and Sullivan, Inc.[a] of the market demand for these isotopes during the first two decades of the 21st century, strongly support the feasibility of initiating a dual FFTF tritium/medical isotopes mission. The results of studies described in this report demonstrate that the FFTF, because of its high neutron flux and flux-tailoring capability, can serve an essential role over a 20-30 year period of supplying medical isotopes that are either not available, or not available in adequate quantities, from other U.S. sources. These isotopes include many of the beta and alpha emitters that are expected to play an increasingly important role in the treatment of cancer and other life-threatening or debilitating diseases such as brain disorders, heart disease and arthritis.

The technical feasibility of jointly producing at least 30 medical isotopes in parallel with the primary FFTF tritium production mission has been confirmed. In addition, it has been established that sufficient capacity exists within the FFTF reactor core region to begin the production of 20 of these isotopes at the onset of operations in year 2002. Using realistic estimates of the number of patients that would be treated in the United States during the period 2002-2020, it has been concluded that: 1) sufficient revenue will be generated by the sales of medical isotopes to cover the annual costs of production and processing at the onset of FFTF operations in year 2002; 2) after 10 years of operation (i.e., in year 2012), it is projected that approximately 50-60% of the cost of operating FFTF can be subsidized from the sale of medical isotopes; 3) by year 2015 to 2020 it is anticipated that FFTF can be operated in a full-cost recovery mode as a major source of medical isotopes for both the U.S. and foreign markets.

An important element of the feasibility of producing medical isotopes at FFTF is the previous demonstration of this capability during the decade of prior FFTF operations during the period 1982-1992. In addition, the facilities used at that time are still available and can be upgraded in order to accommodate an expanded medical isotopes mission over the coming 20 to 30 year period. The cost of performing these facility upgrades and fabricating state-of-the-art FFTF irradiation vehicles, which totals approximately $50 million, is reasonable in the context of the large annual revenues that will result from medical isotope sales beginning in year 2002. These sales revenues are expected to grow at an annual rate of 7 to 15% on the basis of conclusions drawn from the Frost and Sullivan medical isotopes market study. This study also verified previous market studies in finding that FFTF is fully capable of producing large quantities of a variety of medical isotopes that will be needed to meet the U.S. requirements over the coming 20-30 year period.

(a) FFTF Medical Isotopes Market Study (2001-2020), Frost and Sullivan, Inc., Mountain View, California; Pacific Northwest National Laboratory report no. PNNL-11774, Richland, Washington (1997).

In summary, the FFTF and associated staff and laboratory facilities at the Hanford Site are capable of supporting a cost-effective program of medical isotope production in parallel with a primary tritium production mission. In view of the growing U.S. demand for therapeutic quantities of a wide variety of reactor-produced isotopes, it is critical to move forward and capitalize on this unique opportunity to establish FFTF as a major new U.S. supply of medical radioisotopes.

Appendix

Cost Estimates for Facilities Modifications and Equipment for Medical Isotopes Production at FFTF and Radiochemical Processing

(Tables A-1 through A-11)

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Table A-1. Summary - Facilities and Equipment Estimates for Medical Isotopes, 1996 $s

Cost Element	Direct. Total	Escalation %	Escalation	Direct+ Escal	Contingency %	Contingency	Total
300 AREA & FMEF COSTS							
TASK MANAGEMENT (10% of total)	$2,136,081	0%	$0	$2,136,081	35%	$747,628	$2,883,709
ENGINEERING, DESIGN & INSPECTION							
Title I & II Design (12% of Proc &Constr)	$2,101,063	0%	$0	$2,101,063	35%	$735,372	$2,836,435
Title III Eng & Insp (10% of Proc & Constr)	$1,750,886	0%	$0	$1,750,886	35%	$612,810	$2,363,696
SUBTOTAL ED&I	$3,851,949		$0	$3,851,949		$1,348,182	$5,200,131
PROCUREMENT							
Sheet 2: 325 Bldg, 500 Corridor	$7,673,700	0%	$0	$7,673,700	35%	$2,685,795	$10,359,495
Sheet3: 325 Bldg, Room 30A	$159,500	0%	$0	$159,500	35%	$55,825	$215,325
Sheet 4: 325A, A-Cell and C-Cell	$33,500	0%	$0	$33,500	35%	$11,725	$45,225
Sheet 5: 325A, Room 603	$39,000	0%	$0	$39,000	35%	$13,650	$52,650
Sheet 6: 325 Bldg Office Mods	$35,000	0%	$0	$35,000	35%	$12,250	$47,250
Sheet 7: 306E Target Fab	$1,203,000	0%	$0	$1,203,000	35%	$421,050	$1,624,050
Sheet 8: Recycle Target Fab, Rm tbd	$760,000	0%	$0	$760,000	35%	$266,000	$1,026,000
Sheet 9: 306E Gas Tag Fabrication	$310,000	0%	$0	$310,000	35%	$108,500	$418,500
Sheet 11: FMEF LIV Target Assembly	$1,115,000	0%	$0	$1,115,000	35%	$390,250	$1,505,250
SUBTOTAL PROCUREMENT	$11,328,700		$0	$11,328,700		$3,965,045	$15,293,745
CONSTRUCTION							
Construction Mgmt (12% of Constr)	$662,160	0%	$0	$662,160	35%	$231,756	$893,916
Sheet 2: 325 Bldg, 500 Corridor	$3,229,500	0%	$0	$3,229,500	35%	$1,130,325	$4,359,825
Sheet3: 325 Bldg, Room 30A	$476,500	0%	$0	$476,500	35%	$166,775	$643,275
Sheet 4: 325A, A-Cell and C-Cell	$285,000	0%	$0	$285,000	35%	$99,750	$384,750

Table A-1. (contd)

Cost Element	Direct. Total	Escalation %	Escalation	Direct+ Escal	Contingency %	Contingency	Total
Sheet 5: 325A, Room 603	$80,000	0%	$0	$80,000	35%	$28,000	$108,000
Sheet 6: 325 Bldg Office Mods	$132,000	0%	$0	$132,000	35%	$46,200	$178,200
Sheet 7: 306E Target Fab	$560,000	0%	$0	$560,000	35%	$196,000	$756,000
Sheet 8: Recycle Target Fab, Rm tbd	$525,000	0%	$0	$525,000	35%	$183,750	$708,750
Sheet 9: 306E Gas Tag Fabrication	$60,000	0%	$0	$60,000	35%	$21,000	$81,000
Sheet 11: FMEF LIV Target Assembly	$170,000	0%	$0	$170,000	35%	$59,500	$229,500
Subtotal Construction	$5,518,000		$0	$5,518,000		$1,931,300	$7,449,300
SUBTOTAL PROC, CONSTR & CM	$17,508,860		$0	$17,508,860		$6,128,101	$23,636,961
TOTAL ED&I, PROC, CONSTR & CM	$21,360,809		$0	$21,360,809		$7,476,283	$28,837,092
PERMITS: NESHAPS, NOCs,	$100,000	0%	$0	$100,000	35%	$35,000	$135,000
OPERATIONAL READINESS REVIEW	$250,000	0%	$0	$250,000	35%	$87,500	$337,500
SUBTOTAL 300 AREA & FMEF	$23,846,890		$0	$23,846,890		$8,346,412	$32,193,302
Sheet 10: Reactor HDW & Isotope Casks	$14,083,200	0%	$0	$14,083,200	35%	$4,929,120	$19,012,320
TOTAL MEDICAL ISOTOPES	$37,930,090		$0	$37,930,090		$13,275,532	$51,205,622

Table A-2. 325 Building, 500 Corridor Labs

Cost Element	Quantity	Unit Price	Direct Total	Escalation %	Escalation	Direct+ Escal	Contingency %	Contingency	Total
325 BLDG 500 CORRIDOR									
PROCUREMENT									
FACILITY EQUIPMENT (10 labs)									
Casework, Base & Wall, Linear ft.	800	$500	$400,000	0%	$0	$400,000	35%	$140,000	$540,000
Small Hot Cells	20	$200,000	$4,000,000	0%	$0	$4,000,000	35%	$1,400,000	$5,400,000
Shielded Gloveboxes	20	$80,000	$1,600,000	0%	$0	$1,600,000	35%	$560,000	$2,160,000
4' Fume Hoods	20	$6,000	$120,000	0%	$0	$120,000	35%	$42,000	$162,000
5' Laminar Flow Hoods	20	$8,000	$160,000	0%	$0	$160,000	35%	$56,000	$216,000
PROCESS EQUIPMENT (10 labs)									
Cutters	20	$5,000	$100,000	0%	$0	$100,000	35%	$35,000	$135,000
Dissolvers	20	$2,000	$40,000	0%	$0	$40,000	35%	$14,000	$54,000
Cozzoli Filling Machine, F400X	20	$22,000	$440,000	0%	$0	$440,000	35%	$154,000	$594,000
Evaporators	20	$2,000	$40,000	0%	$0	$40,000	35%	$14,000	$54,000
Ion Exchange Columns	20	$2,000	$40,000	0%	$0	$40,000	35%	$14,000	$54,000
Pumps	30	$800	$24,000	0%	$0	$24,000	35%	$8,400	$32,400
Glassware	1	$30,000	$30,000	0%	$0	$30,000	35%	$10,500	$40,500
Portable ICP	1	$200,000	$200,000	0%	$0	$200,000	35%	$70,000	$270,000
REAGENT PREP LAB EQPT, Rm 524									
Casework, Linear ft.	100	$500	$50,000	0%	$0	$50,000	35%	$17,500	$67,500
Flamable Storage Cabs	3	$400	$1,200	0%	$0	$1,200	35%	$420	$1,620
6' Fume Hoods	2	$6,000	$12,000	0%	$0	$12,000	35%	$4,200	$16,200
6' Biohazzard Laminar Flow Hoods	2	$15,000	$30,000	0%	$0	$30,000	35%	$10,500	$40,500
Autoclaves	3	$25,000	$75,000	0%	$0	$75,000	35%	$26,250	$101,250
Depyrogen Oven for glassware	2	$1,500	$3,000	0%	$0	$3,000	35%	$1,050	$4,050
Glassware	1	$7,500	$7,500	0%	$0	$7,500	35%	$2,625	$10,125

Table A-2. (contd)

Cost Element	Quantity	Unit Price	Direct Total	Escalation %	Escalation	Direct+ Escal	Contingency %	Contingency	Total
FINAL PRODUCT TEST LAB, Rm 419									
Casework, Linear ft.	100	$500	$50,000	0%	$0	$50,000	35%	$17,500	$67,500
6' Fume Hoods	2	$6,000	$12,000	0%	$0	$12,000	35%	$4,200	$16,200
6' Biohazzard Laminar Flow Hoods	2	$15,000	$30,000	0%	$0	$30,000	35%	$10,500	$40,500
VWR Gen Purpose Incubators	4	$2,000	$8,000	0%	$0	$8,000	35%	$2,800	$10,800
Pyrogen Test Kits	20	$3,000	$60,000	0%	$0	$60,000	35%	$21,000	$81,000
Water Injectors	20	$3,000	$60,000	0%	$0	$60,000	35%	$21,000	$81,000
Microbiol Testing Mtls	20	$3,000	$60,000	0%	$0	$60,000	35%	$21,000	$81,000
Particle counters	3	$7,000	$21,000	0%	$0	$21,000	35%	$7,350	$28,350
SUBTOTAL PROCUREMENT			$7,673,700		$0	$7,673,700		$2,685,795	$10,359,495
CONSTRUCTION									
Relocate Displaced Staff	7	$2,500	$17,500	0%	$0	$17,500	35%	$6,125	$23,625
Bldg Mods reqd for relocated staff	7	$50,000	$350,000	0%	$0	$350,000	35%	$122,500	$472,500
Demolition	12	$55,000	$660,000	0%	$0	$660,000	35%	$231,000	$891,000
Lab Mods: Floor, Walls & Ceiling	12	$50,000	$600,000	0%	$0	$600,000	35%	$210,000	$810,000
Structural Upgrades in Basement	1	$250,000	$250,000	0%	$0	$250,000	35%	$87,500	$337,500
Off-gas Treatment, Silver Zeolite	1	$10,000	$10,000	0%	$0	$10,000	35%	$3,500	$13,500
Off-gas Treatment, Chilled Mol Sieve	3	$10,000	$30,000	0%	$0	$30,000	35%	$10,500	$40,500
HVAC and Utilities Mods	12	$40,000	$480,000	0%	$0	$480,000	35%	$168,000	$648,000
Facility Equipment Installation	12	$30,000	$360,000	0%	$0	$360,000	35%	$126,000	$486,000
Process Equipment Installation	20	$5,000	$100,000	0%	$0	$100,000	35%	$35,000	$135,000
Analytical Equipment Installation	1	$0	$0	0%	$0	$0	35%	$0	$0
Reagent Prep Lab Eqpmt Installation	1	$30,000	$30,000	0%	$0	$30,000	35%	$10,500	$40,500
Final Product Test Lab Eqpmt Installation	1	$30,000	$30,000	0%	$0	$30,000	35%	$10,500	$40,500
Construction Waste Disposal	12	$15,000	$180,000	0%	$0	$180,000	35%	$63,000	$243,000
RCT Support	12	$11,000	$132,000	0%	$0	$132,000	35%	$46,200	$178,200

Table A-2. (contd)

Cost Element	Quantity	Unit Price	Direct Total	Escalation %	Escalation	Direct+ Escal	Contingency %	Contingency	Total
SUBTOTAL CONSTRUCTION			$3,229,500		$0	$3,229,500		$1,130,325	$4,359,825
SUBTOTAL 325 BLDG, 500 CORRIDOR			$10,903,200		$0	$10,903,200		$3,816,120	$14,719,320

Table A-3. 325 Building, Room 30A Costs

Cost Element	Quantity	Unit Price	Direct Total	Escalation %	Escalation	Direct+ Escal	Contingency %	Contingency	Total
BASEMENT: ROOM 30A									
PROCUREMENT									
FACILITY EQUIPMENT									
Fab Airlock Tranfer Ports	3	$5,000	$15,000	0%	$0	$15,000	35%	$5,250	$20,250
PROCESS EQUIPMENT									
Hot & Recycle Target Fab:									
Sampling/Weighing	1	$2,000	$2,000	0%	$0	$2,000	35%	$700	$2,700
Muffle Furnace	1	$2,000	$2,000	0%	$0	$2,000	35%	$700	$2,700
Grinder	1	$1,500	$1,500	0%	$0	$1,500	35%	$525	$2,025
Blender	1	$5,000	$5,000	0%	$0	$5,000	35%	$1,750	$6,750
Seives	2	$20,000	$40,000	0%	$0	$40,000	35%	$14,000	$54,000
Small Pellet Press	1	$50,000	$50,000	0%	$0	$50,000	35%	$17,500	$67,500
Cleaning Eqpt	1	$10,000	$10,000	0%	$0	$10,000	35%	$3,500	$13,500
Misc Fixtures	1	$5,000	$5,000	0%	$0	$5,000	35%	$1,750	$6,750
Isotope Processing									
Cutter	1	$1,000	$1,000	0%	$0	$1,000	35%	$350	$1,350
Cozzoli Filling Machine, F400X	1	$22,000	$22,000	0%	$0	$22,000	35%	$7,700	$29,700
Dissolver	1	$1,500	$1,500	0%	$0	$1,500	35%	$525	$2,025
Precipitator/filter	1	$1,500	$1,500	0%	$0	$1,500	35%	$525	$2,025
Ion Exchange Columns	1	$500	$500	0%	$0	$500	35%	$175	$675
Carbonate Precipitator	1	$2,500	$2,500	0%	$0	$2,500	35%	$875	$3,375
SUBTOTAL PROCUREMENT		$129,500	$159,500		$0.0	$159,500.0		$55,825.0	$215,325.0
CONSTRUCTION									
Relocate LSL II Cask to 325	1	$42,000	$42,000	0%	$0	$42,000	35%	$14,700	$56,700
Relocate 331 cask to 325	1	$32,000	$32,000	0%	$0	$32,000	35%	$11,200	$43,200

Table A-3. (contd)

Cost Element	Quantity	Unit Price	Direct Total	Escalation %	Escalation	Direct+ Escal	Contingency %	Contingency	Total
Install & modify small Glovebox	1	$25,000	$25,000	0%	$0	$25,000	35%	$8,750	$33,750
Install & modify large Glovebox	1	$40,000	$40,000	0%	$0	$40,000	35%	$14,000	$54,000
Relocate Exst Hot Cell	1	$200,000	$200,000	0%	$0	$200,000	35%	$70,000	$270,000
Install Transfer Ports	3	$10,000	$30,000	0%	$0	$30,000	35%	$10,500	$40,500
Process Equipment Installation	1	$15,000	$15,000	0%	$0	$15,000	35%	$5,250	$20,250
Install Radon Holdup Syst.	1	$50,000	$50,000	0%	$0	$50,000	35%	$17,500	$67,500
Buy & Install Rad Area Monitors	1	$30,000	$30,000	0%	$0	$30,000	35%	$10,500	$40,500
Construction Waste Disposal	1	$2,500	$2,500	0%	$0	$2,500	35%	$875	$3,375
RCT Support	1	$10,000	$10,000	0%	$0	$10,000	35%	$3,500	$13,500
SUBTOTAL CONSTRUCTION		$456,500	$476,500		$0.0	$476,500.0		$166,775.0	$643,275.0
SUBTOTAL ROOM 30A		$586,000	$636,000		$0.0	$636,000.0		$222,600.0	$858,600.0

Table A-4. 325A Building, A-Cell and C-Cell

Cost Element	Quantity	Unit Price	Direct Total	Escalation %	Escalation	Direct+ Escal	Contingency %	Contingency	Total
325A: A-CELL AND C-CELL									
PROCUREMENT									
FACILITY EQUIPMENT									
A-Cell Load-in Air Lock & Ports/by others	0	$0	$0	0%	$0	$0	35%	$0	$0
PROCESS EQUIPMENT									
Cutter	1	$2,500	$2,500	0%	$0	$2,500	35%	$875	$3,375
Dissolver	1	$2,000	$2,000	0%	$0	$2,000	35%	$700	$2,700
Separations	1	$2,000	$2,000	0%	$0	$2,000	35%	$700	$2,700
Band-Displ Cation Exch Chromatography	1	$15,000	$15,000	0%	$0	$15,000	35%	$5,250	$20,250
Zinc Cation Exchange Columns	1	$2,000	$2,000	0%	$0	$2,000	35%	$700	$2,700
Miscellaneous in-cell eqpt.	1	$10,000	$10,000	0%	$0	$10,000	35%	$3,500	$13,500
SUBTOTAL PROCUREMENT			$33,500		$0	$33,500		$11,725	$45,225
CONSTRUCTION									
Demolition & Clean-up of A- and C-Cells	1	$150,000	$150,000	0%	$0	$150,000	35%	$52,500	$202,500
Hot Cell Utilities Mods	1	$25,000	$25,000	0%	$0	$25,000	35%	$8,750	$33,750
Process Equipment Installation	1	$50,000	$50,000	0%	$0	$50,000	35%	$17,500	$67,500
Construction Waste Disposal	1	$25,000	$25,000	0%	$0	$25,000	35%	$8,750	$33,750
RCT Support	1	$35,000	$35,000	0%	$0	$35,000	35%	$12,250	$47,250
SUBTOTAL CONSTRUCTION			$285,000		$0	$285,000		$99,750	$384,750
SUBTOTAL 325A: A-CELL AND C-CELL			$318,500		$0	$318,500		$111,475	$429,975

Table A-5. 325A Building, Room 603

Cost Element	Quantity	Unit Price	Direct Total	Escalation %	Escalation	Direct+ Escal	Contingency %	Contingency	Total
325A: ROOM 603									
PROCUREMENT									
FACILITY EQUIPMENT									
Load-in Ports for Exst Shielded Glovebox	1	$2,500	$2,500	0%	$0	$2,500	35%	$875	$3,375
PROCESS EQUIPMENT									
Cozzoli Filling Machine, F400X	1	$22,000	$22,000	0%	$0	$22,000	35%	$7,700	$29,700
Precipitator	1	$2,500	$2,500	0%	$0	$2,500	35%	$875	$3,375
Calciner	1	$2,000	$2,000	0%	$0	$2,000	35%	$700	$2,700
Pellet Press	0	$10,000	$0	0%	$0	$0	35%	$0	$0
Miscellaneous eqpt.	1	$10,000	$10,000	0%	$0	$10,000	35%	$3,500	$13,500
SUBTOTAL PROCUREMENT			$39,000		$0	$39,000		$13,650	$52,650
CONSTRUCTION									
Clean out of existing Shielded Glovebox	1	$35,000	$35,000	0%	$0	$35,000	35%	$12,250	$47,250
Process Equipment Installation	1	$20,000	$20,000	0%	$0	$20,000	35%	$7,000	$27,000
Construction Waste Disposal	1	$15,000	$15,000	0%	$0	$15,000	35%	$5,250	$20,250
RCT Support	1	$10,000	$10,000	0%	$0	$10,000	35%	$3,500	$13,500
SUBTOTAL CONSTRUCTION			$80,000		$0	$80,000		$28,000	$108,000
SUBTOTAL 325A: ROOM 603			$119,000		$0	$119,000		$41,650	$160,650

Table A-6. 325 Building Office Mods

Cost Element	Quantity	Unit Price	Direct Total	Escalation %	Escalation	Direct+ Escal	Contingency %	Contingency	Total
325 BLDG OFFICE MODS									
PROCUREMENT									
FACILITY EQUIPMENT									
Furnishings	1	$25,000	$25,000	0%	$0	$25,000	35%	$8,750	$33,750
Copy Machines	2	$5,000	$10,000	0%	$0	$10,000	35%	$3,500	$13,500
SUBTOTAL PROCUREMENT			$35,000		$0	$35,000		$12,250	$47,250
CONSTRUCTION									
Relocate Displaced Staff	1	$0	$0	0%	$0	$0	35%	$0	$0
Bldg Mods reqd for relocated staff	1	$0	$0	0%	$0	$0	35%	$0	$0
Demolition	1	$50,000	$50,000	0%	$0	$50,000	35%	$17,500	$67,500
Arch. Mods: Floor, Walls & Ceiling	1	$50,000	$50,000	0%	$0	$50,000	35%	$17,500	$67,500
HVAC and Utilities Mods	1	$20,000	$20,000	0%	$0	$20,000	35%	$7,000	$27,000
Facility Equipment Installation	1	$2,000	$2,000	0%	$0	$2,000	35%	$700	$2,700
Construction Waste Disposal	1	$5,000	$5,000	0%	$0	$5,000	35%	$1,750	$6,750
RCT Support	1	$5,000	$5,000	0%	$0	$5,000	35%	$1,750	$6,750
SUBTOTAL CONSTRUCTION			$132,000		$0	$132,000		$46,200	$178,200
SUBTOTAL 325 BLDG, OFFICE MODS			$167,000		$0	$167,000		$58,450	$225,450

Table A-7. Isotope Target Fabrication -306E Building

Cost Element	Quantity	Unit Price	Direct Total	Escalation %	Escalation	Direct+ Escal	Contingency %	Contingency	Total
306E TARGET FAB									
PROCUREMENT									
FACILITY EQUIPMENT									
6' Fume Hoods	2	$8,000	$16,000	0%	$0	$16,000	35%	$5,600	$21,600
Product Recpt Glovebox, 4', unshielded	2	$25,000	$50,000	0%	$0	$50,000	35%	$17,500	$67,500
Powder Cond Glovebox, 6', unshielded	2	$35,000	$70,000	0%	$0	$70,000	35%	$24,500	$94,500
Pelletizing Glovebox, 6', unshielded	2	$35,000	$70,000	0%	$0	$70,000	35%	$24,500	$94,500
Grinding Glovebox, 6', unshielded	2	$35,000	$70,000	0%	$0	$70,000	35%	$24,500	$94,500
Quartz Capsule Fab G-box, 4', unshld, He atm	1	$30,000	$30,000	0%	$0	$30,000	35%	$10,500	$40,500
Pellet Load G-box, 4', unshielded	2	$25,000	$50,000	0%	$0	$50,000	35%	$17,500	$67,500
Move & refurbish existing 15' Gbox forLIVs, He atm	1	$50,000 0	$50,000	0%	$0	$50,000	35%	$17,500	$67,500
Move & refurbish existing 4' Gbox for SIVs, He atm	1	$50,000	$50,000	0%	$0	$50,000	35%	$17,500	$67,500
PROCESS EQUIPMENT									
SST Cleaning Eqpt.	1	$50,000	$50,000	0%	$0	$50,000	35%	$17,500	$67,500
Sampling/Weighing	1	$2,000	$2,000	0%	$0	$2,000	35%	$700	$2,700
Blending/Binding	1	$10,000	$10,000	0%	$0	$10,000	35%	$3,500	$13,500
Seives	1	$10,000	$10,000	0%	$0	$10,000	35%	$3,500	$13,500
Pellet Press	1	$150,000	$150,000	0%	$0	$150,000	35%	$52,500	$202,500
Centaurr Furnace	1	$50,000	$50,000	0%	$0	$50,000	35%	$17,500	$67,500
Centerless Grinder	1	$5,000	$5,000	0%	$0	$5,000	35%	$1,750	$6,750
Cleaning/Decon Eqpt	1	$10,000	$10,000	0%	$0	$10,000	35%	$3,500	$13,500
Qtz Capsule Fab Gbox, Misc eqpt	1	$5,000	$5,000	0%	$0	$5,000	35%	$1,750	$6,750

Table A-7. (contd)

Cost Element	Quantity	Unit Price	Direct Total	Escalation %	Escalation	Direct+ Escal	Contingency %	Contingency	Total
Pellet Load Gbox, Misc eqpt	1	$5,000	$5,000	0%	$0	$5,000	35%	$1,750	$6,750
Pencil & LIV Pin GTAW welders & Pwr supplies	2	$20,000	$40,000	0%	$0	$40,000	35%	$14,000	$54,000
Qtz Capsule Carrier GTAW welder & Pwr supply	1	$20,000	$20,000	0%	$0	$20,000	35%	$7,000	$27,000
Misc Fixtures for welding Gboxes	2	$10,000	$20,000	0%	$0	$20,000	35%	$7,000	$27,000
NDE Eqpt, UT Exam Eqpt	1	$150,000	$150,000	0%	$0	$150,000	35%	$52,500	$202,500
NDE Eqpt, In-Motion RT	1	$150,000	$150,000	0%	$0	$150,000	35%	$52,500	$202,500
He Leak Test Eqpt	2	$30,000	$60,000	0%	$0	$60,000	35%	$21,000	$81,000
General Eqpt, Pin boxes, carts, etc.	1	$10,000	$10,000	0%	$0	$10,000	35%	$3,500	$13,500
SUBTOTAL PROCUREMENT			$1,203,000		$0	$1,203,000		$421,050	$1,624,050
CONSTRUCTION									
Cleaning Room mods & Eqpt Installation	1	$25,000	$25,000	0%	$0	$25,000	35%	$8,750	$33,750
High Bay and General Bldg mods	1	$225,000	$225,000	0%	$0	$225,000	35%	$78,750	$303,750
Install & Set up Target Mtl Receipt Area & Eqpt	1	$25,000	$25,000	0%	$0	$25,000	35%	$8,750	$33,750
Install & Set up Pellet Processing Line Eqpt	2	$25,000	$50,000	0%	$0	$50,000	35%	$17,500	$67,500
Install & Set up Qtz capsule/carrier Line Eqpt	1	$25,000	$25,000	0%	$0	$25,000	35%	$8,750	$33,750
Install & Set up Pencil/Pin Final Assy & Weld Eqpt	1	$100,000	$100,000	0%	$0	$100,000	35%	$35,000	$135,000
Install and Set up Qtz carrier Final Assy/weld Eqpt	1	$30,000	$30,000	0%	$0	$30,000	35%	$10,500	$40,500
Install & Set up NDE & Leak Test Eqpt	1	$25,000	$25,000	0%	$0	$25,000	35%	$8,750	$33,750
Set up Package/Shipping Station	1	$25,000	$25,000	0%	$0	$25,000	35%	$8,750	$33,750

Table A-7. (contd)

Cost Element	Quantity	Unit Price	Direct Total	Escalation %	Escalation	Direct+ Escal	Contingency %	Contingency	Total
Construction Waste Disposal	1	$20,000	$20,000	0%	$0	$20,000	35%	$7,000	$27,000
RCT Support	1	$10,000	$10,000	0%	$0	$10,000	35%	$3,500	$13,500
SUBTOTAL CONSTRUCTION			$560,000		$0	$560,000		$196,000	$756,000
SUBTOTAL 306E TARGET FAB			$1,763,000		$0	$1,763,000		$617,050	$2,380,050

Table A-8. Hot and Recycled Target Fab, Rooms 31/31A, 325 Building

Cost Element	Quantity	Unit Price	Direct Total	Escalation %	Escalation	Direct+ Escal	Contingency %	Contingency	Total
HOT & RECYCLE TARGET FAB, Rms 31/31A									
PROCUREMENT									
FACILITY EQUIPMENT									
Hot & Recycle Assy & Weld Gbox, 12', Shielded, He atm	1	$250,000	$250,000	0%	$0	$250,000	35%	$87,500	$337,500
NDE Glovebox, 12', Shielded	1	$200,000	$200,000	0%	$0	$200,000	35%	$70,000	$270,000
Misc. Eqpt	1	$25,000	$25,000	0%	$0	$25,000	35%	$8,750	$33,750
PROCESS EQUIPMENT									
Pin Magazine	1	$150,000							
Pencil & LIV Pin GTAW welders & Pwr supplies	1	$20,000	$20,000	0%	$0	$20,000	35%	$7,000	$27,000
Qtz Capsule Carrier GTAW welder & Pwr supply	1	$20,000	$20,000	0%	$0	$20,000	35%	$7,000	$27,000
Misc Fixtures for welding Gboxes	1	$25,000	$25,000	0%	$0	$25,000	35%	$8,750	$33,750
NDE Eqpt, In-Motion RT	1	$150,000	$150,000	0%	$0	$150,000	35%	$52,500	$202,500
He Leak Test Eqpt	2	$30,000	$60,000	0%	$0	$60,000	35%	$21,000	$81,000
General Eqpt, Pin boxes, carts, etc.	1	$10,000	$10,000	0%	$0	$10,000	35%	$3,500	$13,500
SUBTOTAL PROCUREMENT			$760,000		$0	$760,000		$266,000	$1,026,000
CONSTRUCTION									
Remodel Rooms 31/31A	1	$250,000	$250,000	0%	$0	$250,000	35%	$87,500	$337,500
Install Final Assy & Weld Gbox & Hookup Utilities	1	$150,000	$150,000	0%	$0	$150,000	35%	$52,500	$202,500
Install & Set up Pencil/Pin Final Assy & Weld Eqpt	1	$10,000	$10,000	0%	$0	$10,000	35%	$3,500	$13,500
Install and Set up Qtz carrier Final Assy/weld Eqpt	1	$10,000	$10,000	0%	$0	$10,000	35%	$3,500	$13,500

Table A-8. (contd)

Cost Element	Quantity	Unit Price	Direct Total	Escalation %	Escalation	Direct+ Escal	Contingency %	Contingency	Total
Install & Set up NDE & Leak Test Eqpt	1	$25,000	$25,000	0%	$0	$25,000	35%	$8,750	$33,750
Set up Package/Shipping Station	1	$25,000	$25,000	0%	$0	$25,000	35%	$8,750	$33,750
Misc Mods to Storage Room 40C	1	$25,000	$25,000	0%	$0	$25,000	35%	$8,750	$33,750
Construction Waste Disposal	1	$20,000	$20,000	0%	$0	$20,000	35%	$7,000	$27,000
RCT Support	1	$10,000	$10,000	0%	$0	$10,000	35%	$3,500	$13,500
SUBTOTAL CONSTRUCTION			$525,000		$0	$525,000		$183,750	$708,750
SUBTOTAL RECYCLE TARGET FAB			$1,285,000		$0	$1,285,000		$449,750	$1,734,750

Table A-9. Gas Tag Fab, 306E Building

Cost Element	Quantity	Unit Price	Direct Total	Escalation %	Escalation	Direct+ Escal	Contingency %	Contingency	Total
306E GAS TAG FAB									
PROCUREMENT									
FACILITY EQUIPMENT									
Relocate & Refurbish existing Gboxes	1	$50,000	$50,000	0%	$0	$50,000	35%	$17,500	$67,500
PROCESS EQUIPMENT									
Laser beam Welding System	1	$50,000	$50,000	0%	$0	$50,000	35%	$17,500	$67,500
Upgrade Existing Electron Beam Welder	1	$150,000	$150,000	0%	$0	$150,000	35%	$52,500	$202,500
Gas Tag Rupture Station	1	$10,000	$10,000	0%	$0	$10,000	35%	$3,500	$13,500
Fixtrues	1	$50,000	$50,000	0%	$0	$50,000	35%	$17,500	$67,500
SUBTOTAL PROCUREMENT			$310,000		$0	$310,000		$108,500	$418,500
CONSTRUCTION									
Install & Hook up Utilities	1	$50,000	$50,000	0%	$0	$50,000	35%	$17,500	$67,500
Construction Waste Disposal	1	$5,000	$5,000	0%	$0	$5,000	35%	$1,750	$6,750
RCT Support	1	$5,000	$5,000	0%	$0	$5,000	35%	$1,750	$6,750
SUBTOTAL CONSTRUCTION			$60,000		$0	$60,000		$21,000	$81,000
SUBTOTAL 306E TARGET FAB			$370,000		$0	$370,000		$129,500	$499,500

Table A-10. FFTF Reactor Hardware and Isotope Casks

Cost Element	Quantity	Unit Price	Direct Total	Escalation %	Escalation	Direct+ Escal	Contingency %	Contingency	Total
REACTOR HDW & ISOSTOPES CASKS									
IN-REACTOR HARDWARE									
Design & Fab Two Diff Design 40 ft Thimbles	1	$5,473,300	$5,473,300	0%	$0	$5,473,300	35%	$1,915,655	$7,388,955
Design & Fab LIV (does not include cost of target mtl)	1	$869,600	$869,600	0%	$0	$869,600	35%	$304,360	$1,173,960
EX-REACTOR HARDWARE									
Hardware & Procedures for Dissassembly of LIV	1	$258,700	$258,700	0%	$0	$258,700	35%	$90,545	$349,245
Rapid Retrieval System (R3) Adapter Hdw for Center Island	1	$1,985,700	$1,985,700	0%	$0	$1,985,700	35%	$694,995	$2,680,695
He Circulaton/Sodium Detection Syst for R3	1	$584,300	$584,300	0%	$0	$584,300	35%	$204,505	$788,805
Gas Target Circulation & Recovery System	1	$1,068,500	$1,068,500	0%	$0	$1,068,500	35%	$373,975	$1,442,475
R3 Target Chain (does not include cost of target mtl)	1	$246,400	$246,400	0%	$0	$246,400	35%	$86,240	$332,640
R3 Target Insertion/retrieval/shipping devices	1	$1,034,200	$1,034,200	0%	$0	$1,034,200	35%	$361,970	$1,396,170
Integrated Mockup System Testing	1	$584,500	$584,500	0%	$0	$584,500	35%	$204,575	$789,075
SUBTOTAL REACTOR HARDWARE			$12,105,200		$0	$12,105,200		$4,236,820	$16,342,020
Safety Evaluation/SAR Input/Changes	1	$417,500	$417,500	0%	$0	$417,500	35%	$146,125	$563,625
Project Management/Admin	1	$668,000	$668,000	0%	$0	$668,000	35%	$233,800	$901,800

Table A-10. (contd)

Cost Element	Quantity	Unit Price	Direct Total	Escalation %	Escalation	Direct+ Escal	Contingency %	Contingency	Total
TOTAL REACTOR HARDWARE			$13,190,700		$0	$13,190,700		$4,616,745	$17,807,445
ISOTOPE CASKS									
Design	1	$333,700	$333,700	0%	$0	$333,700	35%	$116,795	$450,495
Fabrication & Assembly	3	$125,200	$375,600	0%	$0	$375,600	35%	$131,460	$507,060
Cask Qualification	1	$183,200	$183,200	0%	$0	$183,200	35%	$64,120	$247,320
SUBTOTAL ISOTOPE CASKS			$892,500		$0	$892,500		$312,375	$1,204,875
TOTAL REACTOR HDW & ISOTOPE CASKS			$14,083,200		$0	$14,083,200		$4,929,120	$19,012,320

Table A-11. FMEF LIV Target Assembly

Cost Element	Quantity	Unit Price	Direct Total	Escalation %	Escalation	Direct+ Escal	Contingency %	Contingency	Total
FMEF LIV TARGET ASSEMBLY									
PROCUREMENT									
FACILITY EQUIPMENT									
Hot & Recycle Wire Wrap Gbox, 12', Shielded	1	$200,000	$200,000	0%	$0	$200,000	35%	$70,000	$270,000
Hot & Recycle Final Assy Gbox, 15', Shielded	1	$250,000	$250,000	0%	$0	$250,000	35%	$87,500	$337,500
PROCESS EQUIPMENT									
Shielded Pin Magazine	1	$150,000	$150,000	0%	$0	$150,000	35%	$52,500	$202,500
Wire Wrap Machine	1	$150,000	$150,000	0%	$0	$150,000	35%	$52,500	$202,500
Wire Wrap GTAW welders & Pwr supplies	1	$20,000	$20,000	0%	$0	$20,000	35%	$7,000	$27,000
Bundle Assy GTAW welder & Pwr supply	1	$20,000	$20,000	0%	$0	$20,000	35%	$7,000	$27,000
Misc Fixtures for Gboxes	1	$150,000	$150,000	0%	$0	$150,000	35%	$52,500	$202,500
NDE Eqpt, In-Motion RT	1	$150,000	$150,000	0%	$0	$150,000	35%	$52,500	$202,500
General Eqpt, Pin boxes, carts, etc.	1	$25,000	$25,000	0%	$0	$25,000	35%	$8,750	$33,750
SUBTOTAL PROCUREMENT			$1,115,000		$0	$1,115,000		$390,250	$1,505,250
CONSTRUCTION									
Install Hot & Recycle Wire Wrap Gbox, 12', Shielded	1	$25,000	$25,000	0%	$0	$25,000	35%	$8,750	$33,750
Install Hot & Recycle Final Assy Gbox, 15', Shielded	1	$25,000	$25,000	0%	$0	$25,000	35%	$8,750	$33,750
Install Wire Wrap Machine	1	$25,000	$25,000	0%	$0	$25,000	35%	$8,750	$33,750
Install and set up welders	2	$20,000	$40,000	0%	$0	$40,000	35%	$14,000	$54,000
Install and set up RT Eqpt	1	$25,000	$25,000	0%	$0	$25,000	35%	$8,750	$33,750
Install fixtures	1	$25,000	$25,000	0%	$0	$25,000	35%	$8,750	$33,750
Construction Waste Disposal	1	$5,000	$5,000	0%	$0	$5,000	35%	$1,750	$6,750

Table A-11. (contd)

Cost Element	Quantity	Unit Price	Direct Total	Escalation %	Escalation	Direct+ Escal	Contingency %	Contingency	Total
RCT Support	1	$0	$0	0%	$0	$0	35%	$0	$0
SUBTOTAL CONSTRUCTION			$170,000		$0	$170,000		$59,500	$229,500
SUBTOTAL RECYCLE TARGET FAB			$1,285,000		$0	$1,285,000		$449,750	$1,734,750

PNNL-11774

FFTF Medical Isotopes

Market Study (2001-2020)

November 20, 1997

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1

Executive Summary

Scope of the Study

Frost & Sullivan was commissioned by Battelle Pacific Northwest National Laboratory to provide an assessment of nuclear medicine diagnostics and therapeutics markets in the United States in the years 2001-2020. This study focuses on reactor-produced isotopes specifically and does not evaluate cyclotron or linear accelerator produced isotopes.

Objectives of the Study

The objectives of this research are to:

- Identify disease indications currently being treated with medical isotopes in the United States
- Provide an overview of the nuclear diagnostics market in the United States and forecast revenues in the years 2001-2020
- Identify specific medical isotopes that offer the greatest market opportunities in nuclear therapeutics

- Determine and forecast revenues and the revenue growth rate for the total nuclear medicine therapeutic market in the United States from 2001 to 2020
- Identify the radiopharmaceutical companies currently involved in nuclear therapy development
- Assess the market with respect to the FFTF reactor and its capabilities

Research Methodology

Frost & Sullivan adopted a three-fold approach for this study:

- Primary research focusing on interviews with leading nuclear medicine physicians, industry executives, and regulatory officials
- Secondary research focusing on utilizing the vast information provided on the Internet and in published articles, and reports on nuclear medicine
- Quantitative and qualitative analysis of the primary and secondary data utilizing Frost & Sullivan's extensive market research and consulting experience in nuclear medicine and a comprehensive understanding of the marketplace

The analyst team conducted over 70 interviews with opinion leaders and experts with vast knowledge and experience in nuclear medicine. Respondents to the study were selected from four areas of the nuclear medicine community:

- Manufacturers of radiopharmaceuticals
- Distributors of radiopharmaceuticals, specifically radiopharmacies
- Nuclear medicine physicians and scientists
- Regulatory authorities

The quantitative and qualitative analysis was conducted in accordance with a research methodology developed by Frost & Sullivan. Under this methodology, revenue forecasts were determined based on the following factors:

- Patient populations in targeted disease indications.
- Acceptance and adoption of nuclear medicine as an alternative or used in combination with other modalities by the physician community.
- Treatment costs in 1997.
- Penetration rate achieved by nuclear medicine products in the marketplace. The estimated penetration rates are based on the impact of successful deployment of key marketing and product position strategies by the manufacturers and the nuclear medicine community.
- Quantification of awareness and increased referral base established by various programs undertaken by manufacturers and physician groups.
- Strengths and weaknesses of competing modalities.

The study is divided into six chapters. These chapters are:

- Chapter 1: Executive Summary
- Chapter 2: Assessment of the U.S. Diagnostic Radiopharmaceuticals Market (2001-2020)
- Chapter 3: Assessment of the U.S. Therapeutic Radiopharmaceuticals Market (2001-2020)
- Chapter 4: Profiles of Leading Market Participants
- Chapter 5: FFTF Opportunity Analysis
- Chapter 6: Strategic Recommendations

Current Market Overview

Nuclear medicine is divided into two major areas: diagnostics and therapeutics. The diagnostic side is mature, while the therapeutic side of nuclear medicine is in its infancy.

Over 100 diagnostic radiopharmaceutical products are available. The largest number of these radiopharmaceuticals have applications in cardiology, followed by oncology and neurology. A few radiopharmaceuticals have applications in other areas, such as infection imaging and nephrology.

Nuclear medicine is used as a therapeutic modality to treat three conditions:

- Thyroid cancer
- Hyperthyroidism
- Bone pain palliation

Polycythaemia vera is also treated with nuclear medicine on a small scale.

On-going research trials throughout the United States are investigating new radiopharmaceuticals for more than 35 other potential diseases. Many of these new drugs are expected to enter the marketplace by 2005. Table 1-1 lists some medical isotopes in trial research programs in the United States.

Most participants in this study believe the future of nuclear medicine resides in the growth potential of the emerging therapeutics market. Respondents also believe that healthy growth in nuclear diagnostics will contribute to market expansion.

Table 1-1

Diagnostic and Therapeutic Radiopharmaceuticals Market: List of Selected Therapeutic Isotopes and Disease Indications Under Research (U.S.), 1997

Disease indication	*Isotope*
Leukemia, Lymphoma, Breast cancer	Y-90
Hemophilia, Heart disease, Polycythemia	P-32
Prostate cancer, Uterine cancer	Ir-192
Brain tumor, Ovarian cancer	Au-198
Rheumatoid arthritis, Prostate cancer	Re-186

Source: Frost & Sullivan

Frost & Sullivan estimates that 90 percent of the medical isotopes currently utilized by U.S. nuclear medicine come from overseas. While the United States accounts for 47 percent of revenues in the total world nuclear medicine market, the country accounts for only 10 percent of the world's production of medical isotopes.

Despite these statistics, the Department of Energy (DOE) has ordered the shutdown of several of its nuclear reactors. Fewer facilities in the United States are able to supply nuclear medicine with the isotopes that the industry needs. Future expansion in nuclear diagnostics and therapeutics will create higher demand for medical isotopes. The DOE should design a strategy to supply this increasing demand for medical isotopes so that U.S. nuclear medicine can continue to grow.

Indications and Isotopes

The most utilized isotope in nuclear diagnostics is Technetium-99m (Tc-99m), a daughter isotope of Molybdenum-99 (Mo-99). The largest supplier of Tc-99m to the United States

nuclear medicine diagnostics market is MDS Nordion, located near Ottawa, Canada. Recently, Mallinckrodt received FDA approval to sell the Mo-99 produced at the company's reactor in Petten, the Netherlands, in the United States. Table 1-2 exhibits a selected list of medical isotopes commonly used in nuclear medicine diagnostics.

Table 1-2

Diagnostic and Therapeutic Radiopharmaceuticals Market: Selected Isotopes Commonly Used in Nuclear Diagnostics (U.S.), 1997

Isotope	*Application*	*Source*
Tc-99m	Cardiology	Reactor
Tl-201	Cardiology	Accelerator
I-131	Oncology	Reactor
Xe-133	Respiratory	Reactor
In-111	Neurology	Accelerator
Ga-67	Oncology	Accelerator
P-32	Oncology	Reactor

Source: Frost & Sullivan

Table 1-3 presents Frost & Sullivan's estimates of the percentage breakdown of diagnostic radiopharmaceutical revenues by application.

There are only four therapeutic applications for radioisotopes. Table 1-4 exhibits the medical isotopes used in nuclear therapeutics and also the percentage breakdown of therapeutic radiopharmaceutical revenues by application.

Table 1-3

Diagnostic and Therapeutic Radiopharmaceuticals Market: Percentage of Market Revenues by Diagnostic Applications (U.S.), 1996

Application	*% of Market Revenues*
Cardiology	46
Oncology	34
Neurology	10
Other	10
TOTAL	100

Note: All figures are rounded. *Source: Frost & Sullivan*

Table 1-4

Diagnostic and Therapeutic Radiopharmaceuticals Market: Percentage of Market Revenues by Therapeutic Applications (U.S.), 1996

Application	*Isotope*	*% of Market Revenues*
Thyroid cancer	I-131	50
Bone pain palliation	Sr-89/Sm-153	31
Hyperthyroidism	I-131	15
Polycythaemia Vera	P-32	4
TOTAL		100

Note: All figures are rounded. *Source: Frost & Sullivan*

Revenues and Market Data

Frost & Sullivan estimates that revenues for the United States nuclear medicine diagnostics market were $531 million in 1996. Revenues for the nuclear medicine therapeutics market are estimated to have been $48 million in 1996. Table 1-5 exhibits total nuclear medicine market revenues and revenue breakdown by market segments in 1996.

Table 1-5
Diagnostic and Therapeutic Radiopharmaceuticals Market: Market Revenues by Segment (U.S.), 1996-2020

Year	Diagnostics ($ Million)	Therapeutics ($ Million)
1996	531	48
2001	869	440
2006	1,873	699
2010	3,303	1,587
2016	8,773	4,036
2020	16,400	6,014

Note: All figures are rounded. *Source: Frost & Sullivan*

Many of the companies involved in nuclear medicine offer radiopharmaceutical products for diagnostic and therapeutic procedures. Table 1-6 lists radiopharmaceutical companies that offer products in the United States marketplace.

Market Outlook

In its early years, nuclear medicine diagnostics largely concentrated on bone scanning and cardiology applications. This changed as competition from other imaging modalities cut into nuclear medicine diagnostics' market. To regain market share, nuclear medicine diagnostics expanded into applications where other imaging modalities were not as effective. Oncology is a very promising area—experts believe this to be an application where nuclear medicine diagnostics can outperform its competitors. Nuclear medicine is also expanding into neurology and infection imaging.

Table 1-6

Diagnostic and Therapeutic Radiopharmaceuticals Market: Radiopharmaceutical Companies (U.S.), 1997

Company	*Product Applications*
Amersham Medi-Physics	Diagnostics, Therapeutics
Mallincrodt Medical	Diagnostics, Therapeutics
DuPont Merck	Diagnostics
Bracco Diagnostics	Diagnostics, Therapeutics
CIS US	Diagnostics, Therapeutics
Cytogen	Diagnostics, Therapeutics
Biomira, Inc	Diagnostics, Therapeutics
Medco Research	Diagnostics
Coulter Pharmaceuticals	Diagnostics, Therapeutics
Centocor	Diagnostics
NeoRX	Diagnostics
Neoprobe	Diagnostics
Diatide	Diagnostics
Immunomedics	Diagnostics
Guilford Pharmaceutical	Diagnostics

Source: Frost & Sullivan

Nuclear therapy provides effective pain relief from metastatic bone pain and treating bone marrow disease. It is also successfully used for treatment of thyroid-related diseases.

Frost & Sullivan expects that nuclear medicine will expand into other therapeutic areas. Currently, over 35 clinical trials throughout the United States are researching the potential of nuclear therapeutics. These trials are investigating the use of a large number of isotopes in treating several diseases. Some radiopharmaceutical companies are trying to design "smart bullets" to deliver therapeutic radiopharmaceutical drugs to disease sites without affecting healthy tissue.

Future Revenues and Market Data

Frost & Sullivan forecasts that nuclear medicine diagnostics could grow into a $17 billion market by 2020 from about $531 million in 1996. Table 1-5 exhibits potential market revenue growth for nuclear diagnostics and nuclear therapeutics from 1996 to 2020. For the diagnostic radiopharmaceuticals market forecast to be realized, several challenges need to be overcome. These challenges are discussed in Chapter 2.

Currently, over 100 diagnostic radiopharmaceuticals are available in the marketplace. Several diagnostic radiopharmaceutical products are awaiting FDA approval; many more are in research trials around the country. Market growth is likely to be enhanced by nuclear diagnostics' expansion into oncology, as well as into other areas in which it currently has little market presence.

Frost & Sullivan forecasts that the nuclear therapeutics market could reach $6 billion in 2020, compared to an estimated $48 million in 1996. Industry experts expect that smaller radiopharmaceutical companies will play a very important role in designing therapeutic radiopharmaceuticals, while larger companies will most likely handle marketing and distribution.

Nuclear therapeutics is an infant market. It faces very serious challenges which hinder growth. These challenges, as well as other issues, are discussed extensively in Chapter 3.

To realize its growth potential, nuclear therapeutics needs to discover methods to bring therapeutic radiopharmaceuticals to disease sites. Once a "smart bullet" is discovered, this treatment modality can be expected to expand rapidly. However, growth might be hindered by the unreliable

supply of some of the medical isotopes with the most promising future in nuclear therapeutics.

Challenges of the Market

The key challenges for the market are the following:

- Effects of managed healthcare
- High cost of nuclear medicine procedures
- Competition from other imaging modalities
- Lack of education and awareness programs
- Shrinking number of nuclear medicine physicians
- Unreliable supply of medical isotopes
- Excessive FDA and NRC regulation
- Reduction of research budgets in the United States

Drivers of the Market

Although the challenges affecting nuclear medicine constrain the market's current expansion, several market drivers can contribute decisively to future expansion. Among theses drivers are:

- New radiopharmaceuticals for oncology
- Cost-effectiveness of nuclear medicine
- Development of new therapeutic applications
- Nuclear medicine education
- New pediatric applications

- Aging population that demands cost-effective treatment
- Development of targeting techniques

Conclusions and Strategic Recommendations

Cost of Operating the FFTF Raises Concern in the Nuclear Medicine Community

The cost of operating the reactor and the associated facility is the main issue that the FFTF mission has to overcome. A large number of interviewees expressed doubts that the FFTF can ever become financially self-sufficient. Current U.S. demand for medical isotopes, met by domestic and foreign reactors, does not support the re-commissioning of the FFTF reactor. However, this may not be the case in the future. Supplies are likely to be insufficient given anticipated market expansion.

The cost of operating the FFTF, estimated at $88 million per year, might seem very high in 1997. Yet, if projected isotope demand is realized, the United States may not be able to secure reliable supplies to satisfy domestic demand. Restarting the FFTF by 2001 or 2002 would uniquely position the reactor to become the country's leading commercial producer of medical isotopes for the twenty-first century.

Dual-Mission Approach Is Not Favored by the Nuclear Medicine Community

The dual-mission approach is a working strategy developed and pursued by the FFTF mission. The reactor is to

initially focus on tritium production for defense needs, while nuclear therapeutics research develops applications for more radiopharmaceutical products. Opinion leaders interviewed for the study believe that the tritium mission is scheduled to end just as demand for medical isotope in the country (and the world) is expected to increase.

The plan is to then shift the FFTF reactor from tritium production to medical isotope production. Battelle Pacific Northwest is promoting the dual mission to obtain federal funding to restart the FFTF reactor.

The dual mission for the FFTF concerns the nuclear medicine community. This is a concern that the FFTF mission should address. The nuclear medicine community would like to have a reliable source for medical isotopes. Interviewees feel that this national isotope resource should have no involvement in national defense activities.

Respondents interviewed by Frost & Sullivan feel that the DOE is not truly committed to satisfying the isotope needs of the nuclear medicine community. Participants in this study fear that the DOE is using medical isotopes to obtain federal funds to restart the FFTF for defense purposes and that ultimately the DOE will sacrifice medical isotopes and prolong production of tritium at the FFTF reactor.

The FFTF reactor will likely continue to play a role in national defense. The reactor will also be able to satisfy future demand for medical isotopes. The FFTF mission should demonstrate its commitment to dedicating the FFTF reactor to supplying medical isotopes. Such a strategy would strengthen support from the nuclear medicine community by assuring the

potential customer base that the FFTF will securely and reliably supply medical isotopes in the future.

Focusing Solely on Medical Isotope Production Would Reduce the FFTF's Client Base

Not only could the FFTF become the country's leading supplier of medical isotopes, but it could also produce isotopes for non-medical applications. Isotopes are also used in several other areas such as the following:

- Industrial
- Government/national defense
- Electric power utilities
- Academic research

Producing isotopes for other U.S. industries would allow the FFTF mission to expand its client base. With an expanded client base, the FFTF mission will gain strength and wider support. By not only becoming the largest supplier of isotopes for nuclear medicine, but also for other uses, the FFTF mission can enhance the reactor's financial sustainability.

Production of Exotic Isotopes Would Increase Revenues for the FFTF

Table 1-1 lists some therapeutic isotopes that are currently under clinical research trials in the United States. Several isotopes are being researched across multiple disease applications. This is being done to identify the most effective isotope for each disease.

Nuclear therapeutics requires higher doses of isotopes than nuclear diagnostics. This would create a higher demand for isotopes in the future, particularly after new therapeutic radiopharmaceutical products enter the marketplace. Additionally, some isotopes are more expensive than others.

Frost & Sullivan recommends that the FFTF reactor focus on selected isotopes with greater potential in the nuclear therapy market. This would increase the FFTF's financial security and would build a reliable supply of isotopes to support growth of nuclear therapeutics.

Private Sector Partnerships Could Alleviate the High Cost of Operating the FFTF

Federal dollars for research, both technological and medical, are not as easily available today as they were in the past. Frost & Sullivan has learned that this situation is a cause of concern for nuclear physicians. In 1996 alone, the budgets at several national laboratories have been reduced by as much as 12 percent.

Observers of the FFTF mission estimate that the cost of operating the FFTF is about $88 million yearly. In the present climate of budgetary reductions, analysts do not expect the U.S. government to provide funds to pay for the FFTF for a medical isotopes mission. This forces the FFTF mission to seek other ways to finance the reactor.

In discussions with personnel at several national laboratories, Frost & Sullivan discovered their increasing willingness to seek joint agreements or partnerships with private-sector sponsors. Sandia National Laboratory (SNL)

provides one example of a successful partnership between the private sector and a national laboratory. In 1996, corporations contributed $27 million to SNL's budget in exchange for use of the facilities and proprietary rights to some of the research financed with these funds. SNL expects that private financing could soar to $100 million in the year 2000.

The FFTF mission should look closely at this example and possibly develop its own private-sector partnerships.

The Packaging and Transportation System Should Be Strengthened

The FFTF's isotope packaging system and the transportation system of the Tri-City area need to be strengthened if the FFTF is to become a major supplier of isotopes. A strong transportation system is necessary to expediently ship large amounts of time-sensitive isotopes to national and international clients. Given the FFTF's capacity and anticipated demand growth, current facilities are likely to prove inadequate. The region has the foundation for a solid transportation infrastructure that should be further developed.

Inadequacy of the transportation system is a concern expressed by many nuclear medicine participants. If the FFTF does not develop a reliable packaging and transportation system, the nuclear medicine community is unlikely to view the facility as a reliable supplier of isotopes.

MDS Nordion's success has been bolstered by the company's ability to ship isotopes to its customers with very short notice. In Canada, MDS Nordion has close proximity to two major international airports, one in Ottawa, the other in

Vancouver. This is also true of MDS Nordion's facility in Belgium, which has speedy access to Brussels International Airport. In comparison, the FFTF facility would have to ship isotopes from the Tri Cities airports through the Seattle or Salt Lake City airports. This is likely to consume time and resources, endangering the quality of the isotopes by the time they are delivered to customers.

If the FFTF can build a packaging and transportation system that is reliable, timely, and customer-satisfaction oriented, it should be able to compete in this market. Frost & Sullivan considers this to be a very important issue which the FFTF mission should not overlook.

Environmental Contamination Issues Could Become a Major Obstacle

During the summer of 1997, there was increasing press coverage of radioactive contamination at the Hanford nuclear facility. The news media questioned the radioactive safety record at Hanford, a concern that the FFTF mission should not ignore.

Frost & Sullivan believes that environmental contamination is an issue that should be closely looked at by the FFTF mission. Similar radioactive contamination issues have already caused unscheduled shutdowns at both Brookhaven and Los Alamos National Laboratories. The FFTF mission should explain to the local community, as well as to regional critics, that the reactor itself does not constitute a threat to the local environment or to the Columbia River basin.

Frost & Sullivan recommends that the FFTF mission demonstrate its safety record during the decade the reactor was in operation to the DOE and the news media. It is a good, solid safety record that can be used to dispel the environmental contamination issues reported by the news media in 1997. Ignoring this issue could result in a serious obstacle to restarting the FFTF for medical isotope production.

Economic Benefits Should Be Stressed to Gain Community Support

Greater support from the local community, including that in Oregon, should be sought by the FFTF mission. The FFTF reactor has many opponents in Oregon who could easily use the political clout of their representatives in Congress to disrupt the FFTF's plans. Environmental contamination issues easily could be used to derail the FFTF mission's goals. It is necessary that the local community understand that the FFTF poses little, if any, environmental threat.

The FFTF could very well become the nation's largest supplier of medical isotopes and a major nuclear medicine research center. This could make the FFTF one of the largest employers in the Tri-City area, thereby boosting the region's economy. Restarting the FFTF would create jobs, increasing local revenues and revitalizing the entire Tri-City region. This is an important issue that should be presented to the community to generate support.

2

Assessment of the U.S. Diagnostic Radiopharmaceuticals Market (2001-2020)

Chapter Objective

This chapter provides an overview of the current nuclear diagnostics market in the United States and opportunities and challenges in the market through 2020.

Market Overview

Diagnostic radiopharmaceutical agents allow nuclear physicians to obtain valuable information of a patient's condition by imaging organ metabolism. Currently there are over 100 diagnostic radiopharmaceutical products available in the U.S. Although market growth was sluggish during the early 1990's, nuclear diagnostics are beginning to experience renewed

growth. This expansion is a consequence of new applications for nuclear diagnostics, as well as the introduction of new radiopharmaceutical products.

The presence of other imaging modalities, such as Magnetic Resonance Imaging (MRI), ultrasound, X-ray, and Computed Tomography (CT), has resulted in intense competition in the U.S. diagnostics imaging market. Table 2-1 shows total diagnostic imaging market shares by imaging modality. Competition from these above mentioned modalities has prevented nuclear diagnostics from achieving widespread acceptance.

Table 2-1

Diagnostic Radiopharmaceuticals Market: Market Share by Modality (U.S.), 1997

Diagnostic Imaging Modality	*Market share (%)*
X-Ray	35
Ultrasound	24
Computed Tomography	20
Nuclear Medicine	13
Magnetic Resonance	8
TOTAL	100

Note: All figures are rounded. *Source: Frost & Sullivan*

Through 1997, nuclear medicine diagnostic imaging focused on developing radiopharmaceutical products for cardiology applications. This is expected to change in the near future with the availability of newer imaging agents for applications in oncology. In 1997 the FDA approved four radiopharmaceutical products for oncology. Their entry into the marketplace is expected by the end of the year.

Additionally, a number of other oncology radiopharmaceuticals are currently awaiting FDA approval. Frost & Sullivan expects all these product introductions to boost sales of diagnostics radiopharmaceuticals.

The U.S. diagnostics radiopharmaceutical market was worth approximately $531 million in 1996. The United States accounts for 48 percent of world radiopharmaceutical revenues. At a yearly rate of about 8 percent, estimated growth in this market has not met industry expectations. The nuclear medicine industry had expected growth to be closer to 15 percent annually. However, the introduction of new radiopharmaceutical agents is expected to spur growth in the near future.

Over 100 diagnostic radiopharmaceuticals currently are available in the U.S. market. Table 2-2 exhibits some of the leading radiopharmaceutical agents in use. Prices for diagnostic radiopharmaceuticals vary from below $50 to well over $2,000 per dose. Table 2-3 exhibits some pricing samples. Several new diagnostic radiopharmaceutical agents are awaiting Food and Drug Administration (FDA) approval. Table 2-4 exhibits some of these radiopharmaceuticals.

Table 2-2

Diagnostic Radiopharmaceuticals Market: List of Selected Leading Diagnostic Radiopharmaceutical Agents (U.S.), 1996

Radiopharmaceutical	*Application*	*Company*
OctreoScan (In-111)	Colorectal Imaging	Mallinckrodt
Myoview (Tc-99m)	Cardiac Imaging	Amersham
Cardiolite (Tc-99m)	Cardiac Imaging	DuPont Merck

Source: Frost & Sullivan

Table 2-3

Diagnostic Radiopharmaceuticals Market: Prices of Selected Diagnostic Radiopharmaceutical Agents (U.S.), 1996

Radiopharmaceutical	*Price/dose*	*Company*
Cardiolite (Tc-99m)	$85	DuPont Merck
Ceretec (Tc-99m)	$310	Amersham
Neurolite (Tc-99m)	$320	DuPont Merck
Verluma (Tc-99m)	$850	DuPont Merck
TechneScan MAG3 (Tc-99m)	$1,000	Mallinckrodt
ProstaScint (In-111)	$1,200	Mallinckrodt
OctreoScan (In-111)	$1,100	Mallinckrodt
Myoview (Tc-99m)	$2,400	Amersham

Note: All figures are rounded. *Source: Frost & Sullivan*

Table 2-4

Diagnostic Radiopharmaceuticals Market: Selected Diagnostic Radiopharmaceuticals Awaiting FDA Approval (U.S.), 1996

Radiopharmaceutical	*Company*	*Indication*
Miraluma (Tc-99m)	DuPont	Breast cancer imaging
ProstaScint (In-111)	Cytogen	Prostate cancer imaging
Verluma (Tc-99m)	NeoRX/DuPont	Nonsmall cell lung cancer
CEAScan (Tc-99m)	Immunomedics	Colorectal cancer imaging
MacroScint	DuPont	Infection imaging
CC49MAB (I-125)	Neoprobe	Colorectal cancer imaging
Leukoscan (Tc-99m)	Immunomedics	Infection imaging
TechneScan-Q12 (Tc-99m)	Mallinckrodt	Cardiac imaging
I-123 IPPA (I-123)	Medco Research	Cardiac imaging
Dopascan (I-123)	Guilford	Parkinson's disease
Tc-99m P280 (Tc-99m)	Diatide	Blood clot imaging

Source: Frost & Sullivan

The most commonly used radioisotope in nuclear medicine imaging is Technetium-99m (Tc-99m, daughter isotope of

Molybdenum-99). According to nuclear physicians interviewed by Frost & Sullivan, Tc-99m is used in more than 68 percent of the nuclear medicine diagnostic procedures performed in the United States.

The constant and stable supply of Tc-99m is a key concern to nuclear physicians. Any disruption in the supply of isotopes can cause significant revenue losses, not only in the United States, but also around the world. The strike at MDS Nordion in June, 1997, sent a chill through the nuclear medicine community. Disruption of shipping at MDS Nordion, which supplies over 80 percent of the Tc-99m used in the United States, can affect treatment of thousands of patients and also impact the revenues of radiopharmaceutical companies.

Among the most commonly used radioisotopes in nuclear medicine diagnostics, besides Tc-99m, are:

- Iodine-131 (I-131)
- Indium-111 (In-111)
- Thallium-201 (Tl-201)
- Chromium-51 (Cr-51)

Radiopharmaceutical companies are developing newer products and entering new disease applications. In previous years, nuclear medicine focused on cardiology. Nonetheless, fierce competition from other imaging modalities has forced the industry to seek other areas for product expansion. To enlarge its market, nuclear medicine is expanding into applications where competition from other imaging modalities is not as fierce. This has led to the large number of new diagnostic radiopharmaceuticals for oncology currently awaiting FDA approval.

Revenue Forecasts (2001-2020)

Frost & Sullivan forecasts that from 2001 to 2020, nuclear medicine diagnostic imaging will grow into a multi-billion dollar industry in the United States. Revenues in the U.S. market for this imaging modality will be about $17 billion in 2020. The forecast compounded annual growth rate is approximately 16.8 percent. Table 2-5 exhibits revenue forecasts for nuclear diagnostics from 2001 to 2020.

Table 2-5
Diagnostic Radiopharmaceuticals Market: Revenue Forecasts (U.S.), 2001-2020

Year	*Revenues ($ Billion)*	*Revenue Growth Rate (%)*
2001	0.869	---
2002	0.999	15
2003	1.169	17
2004	1.368	17
2005	1.600	17
2006	1.873	17
2007	2.191	17
2008	2.564	17
2009	2.974	16
2010	3.449	16
2011	4.001	16
2012	4.682	17
2013	5.478	17
2014	6.409	17
2015	7.498	17
2016	8.773	17
2017	10.264	17
2018	12.009	17
2019	14.051	17
2020	16.439	17
Compound Annual Growth Rate (2001-2020): 16.8%		

Note: All figures are rounded. *Source: Frost & Sullivan*

Analysts expect that the large number of diagnostic radiopharmaceutical products recently approved by the FDA, as well as those products that are awaiting approval, will significantly increase revenues in the future. Table 2-6 lists the diagnostic radiopharmaceuticals approved by the FDA in 1997. The new group of diagnostic radiopharmaceuticals focuses on areas previously ignored by nuclear medicine.

Table 2-6

Diagnostic Radiopharmaceuticals Market: Radiopharmaceuticals Approved by the FDA (U.S.), 1997

Radiopharmaceutical	*Company*	*Application*
Miraluma (Tc-99m)	DuPont	Breast tumor
ProstaScint (In-111)	Cytogen	Prostate cancer
Verluma (Tc-99m)	DuPont/NeoRX	Non-small cell lung cancer
CEA-Scan (Tc-99m)	Immunomedics	Colorectal cancer

Source: Frost & Sullivan

Market Drivers

New Radiopharmaceuticals for Oncology Applications Are Likely to See Strong Demand

Nuclear medicine has proven its worth in tumor localization, tumor staging, identifying metastatic sites, and judging response to therapy. A good example of the ability of tracers to image cancer abnormalities is Mallinckrodt's agent "OctreoScan," which has been effective in identifying and localizing neuroendocrine tumors.

Cancer is still one of the main causes of death in the United States and worldwide. It drains healthcare budgets and creates untold despair among its victims. With the development of newer diagnostics radiopharmaceutical for oncology, nuclear medicine has found a new source of growth, particularly in the near future. The nuclear medicine industry is awaiting the entry of these radiopharmaceuticals with renewed hope. In particular, DuPont Merck has several oncology agents which should about to receive FDA approval soon.

Interviewees have high hope that these new radiopharmaceuticals for oncology will have a deep and positive effect on the future of nuclear medicine diagnostic imaging. Some of these new agents are designed for:

- Breast cancer imaging
- Neuroendocrine tumor imaging
- Colorectal cancer imaging
- Small-cell lung cancer imaging

Frost & Sullivan expects that revenue growth could reach 15-17 percent per year by the 2020s. This expectation is based on the revenue potential held by the new radiopharmaceuticals which are about to enter the market.

Cost-Effectiveness of Nuclear Medicine Imaging Contributes to Healthcare Costs Reduction

Since nuclear medicine procedures can detect abnormalities smaller than those identified by other imaging modalities, it is intrinsically cost-effective. Since diagnostic radiopharmaceuticals act as indicators of specific physiological

processes, they provide a survey of the disease that anatomic imaging often is unable to provide.

The cheapest imaging tool is an X-ray, which provides a considerable amount of information. MRI and computed tomogrophy (CT) are more expensive, yet they also provide important anatomic information. Each of these modalities has its own niche in the imaging market.

Nuclear medicine uses radiopharmaceuticals to provide a more sensitive image. In the case of small-cell lung cancer, for example, using one injection of the diagnostic radiopharmaceutical might make some of the currently used five-stage tests for lung cancer detection unnecessary. This is cost-effective because one nuclear medicine procedure has the potential to save society thousands of dollars in unnecessary diagnostic procedures.

Diagnostic radiopharmaceuticals, for example, can differentiate between a growing tumor and scar tissue. Since the modality images physiological function, it can tell if an abnormality is living or not. If the abnormality is living, nuclear imaging allows for early and prompt treatment. If the scar tissue is dead, nuclear imaging avoids unnecessary procedures and expenses. Consequently, nuclear medicine contributes to the cost-effectiveness of preventive medicine.

Nuclear physicians interviewed by Frost & Sullivan support these statements. They also deeply regret the fact that nuclear medicine diagnostic imaging has failed to attract more physicians and a loyal customer base. Respondents think that the nuclear medicine community has not fully explained the cost-effectiveness of this imaging modality to potential end-users.

In a managed care environment , where cost savings and outcomes are the primary indicators of product acceptance, such benefits of radiopharmaceuticals can result in significant market opportunities.

Development of Therapeutic Radiopharmaceuticals Creates New Market Opportunities

Nuclear medicine is among the least utilized of the competing imaging modalities, not only because of its high price per procedure, but also because it has failed to educate physicians and patients as to its advantages.

To grow, nuclear medicine should develop special applications that distinguish it from other imaging modalities. Developing therapeutic radiopharmaceutical agents is a possible course for nuclear medicine to follow. Nuclear physicians and industry participants interviewed by Frost & Sullivan expressed hope that the development of nuclear medicine therapy will spur growth on the diagnostics side. This is likely to be done by offering patients and practitioners access to the best available imaging modality, followed by cost-effective and timely treatment.

Some therapeutic radiopharmaceuticals already successfully address the pain caused by bone cancer. The two products offered in this field are:

- Metastron (Amersham Medi-Physics)
- Quadramet (DuPont/Cytogen)

Development of therapeutic nuclear medicine is likely to provide the industry with a much-needed boost.

Nuclear Diagnostics for Older Patients Is Likely to Result in Healthcare Savings

The population of the industrialized world is aging rapidly. The process is not the same for each country in this group, but there certainly will be fewer people contributing towards the healthcare expenses of the next generation of retirees. In the United States, many healthcare analysts already are claiming that the Medicare system will face financial collapse early in the next century. This is a major problem throughout the industrialized world.

Since the late 1980s, radiopharmaceutical companies have been developing new agents for oncology applications. An aging population will create a higher need for cancer identification. For example, 1 in 23 men between the ages of 60 and 79 is a victim of colorectal cancer; for women, the rate is 1 in 30. In comparison, from birth to the late 30s, 1 in 1,667 men and 1 in 2,000 women develops colorectal cancer. Hence the need for promoting the use of nuclear medicine imaging (NMI) as the diagnostic tool of choice among the elderly.

Neurological disease is another area into which this imaging modality is likely to expand. Neurological diseases, particularly Alzheimer's and Parkinson's disease, are more prevalent among the elderly. NMI can provide the elderly with better management of the debilitating neurological diseases that attack them, while also saving money through early identification of these diseases.

Nuclear medicine's ability to image organ function is advantageous for the identification and treatment of these diseases. This can reduce the cost of healthcare by making

treatment of elderly patients less wasteful and more effective while improving the patient's quality of life.

Educating General Practitioners on NMI Would Raise the Referral Rate

Nuclear physicians, as members of a specialty field, do not manage patient care. Patients are provided by referrals from general and family practitioners. Traditionally, this group of doctors have been ignored by nuclear medicine. As a result, fewer patients are referred to nuclear medicine than to CT and ultrasound, for example.

Since its introduction in the 1940s, nuclear medicine has remained a relatively low-key imaging modality. One industry participant called it "an imaging modality kept hidden in the basements of hospitals." This has seriously hurt prospects for nuclear medicine.

Through educating patients and general practitioners, nuclear medicine can enlarge its patient and physician base. The Society of Nuclear Medicine and many radiopharmaceutical companies have developed educational programs to bring nuclear medicine into the mainstream of diagnostic imaging.

Frost & Sullivan believes that education and awareness are critically needed if the industry is going to retain its position. Both are necessary for growth of NMI. Patients and general practitioners should be better informed of the benefits of radiopharmaceuticals in imaging disease sites and in reducing healthcare costs. A better-informed population can help secure and expand the niche that nuclear medicine has built for itself.

Referring physicians have a strong role in the expansion of nuclear medicine. Their cooperation and referral services could provide nuclear medicine diagnostic imaging with a widely expanded patient population.

Nuclear Medicine Improves Pediatric Survival Rate

Diagnostic radiopharmaceuticals have also developed a solid reputation in pediatric care. Children frequently undergo nuclear medicine procedures to evaluate bone pain, injuries, infection, or kidney and bladder function.

Bone-seeking radiopharmaceuticals have uniform uptake throughout much of the pediatric skeleton. Because the pediatric skeleton is in a state of flux, maturing from birth to adulthood, it easily absorbs the tracer. Pediatric urinary studies are also very effective since 50 percent of the radiopharmaceutical is excreted via the kidneys.

Radiopharmaceuticals which are absorbed by the pediatric skeleton can also detect cases of child abuse. When high-specificity lesions are encountered in an otherwise healthy child, a diagnosis of abuse can be made with a high level of certainty. These abnormalities are often subtle and require the high-detail imaging that radiopharmaceuticals can provide.

Nuclear medicine has yet another opportunity for expansion in pediatrics. As more children are being evaluated locally, imaging physicians should be able to offer a broad spectrum of nuclear imaging procedures for pediatric patients. Treatment of these patients is often urgent, and well-performed nuclear imaging procedures may provide information which is pivotal in their care. Frost & Sullivan believes that the

pediatric population is likely to be a major driver for diagnostic radiopharmaceuticals.

Early Detection Is a Key Advantage

Nuclear medicine diagnostics has the capability to image tumors even while they are still very small. This capability enables nuclear diagnostics to play an important role in preventive medicine. By finding abnormalities when they are in the developing stage, doctors can treat these lesions before they spread throughout a patient's body and become life-threatening.

Other Disease Applications Can Also Generate Demand

Besides expanding into oncology applications, nuclear medicine diagnostics is examining its potential in other disease applications. These include infection imaging and neurology applications, which are likely to have great demand among the elderly. Nephrology is another developing field.

Market Restraints

High Cost of NMI Concerns Managed Care Organizations

Primary care physicians perceive NMI as too expensive. This perception rests on the fact that one nuclear medicine scan is costlier than diagnostics procedures done by other imaging modalities, such as ultrasound. Yet patients not receiving NMI will almost certainly need several ultrasound scans to obtain a solid diagnosis. In contrast, nuclear medicine can arrive at that diagnosis with only one scan.

Nuclear medicine procedures are not inexpensive. Nuclear physicians and industry experts readily accept this reality. Prices for nuclear medicine diagnostic procedures range from $1500 to $6000. This compares to about $50 for an X-ray, for example.

Observers of the nuclear medicine industry strongly believe that the industry has failed to explain the difference between apparent costs—the prices quoted above—and total costs. Real cost is lowered by the fact that nuclear imaging is one of the most effective imaging modalities available to healthcare. While an ultrasound can identify an abnormality that is 15 mm in diameter, radiopharmaceuticals can image one that is 5 mm in diameter. This is an impressive advantage, particularly when trying to image minute abnormalities, such as small-cell lung cancer.

Although the cost of a nuclear medicine procedure is high, the precision and accuracy of the diagnosis far outweigh this cost. Real price should not be deduced from the actual cost of the procedure, but from the real benefits that the procedure provides. The nuclear medicine industry as a whole, and radiopharmaceutical companies in particular, should better communicate the pharmacoeconomic benefits of nuclear medicine diagnostics to potential end-users.

The cost conscious nature of managed care has been an obstacle for the expansion of nuclear medicine. Healthcare in the United States is in a period of long-term permanent restructuring. Managed healthcare continues to evolve, and reimbursement is in the process of changing as well. In this atmosphere, nuclear medicine has found it hard to convince managed healthcare of the modality's advantages.

Competition from Other Imaging Modalities Shrinks the Utilization Rate

Medical Imaging is a tremendously competitive market, and nuclear medicine is the most expensive of the available modalities. As a result, nuclear medicine's market is relatively restricted. The current market for nuclear diagnostics is saturated because nuclear diagnostics has failed to expand its patient and physician base.

The state of the market spells serious problems for NMI and radiopharmaceuticals. To address this problem, companies in the NMI industry should continue their efforts to provide new diagnostic radiopharmaceuticals for additional applications. Radiopharmaceutical companies should break new ground and enter applications where competing modalities do not have a strong presence.

Lack of Patient and Physician Education and Awareness Reduces Market Penetration

Nuclear medicine is faced with a slowing market because it has failed to attract new end-users. Nuclear medicine also has failed to educate patients as to the benefits of physiological imaging. While other imaging modalities actively pursued acceptance among referring physicians and promoted themselves to patients, nuclear medicine remains hidden from the mainstream. Consequently, a substantial part of nuclear diagnostics' potentially remains unfulfilled.

Educating patients and physicians can popularize nuclear medicine and convince both groups of the economic benefits of nuclear medicine.

Shrinking Number of Nuclear Medicine Physicians Limits Growth

The declining number of nuclear medicine programs is a cause for concern. This is a consequence of both the industry's sluggish growth and the absence of career opportunity for younger nuclear physicians. In the United States, there are only about 1,500 nuclear physicians. There is a need for a broad educational program in nuclear medicine and radiopharmacy at leading universities in the United States.

Frost & Sullivan believes this is a major problem for the nuclear medicine industry. If the number of nuclear physicians decreases, consumption of radiopharmaceuticals also is likely to decline. Without sufficient nuclear physicians, there is likely to be a vicious circle of declining use.

Not only would a reduced number of nuclear physicians result in reduced use, it would also negatively affect research trials. Fewer opportunities for a new generation of nuclear physicians would deter research and expansion into new applications.

Current Production Capacity for Radiopharmaceuticals Exceeds Demand

Many industry analysts and respondents agree available capacity for medical isotopes far outweighs the present market demand. This has led to industry consolidation in recent years.

Radiopharmaceutical companies have the capacity to manufacture large quantities of radiopharmaceuticals. Many of the nuclear physicians interviewed think that too much product is being manufactured. Respondents believe that nuclear

medicine is failing to expand to meet the consumption levels planned for by the radiopharmaceutical companies. Overproduction may be fueling perception of a shrinking market. Competing modalities are gaining ground, and the market share of nuclear medicine diagnostic is falling.

Investments in education programs that focus on increasing awareness and safety of nuclear medicine can contribute to market growth and may thereby reduce the problem of excess of capacity. If the client base can be expanded, demand would rise to meet capacity.

Fear of Radioactivity Keeps Patients and Referring Physicians at Bay

Another restraint that radiopharmaceuticals face is the fear of radioactivity held by most patients. By their very nature, radiopharmaceuticals carry the stigma of radiation. This poses a concern among patients as well as among referring physicians. Nuclear physicians, on the other hand, believe that this fear is ungrounded. The amount of radiation to which a nuclear medicine diagnostics patient is exposed is very small.

Additionally, radiopharmacies have been established to handle the isotope for the preparation of the dose. Professional handling of isotopes reduces the risk of radiation. The disposal issue related to patients is not a major concern, since most of the radioactive dose is excreted by the patient's body in a controlled environment and following federal guidelines.

Competitive Environment

Structure

Since 1995, the diagnostic radiopharmaceutical market has witnessed a strong move towards industry consolidation. In this time-period alone, three radiopharmaceutical companies have been absorbed by other, much larger, companies. Close to 80 percent of the total U.S. diagnostic radiopharmaceutical market is held by three companies: Amersham Medi-Physics, Mallinckrodt, and DuPont Merck.

The remaining 20 percent is held by smaller companies such as CIS USA, Bracco Diagnostics, Centocor, NeoRX, Immunomedics, and Cytogen. Frost & Sullivan believes that industry consolidation has peaked, leaving the radiopharmaceutical industry with about 15 companies.

Characteristics of the U.S. Market

Frost & Sullivan estimates that the size of the total U.S. diagnostic radiopharmaceutical market was approximately $531 million in 1996. This dollar figure was arrived at by estimating the sales of the radiopharmaceutical companies with a presence in the U.S. market. Although the growth rate forecast for this market is somewhat low at about 10 percent, it is expected to receive a much-needed boost from new agents being developed, as well as from the evolution of therapeutic nuclear medicine.

The largest source of radioisotopes for the United States is MDS Nordion, located in Canada. MDS Nordion supplies about 68 percent of the Tc-99m used by the U.S. nuclear

medicine industry. There are several sources of radioisotopes in the United States, such as the Missouri University Research Reactor, Brookhaven National Laboratory, and Oak Ridge National Laboratory. Yet, for the most part, the United States remains dependent on overseas sources for radioisotopes used in nuclear medicine.

In the United States, most radiopharmaceuticals are used for cardiology applications. This situation is likely to change in the future as newer imaging agents and therapeutic radiopharmaceuticals become available. Several oncological radiopharmaceuticals are about to enter the market, and it is expected that these agents will boost sales.

Characteristics of the World Market

Nuclear medicine is underutilized in many regions of the world. While the United States makes up approximately 47 percent of the world market, South America's share is a paltry 2.5 percent. Differences from country to country, particularly within a region, are considerable. Table 2-7 exhibits shares of the world diagnostic radiopharmaceutical market by region in 1997.

The Pacific Rim has witnessed strong growth of nuclear medicine. Japan, in particular has witnessed increasing use of radiopharmaceuticals, such as DuPont's Neurolite and Amersham's Ceretec, for brain imaging. Taiwan and Korea have also experienced considerable growth. China remains underdeveloped in radiopharmaceuticals, mainly because of a lack of incentives for companies to enter this piracy-plagued market. Companies are greatly concerned about the lack of intellectual property protection for their formulations in China.

Table 2-7

Diagnostic Radiopharmaceuticals Market: Percent of Revenues by Geographic Region (World), 1996

Region	*Revenues ($ Million)*	*Percent of Total*
United States	531.0	47.0
Asia/Pacific	298.3	26.4
Europe	220.4	19.5
Latin America	28.5	2.5
Rest of the World	51.8	4.6
TOTAL	1,130.0	100.0

Note: All figures are rounded. *Source: Frost & Sullivan*

Nuclear medicine also has enormous potential elsewhere in the Pacific Rim. The modality is seriously underutilized in countries such as Indonesia, where there are 100 million people but only 25 gamma cameras.

The Pacific Rim has experienced growth that ranges from 10 to 15 percent per annum. In 1996, the Pacific Rim market was around $298.3 million, or 26.4 percent of the total world radiopharmaceutical market. This region witnessed considerable consolidation with Amersham's acquisition of Nihon Medi-Physics, a move that left Amersham with almost 65 percent of the Japanese radiopharmaceutical market.

In Europe, nuclear medicine has lost ground to other imaging modalities. This market has suffered from cost-cutting by several European governments, which are faced with shrinking healthcare budgets. Some industry experts have argued against implementing a U.S.-style radiopharmacy in Europe, since it is believed that this would cut radiopharmaceutical companies' profits.

Nonetheless, Europe is filled with possibilities. The continent has an aging population, giving radiopharmaceuticals for oncology a very positive outlook. Neuroscience is yet another area of possible expansion. Cost-effectiveness is likely to be a major consideration in this region, particularly as the population ages and healthcare budgets shrink.

The European radiopharmaceutical market is controlled by four companies: Amersham, Mallinckrodt, DuPont Merck, and CIS Biointernational. Amersham's Myoview has a strong presence in cardiology. DuPont Merck has a strong presence in Germany. Europe makes up 19.5 percent of the world market, or about $220.4 million per annum. Growth in Europe is relatively stronger than in North America, although not as strong as in the Pacific Rim.

The main concern of the radiopharmaceutical companies in South America is retaining their presence in the marketplace. The region has tremendous potential, particularly in Brazil, Argentina, Colombia, and Chile. Other countries, such as Mexico, have been affected by financial problems. Nevertheless, the prospects of the region are positive.

Radiopharmaceutical companies wishing to participate in this developing market must adapt to it. As in some Pacific Rim countries, the threat of patent infringement is a major concern for global companies doing business in Latin America. In several cases, local atomic agencies produce cheap radiopharmaceuticals of disputable quality. These same agencies routinely impose regulatory obstacles to protect their market share and avoid competition from radiopharmaceutical companies.

Still, the region is witnessing an unparalleled process of privatization. Privatization of the healthcare system is ongoing, raising the hopes of companies such as Amersham, DuPont Merck, Mallinckrodt, and CIS Biointernational. In Brazil, DuPont's Cardiolite is tremendously popular.

The South American radiopharmaceutical market hovers around $28.5 million, or 2.5 percent of the world market. The market in this region is growing around 10 percent per annum, in the judgment of the radiopharmaceutical industry.

In South America, radiopharmaceuticals are priced differently than in the other three regions covered in this study. Mainly because of economic reasons, radiopharmaceutical companies cannot sell their products at the same prices as in the other regions. Companies also face strong competition from local atomic energy agencies that manufacture and distribution of tracers.

The initial cost of the procedure hampers NMI's expansion into less affluent healthcare markets. This is not to say that nuclear medicine has no future in developing regions. With the current transition to privatization, many countries, particularly in South America, find nuclear medicine a tempting imaging tool because of its cost-effectiveness.

Expansion is not far away if strategic actions are taken by the industry. More emphasis should be placed on developing new radiopharmaceuticals. In the developing world, with its large number of potential patients and physician base, the goals should be to raise public awareness of the benefits of nuclear medicine and to educate physicians.

Leading Medical Isotopes in Nuclear Diagnostics

The quantities of radioisotopes used in radiopharmaceuticals are very small. Some of the most commonly used reactor isotopes include:

- **Molybdenum-99:** Used as a parent in the production of technetium-99m, the most widely used isotope in nuclear medicine.
- **Technetium-99m:** Used in scintigraphy to image the brain, lungs, liver, spleen, thyroid, kidney, bladder, skeleton, blood pool and blood flow dynamics, bone marrow, salivary and lachrymal glands, infection, and in several specialized medical studies.
- **Iodine-125:** Used to evaluate glomerular filtration rate of kidneys and to diagnose deep-vein thrombosis in the leg. It is also widely used in radioimmunoassays and as an X-ray source for bone-density measurements.
- **Iodine-131:** Widely used in functional imaging and therapeutic applications for overactive and underactive thyroid problems, carcinomas and their secondaries, diagnosis of abnormal liver function, renal blood flow, and urinary tract obstruction.

Distribution System

Distribution has become the most competitive element of the radiopharmaceutical industry. An overwhelming number of radiopharmaceutical doses are distributed by nuclear pharmacies. A nuclear pharmacy, also known as a radiopharmacy, is a highly specialized, licensed facility that supplies the hospitals and related healthcare sites with radiopharmaceuticals.

When a doctor orders a radiopharmaceutical, the radiopharmacist compounds the drug and delivers it to the hospital or clinic where a doctor administers it. Proximity to

metropolitan areas is the key to being able to rapidly dispense these time-sensitive products.

Radiopharmacies emerged in the United States in the 1970s to provide convenience to nuclear medicine physicians. Initially, radiopharmacies were designed to provide nuclear imaging centers and hospitals with the necessary services to dispense doses, dispose of waste, and separate hospitals from radiochemists and radiopharmacists. The concept became very popular, and radiopharmacies were quickly established throughout the United States. In 1997, radiopharmacies provide access to radiopharmaceuticals to over 90 percent of the patient population of the United States.

An extensive, well-established network of radiopharmacies is the primary competitive factor in the distribution of radiopharmaceuticals. Syncor International Corporation has established a network of over 120 radiopharmacies in the United States, as well as 10 overseas. Syncor dispensed over 6 million radiopharmaceutical doses in 1996, making it the industry leader in distribution. Syncor's purchasing power is such that it can dictate pricing agreements to radiopharmaceutical companies for almost all tracers being manufactured in 1997.

Syncor delivers prescriptions and bulk radiopharmaceuticals to over 7,000 hospitals, clinics and physicians' offices daily. The company not only provides excellent access to radiopharmaceuticals, but also trains radiopharmacists and recruits technologists.

Syncor also secures long-term customer relationships through a computerized nuclear medicine management system that has more than 1,300 customer installations. Syncor is well-

positioned for future growth through the opening of additional locations. It is also positioned for healthcare reform through high volume, low cost, and a large distribution network.

In February, 1994, Syncor entered into an agreement, which the company calls a strategic alliance, with the DuPont Merck Radiopharmaceutical Company. As a result, nearly 2,000 bulk radiopharmaceutical customers were transferred to Syncor. This alliance is expected to contribute to the expansion of the nuclear medicine market by providing more access to DuPont Merck's radiopharmaceuticals through better distribution.

In the last few years, Amersham and Mallinckrodt decided to compete with Syncor on distribution. Amersham has established 28 radiopharmacies in the United States and one in Canada. Mallinckrodt has established 36 radiopharmacies in the United States and purchased another in London, England, from Amersham. Both companies are well-positioned to compete with Syncor's network of radiopharmacies.

Mallinckrodt, DuPont Merck, Amersham and Syncor distribute and market each other's products worldwide through their radiopharmacies.

Seventy independent radiopharmacies operate in the United States. Table 2-8 displays market shares of the leading radiopharmacy companies in the United States.

Table 2-8

Diagnostic Radiopharmaceuticals Market: Radiopharmacy Company Market Share by Revenues (U.S.), 1996

Company	*Market Share (%)*
Syncor	48
Mallinckrodt	14
Amersham	11
Independent radiopharmacies	27
TOTAL	100

Note: All figures are rounded. *Source: Frost & Sullivan*

Market Share

Market shares presented in this study are based on reported sales of radiopharmaceuticals per company. Table 2-9 exhibits market shares by company in the U.S. diagnostic radiopharmaceutical market.

Table 2-9

Diagnostic Radiopharmaceuticals Market: Company Market Share by Revenues (U.S.), 1996

Company	*Market Share (%)*
Amersham Healthcare	31
DuPont Merck	28
Mallinckrodt	21
Others	20
TOTAL	100

Others include CIS-USA, Bracco Diagnostics, Biomira, Inc., Centocor, Inc., Cytogen Corporation, NeoRX, Neoprobe, and Immunomedics.

Note: All figures are rounded. *Source: Frost & Sullivan*

Some companies, like DuPont Merck, have lost market share mainly because other companies, such as Mallinckrodt, have expanded their distribution networks.

In a stagnant market, industry leaders have decided to cooperate instead of ruthlessly undercutting each other's positions. Several industry participants have expressed their desire to continue, and possibly strengthen, their cooperation. This is more prevalent in markets that are too small for rivalry and excessive competition. However, the radiopharmaceutical companies have recognized that cooperation is also beneficial in markets that are large enough for competition, such as the United States.

In addition to the market leaders carrying proprietary products in their portfolio, for example DuPont Merck's Cardiolite, Amersham's Myoview, Mallinckrodt's OctreoScan, each company also sells a wide array of Tc-99m radiopharmaceuticals. It is very important to these companies to continue to be able to sell each other's products. The three above mentioned companies firmly hold over 80 percent of the U.S. radiopharmaceutical market.

Overview of Market Leaders

Amersham Medi-Physics

Amersham Medi-Physics gained an estimated 10 percentage points of market share over the past year through its highly aggressive and bold acquisition of the radiopharmaceutical division of Sorin Biomedica of Italy, its acquisition of Nihon Medi-Physics, in Japan, and its introduction of new products. Amersham joined with Sumitomo

Chemical to purchase Nihon Medi-Physics, gaining almost unchallenged control of the profitable Japanese radiopharmaceutical market.

These acquisitions have given the company a competitive edge in the U.S. radiopharmaceutical market by reducing the number of participating companies. Consolidation of the market has therefore given Amersham the opportunity to gain terrain relative to its two major competitors, Mallinckrodt and DuPont Merck.

Amersham's product line includes proprietary radiopharmaceuticals such as Metastron for oncology, Ceretec for neurology, and Myoview for cardiology. It also includes several other radiopharmaceuticals like thallium, gallium, and Tc-99 generators. The company's product line is well-positioned in the market, and the price/performance ratio of Amersham's main product Myoview makes it a top choice for end-users worldwide.

Amersham's distribution system is secured by the company's twenty eight radiopharmacies, as well as by agreements with Syncor and Mallinckrodt.

In July 1997, Amersham announced its decision to merge with Nycomed ASA. The new company, which will be a healthcare giant, will be known as Nycomed Amersham.

Mallinckrodt Medical

Mallinckrodt operates globally, with manufacturing and distribution facilities in various countries. Approximately 40 percent of the company's sales are outside the United States. Products are manufactured and marketed through a variety of

subsidiaries, affiliates, and joint ventures. Nuclear medicine products are sold in the United States through a geographically organized sales group and a network of radiopharmacies. Additionally, Mallinckrodt has agreements to distribute its products through Amersham and Syncor radiopharmacies.

Mallinckrodt has introduced innovative radiopharmaceuticals in recent years. In 1994, the FDA authorized OctreoScan, a singular radiopharmaceutical which assists physicians in diagnosing and determining the extend of spread of certain cancers. Four years earlier, it had introduced TechneScan, for improved imaging of the kidneys and the renal system.

Lastly, Mallinckrodt signed an agreement with Immunomedics to market CEA-Scan in selected European countries and North America. In July 1997, the FDA gave Mallinckrodt approval to sell its Netherlands-produced Molybdenum-99 in the United States.

In the spring of 1997, Mallinckrodt entered into an exclusive agreement to supply radiopharmaceuticals to the 1,800 hospitals and affiliates of Premier, Inc., the largest healthcare alliance in the United States. The five-year agreement, which was implemented April 1, includes a full range of products and accessories used in NMI procedures. This business coup surprised the industry, while at the same time providing Mallinckrodt with increased profit potential in the United States by expanding the company's distribution system and taking clients away from competitors.

Mallinckrodt has entered the radiopharmacy business and now has 36 sites in the United States and one in England.

DuPont Merck

The DuPont Merck Pharmaceutical Company was formed in 1991 as a joint venture between DuPont and Merck and Co., Inc. DuPont Merck has witnessed the rapid international expansion of Mallinckrodt and Amersham and has vigorously examined its own opportunities. DuPont Merck believes that discovery of new products and new markets around the world will be the key to its success in the radiopharmaceutical industry since the company has lost market share in the United States. The company has decided to pursue overseas business expansion, not only in Europe, where Germany is its strongest market, but also in the Pacific Rim and South America.

DuPont Merck signed an agreement making Syncor its exclusive distributing arm. In fact, it is Syncor that signs distribution agreements for DuPont's products with other radiopharmacy companies. By doing so, DuPont avoided having to spend resources to open radiopharmacies throughout the United States. Instead, DuPont has earmarked resources for developing new oncology radiopharmaceuticals.

These new products include Verluma for the imaging of small-cell lung cancer and Quadramet for cancer bone pain palliation. The company has recently provided solid data on the ability of Tc-99m, the isotope used for the formulation of the company's best selling radiopharmaceutical, Cardiolite, to better image breast cancer when used with gated SPECT imaging. This product is being marketed as Miraluma.

Cardiolite, is a cardiac imaging agent used to detect heart disease. In fact, Cardiolite is so successful that it has become the standard for cardiac imaging in nuclear medicine, quickly displacing Thallium. Still, competition is just around the

corner. Recently, Amersham positioned Myoview to compete with Cardiolite, but DuPont's tracer has a solid reputation and firm grasp on the cardiac imaging market.

3

Assessment of the U.S. Therapeutic Radiopharmaceuticals Market (2001-2020)

Chapter Objectives

This chapter provides an overview of the current nuclear therapeutics market in the United States and emerging opportunities and challenges in the market through 2020.

Market Overview

Therapeutic radiopharmaceuticals allow nuclear physicians to treat diseases by attacking only the affected cells. Over ninety nuclear therapy research trials are in progress in the United States.

These trials are using several isotopes to combat many diseases, such as:

- Colorectal cancer
- Heart disease
- Rheumatoid arthritis
- Non-Hodgkin's lymphoma

In contrast to nuclear medicine diagnostics, an established $1 billion worldwide market, nuclear medicine therapeutics is mostly in development. Although a large number of therapy trials using radioisotopes are in progress around the country, the nuclear therapy modality is in its developing stages. In fact, only four therapeutic isotopes for four diseases have received FDA approval and are currently used in the United States. A complete list of radioisotopes in clinical trials in the United States is included in the appendix.

Nuclear medicine experienced sluggish market growth during most of the 1990s. This results from cutbacks in healthcare expenditure and from competition from other imaging modalities. The nuclear medicine industry is pinning its hopes on the development and expansion of nuclear therapy. The successful development and introduction of nuclear therapeutics is expected to expand the nuclear medicine industry.

Current Nuclear Medicine Therapies

In 1997, only four radiopharmaceutical-based therapeutic applications are commercialized in the United States. Table 3-1 exhibits the four disease indications, the respective isotopes, and

the respective radiopharmaceutical companies offering nuclear therapy treatment products in the United States.

Table 3-1

Therapeutic Radiopharmaceuticals Market: Approved Indications and Therapeutic Isotopes Currently Sold (U.S.), 1997

Indication	*Isotope*	*Suppliers*
Thyroid cancer	I-131	Amersham Mallinckrodt Bracco Diagnostics CIS US Syncor International
Hyperthyroidism	I-131	Amersham Mallinckrodt Bracco Diagnostics CIS US
Bone pain palliation	Sr-89 Sm-153	Amersham DuPont Merck
Polycythemia rubra vera	P-32	Mallinckrodt

Source: Frost & Sullivan

In the four applications listed in Table 3-1, only thyroid cancer radiopharmaceutical products have experienced unqualified success. Radiopharmaceutical products designed to combat thyroid-related diseases carry a heavy dose of I-131. Since the thyroid gland is receptive to iodine, the I-131 radioisotope is very effective in treating thyroid gland diseases. I-131 has also been successfully used in treating hyperthyroidism.

In the United States, 200,000 patients per year experience the severe and chronic pain of bone metastases. Two radioisotopes, Sr-89 and Sm-153, have shown some success in bone pain palliation. Sr-89 is the foundation for Amersham's

Metastron, one of two therapeutic radiopharmaceutical products approved by the FDA for bone pain palliation.

The other approved product is Cytogen's Quadramet, which uses Sm-153. DuPont Merck has an agreement with Cytogen to market and distribute Quadramet in the United States. Several other radiopharmaceutical products for bone pain palliation are awaiting FDA approval. These do not use either Sr-89 or Sm-153. Instead, they use other radioisotopes, such as:

- Tin-117
- Rhenium-186
- Phosphorus-32
- Radium-223

The fourth product in the marketplace is Mallinckrodt Medical's P-32 Chromic Phosphate Colloid approved for the treatment of Polycythemia rubra vera (a bone marrow disease involving the overproduction of red blood cells). However, sales of this product has been limited due to the low use of this product for polycythemia rubra vera as there are other established treatments available to the patient.

Developmental Activities

Many U.S. clinical trials are exploring new applications for nuclear medicine therapy. A sample of these clinical trials is shown in Table 3-2.

Table 3-2

Therapeutic Radiopharmaceuticals Market: Key Research Institutions, Isotopes, and Disease Indication, (U.S.), 1997

Research Institution	*Isotope*	*Disease Indication*
Memorial Sloan Kettering	Re-186	Bone pain palliation
	I-131	Colon cancer
	Bi-213	Leukemia
Duke University	I-131	Brain tumors
USC Medical Center	P-32	Rheumatoid arthritis
	P-32	Hemophilia
Vanderbilt University	Y-90	Prostate cancer
Arlington Cancer Center	Y-90	Hodgkin's lymphoma
	Y-90	Ovarian cancer
Columbia University	Re-188	Heart disease
Scripps Clinic	Ir-192	Heart disease
Emory University	Y-90	Heart disease
Brigham and Women's	Dy-165	Rheumatoid arthritis
Fred Hutchinson Cancer Center	I-131	Leukemia
Mallinckrodt Institute	Sm-153	Radiation synovectomy

Source: Frost & Sullivan

Research institutions in the United States are experimenting with a wide variety of isotopes. Many early results from clinical trials show great potential for nuclear therapeutics. The advantage of nuclear therapeutics over other therapies is that nuclear therapy can eliminate cancerous cells without harming healthy cells. Other therapies, such as chemotherapy and external beam radiation, affect both non-cancerous and cancerous cells. This approach results in greater pain and longer recovery time for patients, not to mention higher treatment costs.

In contrast, nuclear therapy would:

- Lower the overall cost of the therapeutic procedure
- Reduce the time a patient stays in the hospital
- Reduce pain and suffering experienced by the patient

Thus, nuclear therapy greatly improves quality of life for patients while also reducing the cost of healthcare. The United States places great emphasis on both of these factors. Pharmacoeconomic data could be valuable for achieving acceptance of nuclear therapy in the medical community.

With four commercial therapeutic isotopes, the U.S. nuclear therapy market is estimated to have generated sales of $48 million in 1996.

Competitive Structure

Many radiopharmaceutical companies involved in nuclear diagnostics also offer nuclear therapy products. Table 3-3 exhibits therapeutic radiopharmaceutical company market shares by revenues in the United States for 1996.

Table 3-3

Therapeutic Radiopharmaceuticals Market: Company Market Share by Revenues, (U.S.), 1996

Company	*Market Share (%)*
Amersham	38
Mallinckrodt	19
CIS US	17
Bracco Diagnostics	15
Syncor International	11
TOTAL	100

Note: All figures are rounded. *Source: Frost & Sullivan*

Smaller radiopharmaceutical companies are responsible for a large portion of research programs currently undertaken in the country. The larger radiopharmaceutical companies have not become involved in this process because of the risks and high cost of developing therapeutic radiopharmaceutical. Instead, the larger companies will likely provide marketing and distribution for products developed by smaller radiopharmaceutical companies. The relationship between DuPont Merck and Cytogen is a good example of such cooperative agreements.

Market Outlook: Supply and Demand

The effectiveness of therapeutic nuclear medicine, combined with the development of new products, make rapid market growth in the first years of the next century very likely. So far, nuclear medicine does little to treat the malignancies that it identifies so well. Many nuclear physicians believe that if nuclear therapy develops and expands into a wide variety of applications, there will also be a drastic increase in demand for nuclear diagnostics. This expected market growth would increase demand for radioisotopes.

In 1997, there are not enough U.S. sources of isotopes to support the expected expansion of nuclear therapy in the twenty-first century. Additionally, there is concern about the reliability of the supply of Molybdenum-99, the most widely used isotope in nuclear medicine. Many nuclear physicians have expressed concern that the future expansion of nuclear therapy might be in jeopardy because of an unreliable supply of exotic isotopes. Consequently, it is recommended that the stable

supply of radioisotopes in the United States be discussed extensively.

The MDS Nordion labor unrest of June 1997, as well as expected shutdowns at Brookhaven and Los Alamos National Laboratories, brought the supply issue into the open. Research centers face a serious challenge in their efforts to obtain isotopes for therapy research. Moreover, the unreliable supply of isotopes became apparent during one interview that Frost & Sullivan conducted with a prominent nuclear physician. His requested supply of I-131 was not delivered, causing a serious temporary disruption of patients' treatment.

The supply of isotopes in today's market is not reliable enough to support a higher level of research. If nuclear medicine therapy is to fulfill the expectations generated by the development of leading-edge radiopharmaceutical products, the industry and the United States government need to establish steady and high-quality sources of isotopes.

Disease States and Indications

Current Radiopharmaceutical Indications

Currently, only four diseases are being treated by nuclear medicine therapy in the United States:

- Thyroid cancer
- Hyperthyroidism
- Bone pain palliation
- Polycythaemia rubra vera

The four isotopes are I-131, Sr-89, Sm-153, and P-32. The success of nuclear therapy in treating thyroid-related results

from the thyroid's receptivity to iodine, greatly simplifying the targeting of I-131 to that gland. The I-131 dose administered to the patient is very large to assure that enough I-131 reaches the gland.

In bone pain palliation, several isotopes are thought to be bone seekers. Sr-89 is one of these. Amersham's Metastron is patented, which forces other radiopharmaceutical companies to research other isotopes for bone pain palliation. Cytogen's Quadramet utilizes Sm-153, while other companies have developed proprietary drugs using other unique isotopes. Table 3-4 exhibits bone pain palliation radiopharmaceuticals awaiting FDA approval.

Table 3-4

Therapeutic Radiopharmaceuticals Market: Bone Pain Palliation Radiopharmaceuticals Awaiting FDA Approval (U.S.), 1997

Isotope	*Company*
Rhenium-186	Mallinckrodt
Tin-117	Diatide

Source: Frost & Sullivan

Nonetheless, the above-stated products are not the only ones in commercial use worldwide. MDS Nordion is already marketing a Y-90-based therapeutic agent for treating inoperable liver cancer outside the United States. TheraSphere, MDS Nordion's Y-90 agent is used to treat inoperable liver cancers, those that arise in liver cells and those that spread to the liver from other sites such as the colon and the rectum.

Therapeutic Radioisotopes Under Development

The United States is the center of current therapeutic nuclear medicine research. Work is underway at research institutions and medical centers, in radiopharmaceutical companies, and at the National Institutes of Health (NIH).

Oncology is the field being researched most actively by the nuclear medicine industry. Prestigious research institutions, such as the Fred Hutchinson Cancer Research Center and the Memorial Sloan-Kettering Cancer Center, are playing a leading role in clinical trials. Projects are seeking the most effective isotopes to conquer the devastating effects of cancer. Table 3-2 lists selected projects.

Researchers are also developing drug delivery systems, called "carriers," to transport isotopes to disease sites. Such a delivery system is commonly referred to as a "smart bullet." Developing a successful carrier has proven to be the most challenging obstacle faced by nuclear therapy. While I-131, as well as Sr-89 and Sm-153, are successfully attracted to target areas, that is not the case with other isotopes.

The main problem faced by nuclear therapy is delivering a sufficient isotope dose to the disease site. Currently, a large amount of the dose does not reach the target area because biological processes in the human body act as obstacles. A smart bullet would allow the optimum dose of the radiopharmaceutical to reach the target site and directly treat the disease.

Several radiopharmaceutical companies have developed delivery systems to transport isotopes to disease sites. One of these methods, called Cell-Directed Radiation Therapy or

radioimmunotherapy, delivers more specific radiation to tumor cells while leaving normal tissue untouched. This treatment has raised wide interest among nuclear medicine researchers.

Radioimmunotherapy involves the attachment of isotopes to antibodies, which in turn carry the isotope to the target area. The antibodies attach themselves to the target cells and deliver the isotope dose. Many experts believe that radioimmunotherapy is the most effective nuclear therapy yet developed. Radioimmunotherapy allows patients to recover at home, reduces hospital costs, and decreases the pain experienced by patients. Radioimmunotherapy contributes to a higher quality of life for patients, a key parameter for acceptance in today's managed healthcare environment.

Nonetheless, radioimmunotherapy is not fully developed yet. This therapy uses both beta- and alpha-emitting isotopes to identify which isotope will most effectively treat the target area. Alpha emissions deposit energy over short distances in tissue (~ 3 to 5 cell diameters), while beta emissions deposit energy over much longer ranges. The following are among the most successful beta emitters:

- I-121
- Re-186
- Y-90

Alpha-emitting isotopes currently being researched include the following:

- Bismuth-213
- Radium-223

The successful development of effective carriers will expand the market for nuclear medicine. Many of the nuclear

physicians interviewed expressed hope that effective carriers will be discovered by the beginning of the twenty-first century.

Currently, FDA approval is being sought for more than a dozen radiopharmaceutical drugs. Six of these products are for nuclear therapy while the rest are for nuclear diagnostics. The number of products awaiting FDA approval indicates strong growth potential for nuclear medicine.

Also in the FDA's approval pipeline is Neoprobe Corporation's RIGScan® CR49, a targeting agent that guides surgeons in removing cancers. This method utilizes antibody-labeled Iodine-125 to increase surgical accuracy. Many nuclear physicians consulted by Frost & Sullivan believe combination therapy that is using both a radiopharmaceutical and another treatment modality, will provide the success that is being sought in nuclear therapeutics. Neoprobe's technology combines the use of an isotope with surgery. Some research centers are experimenting with combining an isotope and chemotherapy or external beam radiation.

Revenue Forecasts (2001-2020)

Frost & Sullivan estimates 1996 revenues in the U.S. nuclear therapy market to have been $48 million dollars. The market was very sluggish in recent years as market penetration expectations were not realized.

Currently, several therapeutic radiopharmaceuticals are awaiting FDA approval. Nuclear medicine analysts expect that these new products will spur the market by attracting more practicing physicians to prescribe or recommend this modality for treatment.

Based on the expected performance of new therapeutic radiopharmaceutical products, Frost & Sullivan forecasts that market revenues will be $62 million in the year 2000. From that year on, a growing number of therapeutic radiopharmaceuticals is expected to enter the marketplace. At least eight therapeutic radiopharmaceuticals are expected to enter the market by the year 2000.

Analysts expect that these new products will boost therapeutic radiopharmaceutical sales and have a cumulative effect on revenues in the short term. The introduction of new products is expected to expand the market from $62 million to over $440 million by 2001.

Some interviewees were surprised by this forecast, yet radiopharmaceutical companies and many nuclear medicine experts fully expect such an expansion. Mallinckrodt Medical projects that its bone pain product, Re-186 EDTMP, will generate revenues of almost $30 million in its first year. Table 3-5 exhibits a list of therapeutic radiopharmaceutical that are expected to enter the market by the year 2000.

Table 3-5

Therapeutic Radiopharmaceuticals Market: Therapeutic Radiopharmaceutical Products Expected to Enter the Market by the year 2000 (U.S.), 1997

Radiopharmaceutical	*Application*	*Company*
Re-186 EDTMP	Bone pain palliation	Mallinckrodt
Sn-117m DPTA	Bone pain palliation	Diatide
CC49 MAB	Colorectal cancer	Neoprobe
Therasphere	Liver cancer	MDS Nordion
BEXXAR	Non-Hodgkin's lymphoma	Coulter
Quadramet	Bone pain palliation	Cytogen
Biostent	Restenosis	NeoRX
Avicidin	Solid tumors	NeoRX

Source: Frost & Sullivan

Frost & Sullivan shares this view. At least 90 nuclear therapy trials are underway in the United States. These trials are very promising and are likely to result in stronger market growth by 2005.

The revenue forecast is based on the following factors:

- Incidence rates for the diseases for which nuclear therapy trials indicate likely success
- Market penetration rates for nuclear therapy within each disease indication
- Average annual product cost per patient

Based on this analysis, Frost & Sullivan forecasts that nuclear medicine therapy could become a $6 billion market in 2020. Table 3-6 forecasts U.S. revenues for nuclear medicine therapeutics from 2001 to 2020.

Table 3-6

Therapeutic Radiopharmaceuticals Market: Revenue Forecasts (U.S.), 2001-2020

Year	Revenues ($ Billion)	Revenue Growth Rate (%)
2001	0.44	---
2002	0.47	5.25
2003	0.49	5.44
2004	0.52	5.63
2005	0.66	27.85
2006	0.70	5.88
2007	0.74	6.10
2008	0.79	6.32
2009	0.84	6.55
2010	1.59	88.88
2011	1.78	12.22
2012	1.91	7.11
2013	2.05	7.34
2014	2.20	7.57
2015	3.83	73.90
2016	4.04	5.40
2017	4.37	8.35
2018	4.75	8.57
2019	5.52	16.20
2020	6.01	9.00

Note: All figures are rounded. *Source: Frost & Sullivan*

Market Drivers

Cost-Effectiveness of Nuclear Therapy Can Result in Significant Savings

Nuclear medicine therapy has the potential to save billions of U.S. healthcare dollars. Savings can be achieved by

treating patients more quickly and effectively. Since most nuclear medicine procedures can be performed on an outpatient basis, there would be drastic reductions in treatment costs.

Cost-effectiveness and positive outcomes are the major drivers for nuclear medicine therapeutics. Nuclear therapy promises to improve patient care by:

- Reducing pain
- Improving quality of life
- Reducing overall costs
- Being done on outpatient basis
- Shortening treatment times

The economic aspects of nuclear therapy are positive. By offering substantial savings and improving and extending lives, nuclear therapy is likely to become the treatment of choice for many diseases.

Nuclear Therapy Uses Bigger Doses Than Nuclear Diagnostics

The goal of nuclear therapy is to use radioisotopes to destroy diseased or cancerous tissue without destroying adjacent healthy tissue. In therapy, a radioisotope is chosen for its high affinity for the diseased tissue relative to healthy tissue. Therapeutic radiation doses are higher than the amounts used for diagnostic imaging. Thus, an increased supply of isotopes will be needed to sustain the demand that nuclear therapy is expected to generate.

In 1997, the United States does not produce enough isotopes to satisfy growing demand expected to result from the expansion of nuclear therapy. Increasing supplies of medical

isotopes to support this expansion should be a priority among nuclear physicians, the nuclear medicine industry, and governmental institutions such as the Department of Energy.

Nuclear medicine has not competed effectively against other imaging modalities. In the past, nuclear medicine was seen as an imaging tool. This perception still pervades the medical industry, ignoring the economic benefits of therapeutic radiopharmaceuticals. Analysts believe that the economic, efficacy, and quality-of-care advantages of nuclear therapeutics are overlooked by the general medical community.

Therefore, the medical community should be constantly informed of the benefits of nuclear therapeutics, so that the referral physician base and market penetration will increase.

Education and Awareness Campaigns Are Needed to Expand the Referral Base

One of the most serious failures of nuclear medicine has been its inability to educate referring general practitioners. Nuclear medicine has practically shunned the vast number of potential referring physicians who are the gatekeepers to an increasing number of patients. A leading nuclear physician told Frost & Sullivan that nuclear medicine has "remained in the basement."

Nuclear therapeutics should not make the same mistake that nuclear diagnostics made. If the modality is to succeed in the marketplace, it needs an adequate number of patients. This can only be achieved through education and awareness programs targeted to referring physicians. Instead of viewing non-nuclear physicians as competitors, nuclear medicine should

recognize that referring physicians are the primary source of patients. Cooperation can lead to a growing patient population and greater use of nuclear therapy.

Education and awareness are needed if nuclear therapy is to develop and expand. The nuclear medicine industry, possibly together with academic and professional associations such as the Society of Nuclear Medicine, should continue its efforts to better inform potential primary-care physicians.

Aging Population Demands Cost-Effective and Reliable Therapy

Nuclear therapy has the potential to promptly treat the diseases ravaging our growing elderly population. As the population of the United States ages, the need for effective and reliable therapy becomes more pressing.

U.S. healthcare expenditures are staggering at $1 trillion a year. Analysts expect that the aging of the population will increase the proportion of Gross National Product devoted to healthcare. The elderly population will see an unprecedented expansion in the first decade of the next century.

As the number of retired Americans increases, working people will probably have to contribute a growing proportion of their income to the healthcare system and may feel over-burdened. Additionally, the possible bankruptcy of the Medicare system by the end of this century increases the incentive to develop cost-effective therapies.

Nuclear therapy can address many of these issues by providing fast, painless, reliable, and cost-effective treatment.

New therapeutic radiopharmaceuticals could potentially save billions of dollars in healthcare expenditures.

More Effective Targeting Techniques Promise Growth of Nuclear Therapy

Better targeting of isotopes to disease areas is of great importance for the expansion of nuclear therapeutics. Nuclear therapy research focuses on developing effective methods to deliver isotopes to disease sites once these are identified. Discovery of sophisticated delivery systems still eludes nuclear researchers.

Tremendous progress has been achieved. Successful experimentation with a thyroid-seeking isotope, I-131, inspires further research and development. Development of an antibody-based delivery system allows nuclear therapy to transport sufficient doses to disease areas. This targeting technique not only reduces damage to healthy tissue caused by radiation, but also makes the entire treatment more effective and reliable.

Frost & Sullivan has identified several small biomedical companies trying to develop an effective delivery system. Additionally, several research programs are exploring the use of medical isotopes as a complimentary therapeutic tool to traditional treatments.

Cancer Applications Offer Therapeutic Opportunities

The growing incidence of cancer is likely to support positive public perception of nuclear medicine. The positive aspects of radiation, if properly emphasized, should encourage use of radiopharmaceuticals. The DOE can play a major role in

affecting public perception of the benefits of nuclear therapy. Therapeutic radiopharmaceuticals should be included in the campaign to fight cancer.

Nuclear therapy research primarily seeks treatments for cancer, one of the main killers of Americans. Breast, lung, and prostate cancer, the most common types, claim the lives of nearly one million Americans every year.

Nuclear therapy promises to become a very reliable and effective tool in the fight against this disease. Some of the research institutions consulted by Frost & Sullivan stated that nuclear therapy for treatment of cancer has experienced success rates of up to 80 percent. Success has been achieved at reduced financial and emotional cost compared to other treatment modalities, such as chemotherapy. Furthermore, physicians stated that in many cases even terminal patients have gone into complete remission.

Market Restraints

Lack of Reimbursement for Treatment Could Doom Nuclear Therapy Research and Development

Nuclear medicine therapeutics will not succeed in the marketplace without reimbursement from healthcare organizations such as Medicare and third-party insurers. A very good example of this problem is the failure of Positron Emission Tomography (PET) to obtain full reimbursement. PET is one of the most effective imaging methods available but does not qualify for reimbursement from federal agencies because it has failed to prove its cost-effectiveness. Many federal regulators

mistakenly consider PET just another imaging tool that researchers use in their laboratories.

Nuclear therapy should work to avoid this problem. One very practical way of doing this is to form alliances with those communities which will profit the most from nuclear therapy. One likely ally is the American Association of Retired Persons (AARP), a lobbying group for the elderly. The high incidence of cancer among the elderly should cause AARP to support better treatments.

Support from organizations such as AARP (which has substantial lobbying power) can boost federal funding for nuclear therapy research and also help obtain federal reimbursement for nuclear treatment. Without outside support, nuclear therapy research is less likely to receive the funding that it needs to fulfill its potential.

Unreliable Supply of Isotopes Could Deter Expansion of Nuclear Therapy

The supply disruption caused by the MDS Nordion strike in late June, 1997, sent a chill through the nuclear medicine community. The strike highlighted U.S. dependence on foreign sources for a considerable amount of the isotopes needed by the nuclear medicine community. MDS Nordion's inability to deliver isotopes during that week demonstrated the precarious situation of U.S. nuclear medicine.

U.S. nuclear medicine physicians are concerned about the unreliability of the supply of isotopes. This issue affects both the therapeutic and the diagnostic side of nuclear medicine.

MDS Nordion is a major supplier of therapeutic as well as diagnostic isotopes.

Nuclear therapy research needs a steady and reliable supply of isotopes. Several U.S. reactors could be used exclusively for this purpose. The DOE should evaluate this issue and explore options that can provide a steady supply of high-quality isotopes.

The High Cost of Isotopes Is Likely to Slow Expansion of Nuclear Therapy

Many industry participants are concerned about the high cost of isotopes. For example, Amersham's Metastron, the first bone pain palliation radiopharmaceutical, costs well over $2,000 per dose. This product is made from Sr-89, which Amersham imports. It is expensive because of low demand and because of the price of the isotope.

Lower isotope prices can reduce radiopharmaceutical prices, expanding the industry by increasing the number of referred patients. The nuclear medicine industry should pursue strategies to lower the prices of the isotopes.

Lower prices for isotopes can also increment research and development activity. Research and development funds are limited, forcing research institutions to squeeze their budgets. This slows clinical research. Many of the nuclear physicians approached by Frost & Sullivan believe isotope pricing could be affected by a government- and industry-sponsored national isotope policy. Increased production of isotopes can bring economies of scale. Domestic production reduces transportation costs.

FDA and NRC Regulations Are a Serious Obstacle

FDA and Nuclear Regulatory Commission (NRC) regulations concerning the approval of radiopharmaceutical products are obstacles to the expansion of nuclear therapy. The NRC, because of fears of radiation exposure, has been unwilling to speed up review of new radiopharmaceuticals. Delays in the approval process contribute to the high cost of radiopharmaceuticals.

One of the biggest problems affecting the FDA is the shortage of informed regulators. Nuclear physicians expressed to Frost & Sullivan that the FDA in particular needs more experts in nuclear medicine. Many nuclear physicians also believe that if the regulatory agencies adopt the reform measures currently proposed for quicker product approval, more radiopharmaceutical products would reach the marketplace faster.

FDA regulations, many nuclear medicine participants believe, negatively affect product innovation and drug development. The agency has not reviewed its treatment of nuclear medicine, but has instead created more restrictions and delayed approval of products. The FDA has become an obstacle instead of a facilitator in the development of new, technologically advanced therapies. This has elevated the cost of producing new radiopharmaceutical products, while deterring companies from increasing their investments in research and development.

Reduction of Research Budgets Slows Expansion of Nuclear Therapy

Nuclear therapy needs funding to develop reliable radiopharmaceuticals. Radiopharmaceutical companies provide substantial private research and development funding for new drugs.

Nuclear medicine research institutions such as UCLA, Stanford, and Sloan-Kettering also play a vital role in developing reliable and effective drugs. Such institutions have more flexibility in conducting basic research than large radiopharmaceutical companies. However, in today's environment of decreasing funding for medical research, the future of many research activities undertaken at these institutions is precarious.

If more federal funding is not made available, the pace of nuclear research will continue to slow. However, in an environment of budgetary cuts, nuclear medicine should join forces with other treatment modalities, such as chemotherapy and gene therapy, in its efforts to offer therapeutic solutions. Partnering is very important for the very survival of nuclear medicine therapy.

Market Gaps and Opportunities

The U.S. supply of exotic isotopes is less than adequate to support the anticipated expansion of nuclear medicine therapy. In its research, Frost & Sullivan notes a deep uneasiness among nuclear physicians involved in therapeutic research stemming from the lack of a reliable supply of moderately priced, high-quality isotopes.

An on-going discussion on the future of the Brookhaven National Laboratory's High-Flux Beam Reactor further complicates the supply issue. Some isotopes supplied by the Brookhaven facility are in jeopardy because of production scheduling and radiation contamination safety issues. These problems might force the DOE to permanently shut down Brookhaven's High-Flux Beam Reactor, which would have dire consequences for research centers involved in nuclear therapy trials around the country. Los Alamos National Laboratory also faces a prolonged shutdown of one of its major isotope processing laboratories.

Since therapeutic radiopharmaceuticals are in the early stages of development, the nuclear medicine community needs to experiment with many isotopes to find the most appropriate isotope for each disease. Research has identified I-131 for thyroid-related diseases. It has also identified Sr-89 and Sm-153 as very effective isotopes for the treatment of bone pain caused by cancer metastases.

A wide array of other isotopes is being tested. A complete list of isotopes and the conditions for which they are being tested is presented in the appendix.

Among the many research institutions Frost & Sullivan contacted, there is a permeating concern about the steady supply of these isotopes. Many patients have suffered delays in treatment because of supply delays. If nuclear therapy is to expand, this supply problem must be solved. Doctors and patients cannot be expected to choose nuclear therapy if the supply of isotopes is not reliable.

The DOE has expended resources and effort attempting to address the need for a reliable supply of isotopes. The DOE has

analyzed the capability of several reactors for medical isotope production, but has made few decisions as to which ones should produce which isotopes.

Of the many reactors awaiting a DOE decision on this issue, most experts believe that the FFTF can produce the purest and highest specific activity isotopes for nuclear therapy. Other reactors may be less expensive to run, yet the reliability, quality, and quantity of FFTF isotopes make this reactor the best choice for isotope production.

Reactor-produced isotopes are being used in several research trials around the United States. Table 3-2 exhibits a sample of research institutions conducting early trials, along with the diseases and isotopes with which they are working.

Overview of Research Programs

A number of research programs to identify isotopes with potential uses in nuclear medicine therapy are underway. Frost & Sullivan has contacted many of the nuclear physicians involved in these research programs to discuss their progress, obstacles, potential, and success rates. A list of selected programs appears in Table 3-2.

At the Arlington Cancer Center, in Texas, Y-90 is being tested to fight Hodgkin's lymphoma. The therapy uses monoclonal antibodies to transport the isotope to the disease site. In comparison with chemotherapy and radiation, the Arlington treatment has obtained very encouraging results, achieving complete remission in some cases.

This isotope was chosen because it has the highest beta energy and a half-life that is long enough to reach the tumor

without necessitating hospitalization of the patient. Most procedures are done on an outpatient basis. This therapy has been expanded to include heart disease and rheumatoid arthritis.

Emory University researchers are working to treat the restenosis caused by angioplasty procedures. Restenosis research initially used Ir-192, and eventually Y-90 with far better results. This same treatment has been used at other institutions. Y-90 is also being used in radiopharmaceuticals to fight bone pain and ovarian cancer. Table 3-7 lists diseases under clinical trial using Y-90.

Table 3-7

Therapeutic Radiopharmaceuticals Market: Disease Indications Under Clinical Trials Using Y-90 (U.S.), 1997

Isotope	*Disease Indication*
Y-90	Breast cancer
	Small-cell lung cancer
	Rheumatoid arthritis
	Bladder cancer
	Hodgkin's lymphoma
	Non-Hodgkin's lymphoma
	Heart disease/restenosis
	Bone pain palliation
	Ovarian cancer
	Leukemia
	Lymphoma
	Gastrointestinal carcinoma
	Brain tumors

Source: Frost & Sullivan

I-131 has been very successful in fighting thyroid cancer and hyperthyroidism, yet it also has potential in treating other disease. It is the most widely used isotope at the Fred Hutchinson Cancer Research Center. I-131 is used in combination with chemotherapy and gamma radiation

treatments for leukemia. Monoclonal antibodies are used to transport the isotope to cancerous cells after the cells have been irradiated with external beam gamma rays. These treatment programs produce very positive clinical results.

Other studies using I-131 have been conducted in many institutions around the United States. At Duke University, it is being treated to fight brain tumors and neuroendocrine tumors. This therapy relies on an antibody developed at Duke which transports the isotope directly into the tumor. This therapy allows delivery of a very large dose of I-131, around 100 to 120 millicuries, to the tumor. Duke researchers are also studying this method to attack other diffuse diseases by administering the dose systemically and allowing it to hit multiple areas in the body. Duke is also looking at the alpha emitter Astatine-211 tagged to a monoclonal antibody to treat brain tumors.

Further therapy research using I-131 is being conducted at Memorial Sloan-Kettering in New York. Research centers on combating breast, colon, and head and neck cancer with radiolabeled antibodies. This project is supported by Coulter Pharmaceuticals. Some other research protocols at Memorial Sloan-Kettering utilize Bi-213, an alpha emitter, to treat leukemia and ovarian cancer. Table 3-8 exhibits some diseases under clinical trial using I-131.

At Cooper Hospital in New Jersey, most research seeks to develop Infusional Brachytherapy. This technique allows nuclear physicians to surgically insert the isotope into the patient's body. Brachytherapy avoids losing most of the isotope dose before it reaches the target area. In a recent trial for pancreatic cancer, over 60 percent of the patients retained 86 to

100 percent of the infused P-32. Table 3-9 exhibits some of the disease undergoing clinical trials with P-32.

Table 3-8

Therapeutic Radiopharmaceuticals Market: Disease Indications Under Clinical Trials Using I-131 (U.S.), 1997

Isotope	*Disease Indication*
I-131	Brain tumors
	Breast cancer
	Liver cancer
	Colorectal cancer
	Melanoma
	Hodgkin's lymphoma
	Head and neck cancers
	Leukemia
	Neuroendocrine tumors
	Hodgkin's lymphoma
	Neuroblastoma

Source: Frost & Sullivan

Table 3-9

Therapeutic Radiopharmaceuticals Market: Disease Indications Under Clinical Trial Using P-32 (U.S.), 1997

Isotope	*Disease Indication*
P-32	Leukemia
	Hemophilia
	Bone pain palliation
	Pancreatic cancer
	Polycythemia
	Head and neck tumors
	Hepatocarcinomas

Source: Frost & Sullivan

Adoption and Use of Isotopes in Treatment of Leading Disease States

Nuclear therapy is one of the most effective treatments known to the medical community. Nuclear therapy offers the possibility of targeting radiation more effectively to a tumor site than treatments such as external beam radiation. In practice, this has not been the case because of the difficulty of discovering effective systems to bring isotopes to target areas.

Now there is considerable excitement in the nuclear medicine community about the prospects of nuclear therapy and its ability to treat many diseases. Monoclonal antibodies have been particularly successful in identifying cells where the isotope needs to be deposited. The mechanics of this delivery methodology are being perfected since they are not completely effective yet. The goal is to develop highly efficacious therapeutic radiopharmaceuticals that will only affect the target areas. This is the biggest challenge to the development of nuclear therapy.

Nuclear diagnostics is a very effective imaging modality. Nuclear diagnostic imaging can precisely locate tumor sites and differentiate between live tissue and scar tissue. Yet, nuclear medicine has failed thus far to gain a large following. Nuclear physicians developing therapeutic applications fear that their field may face the same problem. There is no question that nuclear therapy will offer curative advantages over other treatments, yet it will not succeed in the marketplace without support from referring physicians.

Amersham's Metastron and DuPont Merck's new Quadramet have performed well, although not always meeting

initial expectations. The success of I-131 for the treatment of thyroid cancer and hyperthyroidism has been unique.

The development of new therapeutic radiopharmaceuticals should be accompanied by strong efforts to popularize their use as the primary treatments for specific diseases. New drugs will have little chance of developing a substantial presence in the marketplace without such efforts.

Market Structure

Supply Side Overview

In addition to the university research programs discussed earlier in this chapter, smaller radiopharmaceutical companies are developing monoclonal antibodies. Companies conducting such work include:

- NeoRX
- Diatide
- Neoprobe
- Coulter Pharmaceuticals

Research on therapeutic radiopharmaceuticals is also being supported by the three largest radiopharmaceutical companies:

- Amersham Medi-Physics
- Mallinckrodt Medical
- DuPont Merck
- MDS Nordion recently formed its own radiopharmaceutical development company, Resolution

Pharmaceuticals, and is researching new therapeutic and diagnostic agents

Distribution System

Distribution of these time-sensitive products will be a key issue. Chapter 2 discusses distribution of diagnostic isotopes. Therapeutic isotopes are likely to be distributed through the same system.

Demand Side Overview

Availability of isotopes remains the main concern of many of the nuclear medicine participants interviewed by Frost & Sullivan. Nuclear therapy researchers obtain isotopes from a wide variety of sources. MDS Nordion, a large isotope manufacturing company, plays an instrumental role in supplying Molybdenum-99 and other isotopes. Table 3-10 exhibits some of the isotopes offered by MDS Nordion.

Table 3-10
Therapeutic Radiopharmaceuticals Market: MDS Nordion Reactor Produced Isotopes, 1997

Isotope	*Country of Origin*
C-14	Canada
Cl-36	Canada
Cr-51	Belgium
Fe-59	Belgium
I-125	Canada
I-131	Canada/Belgium
Ir-192	Canada
Mo-99	Canada
Ni-63	Canada
P-32	Belgium
Xe-133	Canada/Belgium

Source: Frost & Sullivan

Research reactors around the United States also supply isotopes. Brookhaven National Laboratory seems to be the most reliable source for research isotopes. The Missouri University Research Reactor also offers a wide selection of isotopes for therapy, and has gained strong support among nuclear physicians. Oak Ridge National Laboratory, Idaho; Massachusetts Institute of Technology; and Georgia Institute of Technology offer a smaller numbers of isotopes for research.

Some U.S. isotope needs are being met by foreign reactors. During the MDS Nordion strike in late June, 1997, reactors as far away as South Africa quickly mobilized in preparation for supplying considerable quantities of Mo-99 to the world market.

However, this is little consolation for nuclear physicians involved in therapeutic research. Isotopes used in therapeutic applications are considerably less common than Mo-99. Issues concerning half-life, purity, high specific activity, and transportation become very important. Some reactors in Russia offer I-131, yet the quality of this product is debatable. Product purity is essential in therapy. No contamination can be allowed to enter the patient's body as this could lead to treatment complications.

These issues underline the need for a national policy to support future demand for isotopes. Nuclear therapeutics is forecast to expand considerably in the future. This expansion cannot occur if there are not adequate supplies of isotopes.

Most of the research projects examined by Frost & Sullivan are not expected to have a radiopharmaceutical product on the market for seven to ten years. This time frame allows for formulation of an isotope policy that will secure supplies when

demand rises. This policy should emphasize isotopes most needed for therapeutic nuclear medicine rather than isotopes for which there is abundant supply.

Industry Structure and Economics

Research and Development

Developing a new therapeutic radiopharmaceutical is very costly. Of all the companies Frost & Sullivan contacted for this study, none gave the dollar figure required for the development of these products. Yet, Frost & Sullivan has learned that developing a new therapeutic radiopharmaceutical can cost close to $50 million dollars, excluding marketing costs. This causes companies developing new drugs serious financial concerns.

Manufacturing

Therapeutic radiopharmaceutical companies include some large players that also manufacture diagnostic products and some smaller specialized companies such as NeoRX, NeoProbe, and Coulter Pharmaceuticals that focus on the development of nuclear therapeutics. Additionally, Syncor Corporation, a specialized radiopharmacy company, recently acquired manufacturing capability from Golden Pharmaceuticals to produce I-131 based therapeutic radiopharmaceuticals.

Regulatory Approval

The cost of producing a new therapeutic radiopharmaceutical is increased by FDA and NRC regulations. Companies developing new radiopharmaceutical hope that the FDA in particular will apply a more expeditious approval mechanism.

Companies must show a compelling amount of research data and must demonstrate low toxicity. Once this is done, the FDA should take a more responsive stand towards the approval of therapeutic radiopharmaceuticals. The FDA should also consider the financial issues involved in unnecessary delays.

Acceleration of the approval process would encourage development of more therapeutic radiopharmaceuticals by encouraging radiopharmaceutical companies to increase research and development programs. On the other side, if approval continues to be slow and resource consuming, fewer companies will venture into this new branch of nuclear medicine.

Market Maturity

Nuclear medicine is over half a century old. For most of this period, the overwhelming majority of radiopharmaceutical products offered were for diagnostic applications. Not until the 1960s was iodine looked at as an isotope with therapeutic applications. The first isotope with therapeutic applications was P-32, but it damaged the bone marrow of most patients.

Until the late 1980s, iodine was the only therapeutic radiopharmaceutical available. The arrival of Amersham's Metastron changed the dynamics of the market, bringing

therapeutics to the forefront of nuclear medicine. In 1997, P-32, I-131, Sr-89, and Sm-153 are the only therapeutic isotopes offered in the United States. Frost & Sullivan judges nuclear medicine to be both a mature and an infant market.

Diagnostics is very mature, but is still developing new radiopharmaceuticals for oncology, neurology, and infection imaging. Therapeutics is fairly new, with a large number of radiopharmaceuticals in research. Both branches of this science have tremendous revenue potential.

Competitive Analysis

Overview

There are few competitors in the U.S therapeutic radiopharmaceutical market currently that offer products. These are the established radiopharmaceutical companies. In addition to the traditional radiopharmaceutical companies, there are specialized therapeutic radiopharmaceutical companies that are beginning to make entries into the therapeutic market segment.

Radiopharmaceuticals are available for four therapeutic applications. Amersham Medi-Physics and Mallinckrodt Medical are the only two companies that offer products for three applications. Other radiopharmaceutical companies offer products only for thyroid-related therapy. DuPont Merck offers Quadramet for bone pain palliation.

DuPont Merck signed a marketing and distribution agreement for Cytogen's Quadramet. Mallinckrodt Medical has

one bone pain palliation radiopharmaceutical awaiting FDA approval. This exhausts the list of companies offering therapeutic radiopharmaceuticals.

In the future, smaller companies are expected to offer new therapeutic radiopharmaceuticals. New product introductions are expected only after development of sophisticated delivery systems, such as those based on monoclonal antibodies and peptides. Two diagnostic radiopharmaceutical companies, Centocor and Cytogen, may join the enterprises involved in nuclear therapy. Smaller companies involved in therapeutic research include:

- NeoRX
- Diatide
- Neoprobe
- Coulter Pharmaceuticals

Market Competition Analysis

Intensity of Competition

Nuclear medicine is an intensely competitive field, in part because of nuclear medicine's failure to attract more patients. Radiopharmaceutical companies cooperate by selling many of each other's products instead of embarking in protracted battles for a small number of patients. Doctors can obtain many of Mallinckrodt's products at Amersham radiopharmacies, while Syncor radiopharmacies offer some radiopharmaceuticals from other competitors.

Although this description of the competitive environment mainly applies to nuclear diagnostics, it will most likely also apply to the emerging nuclear therapy market. Already, two companies offer different bone pain palliation therapies, while most other competitors have products for thyroid gland diseases.

Among the radiopharmaceutical products awaiting FDA approval are two agents designed for bone pain palliation that will compete directly with the two radiopharmaceuticals currently available. However, the number of patients receiving radiopharmaceuticals has not increased, and demand has not met the expectations of the suppliers.

If the patient population expands, that is, if nuclear therapeutics is chosen more often, nuclear therapeutic products may not face the level of competition currently affecting nuclear diagnostics products.

Radiopharmaceutical Manufacturers Holding 15 Percent or More of the Market

Amersham Medi-Physics

Amersham is the world's leading radiopharmaceutical company. Founded in 1946, Amersham has 3,300 employees worldwide and a strong presence in the United States, Japanese, and European markets. Amersham has 28 radiopharmacies in the United States.

Metastron for bone pain palliation (Sr-89), had worldwide sales in 1996 of $36 million. U.S. revenues from Metastron were approximately $17 million. Until June, 1997, Metastron was the only radiopharmaceutical for bone pain palliation offered in the United States. Amersham also offers a thyroid disease

therapeutic radiopharmaceutical, but revenue information for this product was not released by the company.

Mallinckrodt Medical

Mallinckrodt was founded in 1867. The company's North American headquarters is located in St. Louis, Missouri. The company has a total worldwide work force of 10,400, of which 6,200 work in the United States. Mallinckrodt has 36 radiopharmacies in the United States, thus being the second largest radiopharmacy company after Syncor International.

Mallinckrodt offers one therapeutic radiopharmaceutical for thyroid disease, I-131 MIBG. The company does not reveal revenues for any of its radiopharmaceuticals. At the present time, Mallinckrodt is seeking to expand its presence in nuclear therapy with a bone pain palliation product (Re-186), which is awaiting FDA approval. Mallinckrodt is also researching therapy for rheumatoid arthritis.

CIS USA and Bracco Diagnostics

CIS USA and Bracco Diagnostics are two radiopharmaceutical companies that each offer a wide array of diagnostic tracers, as well as thyroid disease nuclear therapy. Since both companies are privately held, it is impossible to obtain revenue information about their products. Syncor distributes CIS USA's thyroid disease therapy radiopharmaceutical (I-131) in the United States, giving this drug wide distribution.

DuPont Merck Pharmaceuticals

DuPont Merck, also known as DuPont Pharma, does not offer any thyroid disease therapy drugs. In 1997 the company

obtained manufacturing and marketing rights in the United States and Canada for Quadramet (Sm-153), Cytogen's bone pain palliation product. This new therapeutic radiopharmaceutical has entered the market and will compete directly with Amersham's Metastron.

Others: Diatide, NeoRX, Coulter Pharmaceuticals, & Neoprobe

Diatide, NeoRX, Coulter Pharmaceuticals, and Neoprobe are four relatively small, yet highly specialized, technology companies. Although none of these companies yet offers a therapeutic radiopharmaceutical, they may have a future market presence. All are involved in monoclonal antibody and peptide nuclear therapeutic research.

Diatide has one therapeutic radiopharmaceutical, for the pain of metastatic bone cancer, in the FDA pipeline: Tin-117m DPTA. Diatide estimates that its product has the potential, since it is expected to be less toxic than Metastron and Quadramet, to be used in up to 250,000 procedures annually worldwide. The company is discussing possible partnership arrangements with several major radiopharmaceutical companies that would provide financial support and would market the product to oncologists.

The company estimates that the average price per dose of Tin-117m DPTA will be around $2,000. Annual sales of this product could amount to $50 million several years after approval and introduction to the market.

Coulter Pharmaceutical, Inc. is an emerging biotechnology company focused on developing proprietary cancer therapeutics. The company is a leader in the development of a novel class of products, radioimmuno-therapeutics, which are

designed to combine the specificity of antibodies with the anti-tumor effects of radiation.

Coulter seeks to link an B-1 antibody to I-131 as a therapy for non-Hodgkin's lymphoma (NHL). The B-1 therapy is targeted to treat the low-grade and transformed low-grade NHL patients. Statistics from the National Cancer Institute state that there are approximately 270,000 people afflicted with NHL in the United States.

The company estimates that approximately 140,000 patients have low-grade or transformed low-grade NHL in the United States. Coulter also estimates that its therapy will be priced at around $8,000 per dose, resulting in a market potential of over $500 million annually in the United States.

NeoRX's pre-targeting delivery system, licensed from Stanford University, encompasses three steps. The first step uses an antibody to deliver a protein receptor, streptavidin (SA), to a specific location such as a tumor. SA is used to capture a therapeutic molecule.

The second step removes antibody/SA from circulation without removing it from the tumor. When more antibody/SA is removed from the blood, fewer therapeutic molecules bind to it in the blood, decreasing exposure of normal tissue such as bone marrow. The third step is the delivery of therapeutic molecules to those sites where the antibody/SA has attached.

The goal of this treatment is to deliver high isotope doses to the tumor sites with limited exposure of normal tissue. Avicidin, NeoRX's first product using this delivery system, employs Y-90 as the therapeutic molecule. It is expected that this pre-targeting system will allow Avicidin to deliver radiation

effectively and safely to solid tumors, such as lung, breast, and colorectal cancer tumors.

Other NeoRX research seeks to develop a radioactive device used after angioplasty to avoid restenosis, the reblocking of a treated artery.

Neoprobe has focused its efforts on developing a combination therapy. This method, an effort to combat the solid tumor cancers that afflict over 1 million people annually, uses a radiation detector during surgery. This detector locates abnormal tissue that has accumulated a radioactive targeting agent. The targeting agent is commonly a monoclonal antibody that has been labeled with a gamma-emitting radioisotope.

The instrument emits an audible signal triggered by gamma rays emanating from the abnormal tissue. This signal alerts the surgeon to the location of cancerous tissue that cannot be seen or felt. This technology is potentially applicable to all solid tumors, although it has mainly been used on colorectal cancer.

MDS Nordion supplies Neoprobe with the I-125 labeled monoclonal antibodies used in this therapy.

Therapeutic Radioisotope Manufacturers Holding 15 Percent or More of the Market

MDS Nordion

MDS Nordion is a global leader in the production and supply of radioisotopes, producing tens of thousands of doses daily.

MDS Nordion's headquarters and main operations are in Kanata, Ontario. These operations process isotopes supplied by Canadian reactors. A facility on the campus of the University of British Columbia in Vancouver produces isotopes from three cyclotrons operated by the Tri-University Meson Facility (TRIUMF). MDS Europe in Fleurus, Belgium, supplies reactor- and cyclotron-produced isotopes, as well as radiopharmaceutical products. MDS Nordion is building two new reactors, Maple I and II, dedicated to the production of medical isotopes. Both will be finished by 2001.

MDS Nordion serves customers around the world. The company supplies a large number of the isotopes needed by radiopharmaceutical companies in the United States. In fact, MDS Nordion supplies about two-thirds of the world's reactor-produced isotopes, as well as close to 70 percent of the Mo-99 used in the United States.

Others

The overwhelming presence of MDS Nordion in the market leaves very little space for other reactors to compete. Nonetheless, DOE reactors, such as the ones at Brookhaven and Oak Ridge, and the Idaho Falls reactor operated by MAC Isotopes, supply isotopes to the U.S. nuclear medicine community. Some university reactors, such as the MURR, MIT, and Georgia Tech reactors, also produce isotopes for nuclear therapy research projects. The supply of exotic reactor-produced isotopes required by nuclear therapeutics remains unreliable.

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Profiles of Leading Market Participants

Leading Isotope Production Source Competitor Profiles

MDS Nordion
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Kanata, Ontario
Canada K2K 1X8
www.mds.nordion.com

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Fax: (613) 592-6937

Company Background

Services in the Radiopharmaceutical Industry	Production and distribution of medical isotopes. Nordion also manufacturers its own line of radiopharmaceutical agents, both diagnostic and therapeutic.
Market Share in the global isotope production industry	70% (approximately).
Company History	Founded in 1946
Location of Headquarters	Kanata, Ontario, Canada
Ownership	MDS Nordion is a subsidiary of MDS International. The parent company is traded.
Number of Employees	600 employees.

Facilities	Headquarters are located in Kanata, Ontario. Other facilities are located in Vancouver, British Columbia; Laval, Quebec; Fleurus, Belgium; Hong Kong and Tokyo, Japan.
Main Competitors	Mallinckrodt, MURR, MIT, MAC Isotopes, Georgia Tech, Brookhaven, Oak Ridge

Financial Highlights

Year	Revenues	Source	% of MDS revenues
1996	$200 million	95% came from sales from export markets	25%
1995	$191 million	98% came from sales from export markets	28%

Products in the Marketplace

Product Name	Product Description
Radioisotopes	**Target market:** Nuclear medicine diagnostics and therapeutics Applications: Diagnostic imaging, isotope guided therapy, liver cancer treatment. **Price:** Prices are negotiated on a per client/volume basis. **Total revenues in 1996:** $200 million. **Primary customers:** Radiopharmaceutical companies, hospitals, imaging centers, nuclear medicine research at universities.

Strategies

Companywide Strategy or Mission Statement

The unique nature of MDS Nordion's business requires expertise in a number of highly technical areas. The company draws on a broad base of knowledge and skills, with specialists in chemistry, microbiology, pharmacology, physics, engineering, regulatory affairs, and many other disciplines.

MDS Nordion supplies customers in over 100 countries, exporting more than 95% of the products processed in Canada. The company serves its European customers from its subsidiary, MDS Nordion S.A. located in Fleurus, Belgium; while its Asia-Pacific Sales Offices in Hong Kong and Tokyo address the needs of the growing Asia-Pacific market. In addition, an extensive

network of authorized sales agents and distributors guarantees prompt and efficient service for MDS Nordion's customers anywhere in the world.

Industry-Specific Strategy

With an operating philosophy that focuses on meeting the needs of its customers, MDS Nordion maintains close working relationships with companies in the radiation processing and radiopharmaceutical industries. MDS Nordion people know that their customers face increasingly tough, highly competitive and strictly regulated environments, and therefore offer the best service to give them a competitive edge. The company continually strives to understand the needs of its customers and develop solutions based on their requirements.

Partnerships and Alliances

Company Name	Description of Partnership
Allelix Biopharmaceuticals	This joint venture created Resolution Pharmaceuticals (1993), a company dedicated to the development of improved diagnostic imaging products for disease indications where there is a demonstrated need.
CIS Bio International	MDS Nordion purchased (1997) the industrial cobalt 60 business of CIS Bio International, France's national nuclear agency.
Atomic Energy of Canada Limited (AECL)	In 1996 MDS Nordion and AECL announced an agreement that ensures Canada continues to be the leading supplier of isotopes worldwide. This agreement includes the building of two new small reactor, Maple I and II, which will be operational by the beginning of the new century.
Syncor International	In 1995 MDS Nordion signed an agreement with Syncor to distribute TheraSphere, Nordion's non-surgical treatment for primary and secondary liver cancer. Syncor has agreed to market and distribute this product in the Pacific Rim and other countries outside of the United States.
Neoprobe Corporation	Nordion has worked on contract with Neoprobe to develop an I-125 radio labeled monoclonal antibody targeting agent. This agent is going to be used for intraoperative detection of metastases in patients diagnosed with colorectal cancer.

Leading Radiopharmaceutical Company Profiles

Amersham Healthcare
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Arlington Heights, IL 60005
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Fax: (847) 593-8024

Company Background

Company Offerings	Life Science (44.7%) Healthcare (40.2%) Industrial Quality and Safety Assurance (14.0%) Other (1.1%)
Products in the Radiopharmaceutical industry	Myoview Metastron Ceretec
Market Share in the Radiopharmaceutical Industry	32% (approximate)
Company History	Founded in 1946
Location of Headquarters	Amersham, Buckinghamshire, England
Ownership	Publicly held company AMER INTL in the London Stock Exchange
Number of Employees	3,300 worldwide 1,100 in the United States 2,200 in Europe and the Pacific Rim
Facilities	3 manufacturing and repair sites in the United States, Japan and England. 16 sales offices in the North America, Europe, Asia and Australia 7 manufacturing sites in the United States, England, Germany, The Netherlands and Japan.
Radiopharmacies	28 radiopharmacies throughout the United States; one in Ontario, Canada.
Main Competitors	DuPont Merck (Europe, North America) Mallinckrodt Medical (Europe, North America) Daiichi Pharmaceuticals (Pacific Rim)

Financial Highlights

Year	Revenues	Net Earnings	R&D (% of Sales)	Operating Income (% of Sales)
1994	$543.8 million	$44.9 million	$N/A	$233.7 million (42.9 percent)
1995	$572.8 million	$49 million	$35.8 million (6.2 percent)	$316.4 million (55.2 percent)
1996	$695 million	$63.7 million	$44.7 million (6.4 percent)	$338.2 million (48.6 percent)

Products in the Marketplace

Product Name	Product Description
Myoview	**Target market:** Radiopharmaceutical/Nuclear medicine **Applications:** Cardiology **Product features:** Myoview can be used to provide a quick, clear view of restricted blood supply to heart muscle, as in angina or 'heart attacks.' It was first launched in Japan in April 1994. Launch in Europe took place also in 1994. In North America it was done in April 1996. **Price:** $75.00 (per dose, approximate price) **Total product revenues in 1996:** $18 million **Primary customers:** Nuclear medicine facilities and imaging centers.
Metastron	**Target market:** Radiopharmaceutical/Nuclear medicine **Applications:** Oncology Therapy **Product features:** Metastron is a radiopharmaceutical to relieve pain from secondary bone cancer. Metastron improves quality of life for patients with intractable bone pain from metastatic cancer and was the first radiopharmaceutical analgesic granted regulatory approval for clinical use. A single injection of Metastron is usually effective for up to six months. It has been submitted for approval in Japan, the last major country in which it awaits launch. **Price:** $2,000. (per dose, approximate price) **Total product revenues in 1996:** $36 million. **Primary customers:** Nuclear medicine facilities and imaging centers.
Ceretec	**Target market:** Radiopharmaceutical/Nuclear medicine **Applications:** Neurology. **Product features:** Ceretec provides information on subtly altered blood flow of the working brain. It is also providing new diagnostic insights into disorders such as Alzheimer's disease, stroke, epilepsy and head injury. **Price:** $250 (per dose, approximate price) **Total product revenues in 1996:** $36.3 million **Primary customers:** Nuclear medicine physicians and imaging centers.

Strategies

Companywide Strategy or Mission Statement

Amersham's mission statement is serving the peoples of the world in healthcare, life science research and quality and safety assurance in industry and the environment.

Industry-Specific Strategy

Amersham is a world leader in health science, providing products and services for use in healthcare, life science research and industrial quality and safety assurance. The company has a sophisticated international distribution network serving customers throughout the world. It also operates globally, with research and development and manufacturing capabilities in each of the world's principal economic regions of North America, Europe and the Pacific Rim.

Amersham actively pursued the purchase of its competitors in the key markets of Europe and the Pacific Rim. This resulted in the acquisition of Sorin Diagnostics SpA, the radiopharmaceutical business of Sorin Biomedica SpA of Italy in late 1996. Amersham also acquired 50% of Nihon Medi-Physics, in a joint partnership with Sumitomo Chemical Co. Ltd. This particular acquisition has provided Amersham with an overwhelming control, close to 65%, of the profitable radiopharmaceutical market in Japan.

Amersham has also continued expanding its network of radiopharmacies throughout North America. Today, the company has 28 radiopharmacies in the United States and one in Canada. It also has access to more than 100 other radiopharmacies, thus providing its products with wider distribution channels.

Partnerships, Alliances and Acquisitions

Company Name	Description of Partnership
Sumitomo Chemical Co. Ltd.	Strategic merger to acquire Nihon Medi-Physics. Its main goal is to provide Amersham a greater control of the Japanese radiopharmaceutical market, and thus increase the company's overall global standing. It is this acquisition which has made Amersham the world's leading radiopharmaceutical company. Before the acquisition, Nihon controlled almost 60% of the Japanese radiopharmaceutical market. Amersham and Sumitomo both have a 50% share holding in Nihon Medi-Physics. The acquisition of Nihon Medi-Physics was completed in 1996.
Sorin Diagnostics SpA	In late 1996, Amersham announced the acquisition of the radiopharmaceutical company, Sorin Diagnostics, from its owner, Sorin Biomedica SpA. Amersham will combine its radiopharmaceutical business in Italy, Europe's third largest market, with Sorin's and will trade as Amersham Sorin Radiofarmaci. This acquisition strengthens Amersham overall presence in the European radiopharmaceuticals industry
Pharmacia & Upjohn Inc.	In June, 1997, Amersham announced the two companies were to merge their Life Sciences businesses, Amersham Life Science and Pharmacia. This merger will create the world's largest research-based biotechnology supplier.
Amersham India	Amersham, the world's leader in nuclear medicine, announced in April, 1996, that it was expanding its business interests in India. This move is designed to contribute towards the company's overall global presence in nuclear medicine.
Amersham Medi-Physics, Inc.	Syncor International will be able to buy Amersham's proprietary brain imaging and white blood cell labeling agent, Ceretec. The company believes this agreement will allow it to broaden the distribution structure of the Amersham product.
Mallinckrodt Medical	A five-year agreement for Mallinckrodt to distribute the heart imaging agent Myoview. The agreement also provides for a second five-year period. Both companies believe this agreement has the potential to generate $150 million in sales.

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Phone: (800) 280-2410
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Company Background

Company Offerings	Pharmaceutical/Radiopharmaceutical
Products in the Radiopharmaceutical Industry	Cardiolite Neurolite Verluma
Market Share in the Radiopharmaceutical Industry	31%
Company History	Founded in 1991
Location of Headquarters	Wilmington, Delaware
Ownership	Privately held: A joint venture formed by DuPont and Merck and Co. Inc.
Facilities	DuPont Merck's worldwide headquarters are located in Wilmington, Delaware. The Radiopharmaceuticals division is located in North Billerica, Massachusetts. The company also has offices in Canada, the United Kingdom, Belgium, France, Germany, Italy, Puerto Rico and Spain.
Number of Employees	4,000 worldwide
Main Competitors	Amersham: Europe, North America, Pacific Rim, South America) Mallinckrodt: Europe, North America, South America. Daiichi: Pacific Rim. CIS: Europe, North America, South America.

Financial Highlights

Year	Revenues	Net Earnings (Loss)	R&D (% of Sales)	Operating Income (% of Sales)
1993	$1,035 billion	N/A	$266 million (25 percent)	N/A
1994	$1,117 billion	N/A	$235 million (21 percent)	N/A
1995	$1,265 billion	N/A	$258 million (20.4 percent)	N/A

During its first five years of operation, DuPont Merck Pharmaceutical Company has invested over $1.3 billion in research and development. Sales and other revenue, during the

same period, totaled more than $5 billion. DuPont Merck had, at year's end in 1995, more than $1.2 billion in assets.

Products in the Marketplace

Product Name	Product Description
Cardiolite	**Target market:** Radiopharmaceutical/Nuclear medicine **Applications:** Cardiology **Product features:** Cardiolite is the next generation heart imaging agent. When combined with thallium, it provides the world standard for nuclear cardiology. Cardiolite now exceeds 40% of all myocardial perfusion studies. **Price:** $81 per unit dose (1997) **Primary customers:** Nuclear physicians, imaging centers, cardiologists.
Neurolite	**Target market:** Radiopharmaceutical/Nuclear medicine **Applications:** Neurology **Product features:** Neurolite, a SPECT brain perfusion agent, has a 6 hour stability after preparation. This allows for more flexible patient scheduling, usefulness in the acute setting since doses can be prepared beforehand. Neurolite has provided physicians with an excellent tool for pinpointing areas in the brain where a stroke has occurred. The radiopharmaceutical was introduced in 1994. **Price:** $320 per unit dose (1997) **Primary customers:** Nuclear physicians, imaging centers, neurologists.
Verluma	**Target market:** Radiopharmaceutical/Nuclear medicine. **Applications:** Oncology **Product features:** Verluma is a new monoclonal-based diagnostic imaging test that simplifies staging of small-cell lung cancer. Verluma is considered a great step in cost-effectiveness because its accuracy is certain to guarantee the elimination of costly and dangerous traditional tests. It became available in early 1997. Verluma was developed by NeoRx Corporation, manufactured and licensed by an affiliate of Boehringer Ingelheim GmbH, and marketed by DuPont Pharma. **Price:** $825 per dose (1997) **Primary customers:** Nuclear physicians, imaging centers, oncologists.

Strategies

Companywide Strategy or Mission Statement

The DuPont Merck Pharmaceutical Company is a worldwide, research-based pharmaceutical company. It is

focused on the research, development, and delivery of pharmaceuticals to treat unmet medical needs in the fight against heart disease, central nervous system disorders, cancer, and HIV disease. Through scientific research and development, the company has made considerable gifts to the discovery, anticipation, and treatment of many illnesses.

Industry-Specific Strategy

DuPont Merck has made radical changes in its organizational structure with a single goal in mind: meeting customer needs. In 1994 DuPont Merck centralized its European sales organization allowing subsidiaries in Spain, Germany, Italy, France and the United Kingdom, to pool their resources, build on the synergies that exist between them and respond to the changing market situations caused by the European Union.

In North America, DuPont Merck entered into a supply and distribution alliance with their largest radiopharmaceutical customer, Syncor International. This coalition has allowed DuPont Merck access to Syncor's radiopharmacy network, which includes over 120 locations in the United States and almost one dozen overseas.

DuPont Merck's radiopharmaceuticals tend to be centered around the areas of cardiology and neurology. Consequently, the company decided to research and develop agents with applications in oncology. This is the newest area of expansion for radiopharmaceuticals. One of the most promising agents for oncological diagnosis is Miraluma, the first-ever nuclear medicine test approved for breast imaging. Miraluma is indicated for planar imaging as a second line diagnostic drug after mammography to assist in the evaluation of breast lesions

in patients with an abnormal mammogram or a palpable breast mass.

DuPont Merck plans to build on its radiopharmaceutical leadership, find new markets, and invest in research and development, as its strategy for market share growth. In the last two years, DuPont Merck has lost market share to Amersham, mainly due to this company's solid expansion efforts in Europe and the Pacific Rim. Nevertheless, DuPont Merck remains a very strong competitor, with a healthy position in the radiopharmaceutical industry.

Partnerships and Alliances

Company Name	Description of Partnership
Syncor International	An alliance to provide Syncor with the distribution rights for DuPont Merck's gamut of radiopharmaceuticals. Syncor has also signed agreements with other radiopharmacies, Amersham and Mallinckrodt for example, to distribute DuPont Merck's agents through them.
CYTOGEN Corporation	DuPont Merck will manufacture and market Quadramet, a radiopharmaceutical developed by CYTOGEN, to treat the severe pain associated with cancers that have metastasized to the bone.

Mallinckrodt Medical
7733 Forsyth Boulevard
St. Louis, MO 63105-1820
www.mallinckrodt.com

Phone: (314) 854-2000
Fax: (314) 854-5381

Company Background

Company Offerings	Human healthcare Specialty chemicals
Products in the Radiopharmaceutical Industry	OctreoScan TechneScan MAG3 UltraTag RBC
Market Share in the Radiopharmaceutical Industry	23%
Company History	Mallinckrodt was founded in 1867. It was purchased by International Minerals and Chemical Corporation in 1986. After several name changes, shareholders voted, in 1996, to change the name to Mallinckrodt Group Inc.
Location of Headquarters	St. Louis, Missouri
Ownership	Publicly held Stock traded on the New York, Chicago and Pacific Stock Exchanges under the Ticker Symbol: MKG.
Number of Employees	5,300 in the United States 2,000 in other regions
Facilities	North American headquarters are in St. Louis, Missouri, European headquarters are located in Petten, The Netherlands. Imaging agents manufacturing sites are located in Angleton, Texas; Cincinnati, Ohio; Maryland Heights, Missouri; Mexico City, Mexico; Mulhuddart, Ireland; Petten, Netherlands; Pointe Claire, Canada; Raleigh, North Carolina; and St. Louis, Missouri.
Radiopharmacies	36 radiopharmacies throughout the United States; one radiopharmacy in London, England.
Main Competitors	Amersham: Europe, North America, South America. DuPont Merck: North America, Europe, South America. CIS Bio International: Europe, South America.

Financial Highlights*

Year	Revenues	Net Earnings (Loss)	R&D** (% of Sales)	Operating Income** (% of Sales)
1993	$1,178.2 billion	($200.4 million)	$64.7 million (5.5 percent)	$131.1 million (11.1 percent)
1994	$1,348.4 billion	$103.8 million	$72.6 million (5.4 percent)	$160.5 million (11.9 percent)
1995	$1,588.3 billion	$180.3 million	$77.7 million (4.9 percent)	$267.9 million (16.9 percent)
1996	$1,754.4 billion	$211.9 million	$86.1 million (4.9 percent)	$295.2 million (16.8 percent)

(* Revenues and earnings restated to reflect Fiscal 1996 sale of feed ingredients business and Fiscal 1997 divestiture of Tastemaker flavors joint venture and animal health business.)

(**Operating earnings for FY 1993 and FY 1994 include restructuring charges of $51.3 million and $73.1 million respectively.)

Products in the Marketplace

Product Name	Product Description
OctreoScan	**Target market:** Radiopharmaceutical/Nuclear medicine. **Applications:** Oncology/Neuroendocrine tumors. **Product features:** In clinical studies, OctreoScan has been shown to be a safe and highly effective radiopharmaceutical for the localization of primary and metastatic neuroendocrine tumors. OctreoScan, as the first peptide-based imaging agent, goes beyond simply imaging tumor anatomy, providing valuable clinical information about tumor biochemistry. SPECT imaging is recommended at 24 hours post-injection for small neuroendocrine tumors poorly visualized by planar imaging. **Price:** $ 800 per kit (1997) **Primary customers:** Nuclear physicians, imaging centers, endocrinologists.
TechneScan MAG3	**Target market:** Radiopharmaceutical/Nuclear medicine **Applications:** Renal studies. **Product features:** TechneScan MAG3 is an agent used for imaging the renal area. Its clinical uses include: evaluation of renal perfusion and function, evaluation of renal trauma, diagnosis of renovascular hypertension, and detection and evaluation of renal collecting system obstruction. **Price:** $978 per box of five vials (1997) **Primary customers:** Nuclear physicians, imaging centers, medical specialists.
UltraTag RBC	**Target market:** Radiopharmaceutical/Nuclear medicine. **Applications:** Gastrointestinal, blood pool imaging. **Product features:** UltraTag RBC provides excellent image quality, even in demanding procedures such as diagnosis of gastrointestinal bleeding. UltraTag RBC, used for blood pool studies, comes in a for the preparation of Technetium Tc-99m-labeled red blood cells. It provides a six hour window in which to administer the RBC's after they are labeled with Tc-99m, giving physicians more scheduling flexibility. **Price:** $205 for five test kit. **Primary customers:** Nuclear physicians, imaging centers, medical specialists.

Strategies

Companywide Strategy or Mission Statement

Mallinckrodt operates from the foundation of an integrated growth plan built around enhancing management systems and processes, managing their base businesses, discovering and marketing new technology, and enhancing their

business portfolio. The plan incorporates current and near-term initiatives focused on performance improvement and value enhancement over the next two to three years.

A Strategic Change Initiative undertaken in 1995 removed a complete layer of the organization, eliminated duplication and reduced costs. With the recent sale of the Tastemaker flavors joint venture and the animal health business, Mallinckrodt is focusing on its core businesses and is positioned to provide resources to grow those businesses more rapidly as industry consolidation continues.

Today, sales in healthcare represent 80 percent of Mallinckrodt's business, with more than 90 percent of their operating earnings coming from radiopharmaceuticals, medical imaging and critical care products, and bulk and specialty pharmaceuticals.

In the face of extreme measures to reduce global healthcare costs that have slowed volume growth and intensified competition, Mallinckrodt has significantly increased sales volume, particularly through agreements with group purchasing organizations, such as Premier, Inc. These agreements solidify long-term market position and provide leverage in increased volume.

Industry-Specific Strategy

Mallinckrodt plans to expand its market share through an active program in new markets and new geographic territories. This will be done by adding new businesses and products through the right acquisition. Strategically matched acquisitions provide synergies that contribute to growth, add value to existing core businesses, and make good business sense.

The company is anticipating changes and increased acquisition activity in the near future.

Mallinckrodt has also taken secure steps towards expanding its presence in the radiopharmacy business. The company has 36 sites across the United States, and one in London, England. This number makes Mallinckrodt the second largest owner of radiopharmacies after Syncor International Corporation. The nature of the nuclear medicine business, and its extreme competition for a smaller pool of patients and end-users, make the need for a distribution system imperative among the radiopharmaceutical companies. Mallinckrodt has taken an active role in fulfilling this need.

Partnerships and Alliances

Company Name	Description of Partnership
Immunomedics, Inc.	Distribution agreement for the United States, they have received final clearance from the European Commission, to market CEA-Scan, Immunomedics' imaging agent for the diagnosis of colorectal tumors.
Cadila Pharmaceuticals Ltd.	Mallinckrodt Inc. and Cadila Pharmaceuticals, a privately held Indian pharmaceutical company, have signed a five-year agreement for sales and marketing, manufacturing and formulation of various products by both companies in the United States, India and other worldwide markets. It is expected that annual sales from this alliance will exceed $150 million by the year 2002.
Premier, Inc.	Mallinckrodt entered into several supply agreements with Premier, Inc., a company which services some 1,800 owner hospitals and affiliates in the United States.
Syncor International Corp.	Joined forces with Syncor International to broaden the distribution of radiopharmaceutical products to the nuclear medicine community. It will provide Syncor access to Mallinckrodt's radiopharmaceutical products; while providing Mallinckrodt with access to DuPont's Cardiolite, Neurolite and Persantine.
Amersham Medi-Physics	A five-year agreement for Mallinckrodt to distribute the heart imaging agent Myoview. The agreement also provides for a second five-year period. Both companies believe this agreement has the potential to generate $150 million in sales.

Syncor International Corporation
20001 Prairie Street
Chatsworth, CA 91311

Phone: (818) 737-4000
Fax: (818) 737-4499

Company Background

Services in the Radiopharmaceutical Industry	Distribution and on-site drug prescription preparation of radiopharmaceutical agents with applications in cardiology, oncology, infectious diseases and neurology.
Market Share in the Radiopharmacy Industry	48% of the radiopharmacies in the United States.
Company History	Founded in 1974
Location of Headquarters	Chatsworth, California
Ownership	Publicly held Stock traded on NASDAQ stock exchange under SCOR.
Number of Employees	2,300 worldwide, although most are in the United States.
Facilities	Headquarters are located in Chatsworth, California. Syncor has 120 radiopharmacies throughout the United States. Added to this number, Syncor also has several sites in Mexico, Hong Kong, the Philippines, Thailand, Taiwan and the Republic of China.
Main Competitors	Amersham: 28 radiopharmacies in the United States. Mallinckrodt: 36 radiopharmacies in the United States.

Financial Highlights

Year	Revenues	Net Earnings (Loss)	R&D	Operating Income (% of sales)
1993	$241.2 million	$7.8 million	N/A	$162.4 million 67.3 percent
1994	$319.2 million	$1.2 million	N/A	$253.9 million 79.5 percent
1995	$331.4 million	$4.6 million	N/A	$258.9 million 78.1 percent
1996	$366.4 million	$6.9 million	N/A	$286.2 million 78.1 percent

Products in the Marketplace

Product Name	Product Description
Radiopharmaceuticals	**Target market:** Nuclear medicine imaging facilities, imaging centers. **Applications:** Cardiology, oncology, infectious diseases, neurology. **Product features:** Syncor International has distribution agreements for radiopharmaceuticals agents manufactured by companies such as DuPont Merck, Amersham Medi-Physics and Mallinckrodt. **Price:** Syncor counts with a wide array of radiopharmaceutical agents ranging from $5 per unit dose to $2,000 per unit dose. (1997) **Total shipments in 1996:** Over 6.2 million doses of radiopharmaceuticals **Primary customers:** Hospitals, imaging centers, nuclear medicine departments, radiologists.

Strategies

Companywide Strategy or Mission Statement

Syncor International Corporation operates an expanding network of 120 domestic and eight international nuclear pharmacy service centers. The company compounds and dispenses patient specific unit dose radiopharmaceutical prescriptions, as well as distributes bulk radiopharmaceutical products for use in diagnostic imaging and provides a complete range of advanced pharmacy services. Syncor services more than 7,000 customers and is the only national pharmacy network of its kind that provides a combination of diagnostic and information services to hospitals and alternate site markets.

Syncor's mission is to be the premier provider of prepared time-critical pharmaceuticals and comprehensive value-added pharmacy services which meet the needs of the professional healthcare community and their patients.

Industry-Specific Strategy

Syncor International is actively pursuing the establishment of newer alliances with other radiopharmaceutical companies besides DuPont Merck. Consistent with the company's mission to be the premier provider of radiopharmaceuticals, Syncor has signed several distribution agreements with major suppliers. It has also signed an agreement with Mallinckrodt Medical to distribute radiopharmaceuticals. This agreement allows Mallinckrodt access to DuPont Merck's agents, while it allows Syncor to sell Mallinckrodt's.

Additionally, Syncor is broadening its business base beyond its core radiopharmacy operations. Through a joint venture announced in 1997, the company plans on expanding its presence in the medical imaging field. Syncor plans on expanding its presence in the medical imaging field. Syncor anticipates operating 10 open Magnetic Resonance Imaging centers across the United States. Syncor also has decided to enter the radiopharmaceutical manufacturing field with the purchase of Golden Pharmaceuticals' Iodine-123 business.

Partnerships and Alliances

Company Name	Description of Partnership
DuPont Merck	Syncor International signed an alliance with DuPont Merck for the supply, distribution, and resale of its products. Cardiology products continue to represent the largest and fastest-growing segment of Syncor's sales mix. Cardiolite, a proprietary radiopharmaceutical of DuPont Merck, is replacing thallium as the nuclear medicine industry's "gold standard" for stress testing. In 1995, sales of Cardiolite increased by 46%.
Golden Pharmaceuticals, Inc.	Syncor International acquired the assets related to the Iodine-123 business of Golden Pharmaceuticals, Inc. This was done in an effort to enter the manufacturing side of the radiopharmaceutical industry.
Mallinckrodt Medical, Inc.	Syncor International signed a supply agreement with Mallinckrodt Medical, Inc. to broaden the distribution of radiopharmaceutical products to the nuclear medicine community. As a result, Syncor will have broad access to the full range of radiopharmaceuticals within current Mallinckrodt portfolio, including the newest agent, OctreoScan. In exchange, Syncor is to provide to Mallinckrodt access to DuPont Merck's Cardiolite, Neurolite and Persantine, of which Syncor has exclusive and/or preferred distribution rights.
Amersham Medi-Physics, Inc.	Syncor International will be able to buy Amersham's proprietary brain imaging and white blood cell labeling agent, Ceretec. The company believes this agreement will allow it to broaden the distribution structure of the Amersham product.
VHA, Inc.	Syncor International signed a major contract with VHA, Inc. to supply unit dose and bulk radiopharmaceuticals on a national basis. VHA, Inc., based in Texas, services more than 1,300 leading community focused healthcare providers around the United States. The contract has a potential value of $270 million over four years.
PerImmune, Inc.	Syncor International announced an agreement to market and distribute HumaSPECT/CR, a monoclonal antibody for the diagnosis and staging of colorectal cancer. The radiopharmaceutical is the property of PerImmune, a leading developer and manufacturer of unique human monoclonal antibodies with demonstrated ability to image specific cancer, as well as infectious diseases in humans.

5

FFTF Opportunity Analysis

Overview

Frost & Sullivan was commissioned by Battelle Pacific Northwest National Laboratory to develop a strategic market assessment study for medical isotopes with diagnostic and therapeutic applications in nuclear medicine. This analysis evaluates the role that the Fast Flux Test Facility (FFTF) can play in this expanding medical field.

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 the 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 percent of the medical isotopes used in the United States comes from non-U.S. sources.

The Department of Energy (DOE) has not developed a coherent, functioning, and effective medical isotope policy. Every year, a smaller quantity of isotopes is produced in the United States, while imports of reactor-produced isotopes are on the rise. Frost & Sullivan considers this to be a major concern, as it leaves U.S. nuclear medicine dependent on foreign suppliers. The quality of some imported isotopes is a serious concern.

No other country in the world relies on nuclear medicine as much as the United States does. In fact, the United States makes up approximately 48 percent of the world nuclear medicine market. The United States is the world's leader in radiopharmaceutical research and development. Yet, the country relies on foreign reactors to supply approximately 90 percent of its isotope needs. The dependence on foreign isotope sources concerns all of the participants interviewed by Frost & Sullivan.

MDS Nordion produces approximately 80 percent of the Tc-99m used in the United States. The company also offers other reactor-produced isotopes with potential applications in nuclear medicine therapy. Among those other isotopes are:

- Sr-89
- Sm-153
- I-131

Table 5-1 exhibits the regional breakdown of the world nuclear medicine market.

Table 5-1

Diagnostic and Therapeutic Radiopharmaceuticals Market: Market Share by Region (World), 1997

Region	*Market Share (%)*
United States	48
Asia/Pacific	22
Europe	16
Rest of the World	14
TOTAL	100

Note: All figures are rounded. *Source: Frost & Sullivan*

This study highlights the serious concerns of the U.S. nuclear medicine community. Most of the industry participants interviewed believe that the DOE should formulate a new national medical isotope policy. These same industry leaders believe that instead of shutting down more reactors, the DOE should find a solution to the country's dependency on foreign medical isotope sources. This could be achieved by recomissioning several of the DOE reactors which were shut down in the last few years.

Upon comparison with other DOE facilities, Frost & Sullivan concludes that the FFTF reactor offers the greatest capacity, reliability, quality, broad product range, and return on investment among all facilities under consideration by the DOE.

U.S. Supply of Medical Isotopes Inadequate

With cancellation of the breeder reactor program in the late 1980s, it became apparent that the DOE would no longer finance the FFTF. In 1993, the DOE, on the recommendation of an independent panel, ordered the shutdown of the FFTF

reactor. Since then, the reactor has been in standby mode, a condition which allows the FFTF to resume isotope production within three and a half years of a decision to restart the reactor.

Since 1993, the DOE has been examining several options for the FFTF. Shortages of radioisotopes for medical research, diagnosis, and treatment have been well documented in several reports, as well as in hearings before Congress.

Frost & Sullivan estimates that approximately 13,000,000 nuclear medicine diagnostic procedures, 80,000 nuclear therapy procedures, and almost 100,000,000 medical laboratory tests requiring use of radioisotopes were conducted in the United States during 1996.

In the past, the DOE provided radioisotopes from reactors across the United States. For about five years, several of the DOE nuclear reactors have been decommissioned or shut down. Several reactors, such as those at Brookhaven National Laboratory, Idaho National Environmental & Engineering Laboratory, and Oak Ridge National Laboratory, continue isotope production, but not in commercial quantities.

The DOE is only producing approximately 10 percent of the reactor-produced isotopes demanded by U.S. nuclear medicine. Most of the DOE reactors have been shut down or are being shut down, or their primary mission has been refocused by the DOE. 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 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.

Demand for Medical Isotopes Expected to Expand

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.

Therapeutic nuclear medicine is expected to grow rapidly in the near future. This new field seeks to develop radiopharmaceuticals to identify and attack some of the most common cancers. Frost & Sullivan expects that new diagnostic and therapeutic radiopharmaceuticals, especially for oncology, will cause global market expansion.

Given the need for high purity in radiopharmaceuticals, manufacturers need isotopes of the highest quality. Many of the nuclear physicians interviewed by Frost & Sullivan are deeply concerned about the quality of the isotopes available for nuclear therapy. These physicians fear that some medical isotopes, such as those imported from the former Soviet Union, may put patients at risk. Table 5-2 exhibits some foreign reactors which supply isotopes to the United States.

Table 5-2

Diagnostic and Therapeutic Radiopharmaceuticals Market: Selected Foreign Reactors Supplying Isotopes to the United States, 1997

Reactor	*Isotopes*	*Country*
HFR	Mo-99, I-131, Ir-192	The Netherlands
Safari	Mo-99	South Africa
Chalk River	Mo-99, Y-90, Xe-133	Canada
SM3	P-33, Co-60, CF-252	Russia
Moscow	Mo-99	Russia
HIFAR	Mo-99, Sm-153, Re-186	Australia
BR-2	Mo-99, Xe-133, I-131	Belgium

Source: Frost & Sullivan

Alternatives to the FFTF

Other federal reactors being considered for future isotope production are:

- Brookhaven National Laboratory (BNL)
- Oak Ridge National Laboratory (ORNL)
- Los Alamos National Laboratory (LANL)
- Sandia National Laboratory (SNL)
- Idaho Falls Reactor (MAC Isotopes) (MAC)

Several non-gevernment-owned reactors are also possible sources of medical isotopes. Most of these are located in medical research centers. These reactors are:

- Missouri University Research Reactor (MURR)
- Georgia Institute of Technology (GT)
- Massachusetts Institute of Technology (MIT)

These facilities are involved in low-level commercial production. The three reactors have a satisfied client base, particularly among nuclear researchers. Although currently producing some commercial medical isotopes, the MURR, MAC, GT, and MIT reactors lack the size and power required for commercial production of exotic isotopes.

Leading DOE isotope production facilities have faced dramatic cutbacks in their research and development budgets. The total budget for BNL, for example, saw a $25.0 million cutback from 1996 to 1997. ORNL and SNL have suffered cutbacks of $54.7 million and $42.6 million, respectively, in the same time period. Such dramatic cutbacks indicate a weak U.S. commitment to nuclear research. Many nuclear physicians stated that due to such cutbacks, the country could be losing its technological edge in nuclear medicine.

The FFTF may also face competition from another DOE reactor with a similar dual mission. The Accelerator Production of Tritium Facility (APT) at the Savannah River site in South Carolina is conducting feasibility and marketing studies similar to those ordered by the FFTF mission.

Supporters of the APT proposed that the highly versatile linear accelerator that is planned for the Savannah River Site may be suitable for the production of medical isotopes. APT studies identified a long list of medical isotopes with applications in nuclear medicine diagnostics and therapy. APT argues that the facility will be able to supply the growing demand of medical isotopes at the same time that demand is expected to grow. However, this facility will require more than $2 billion to construct, and will not be completed until 2010 or

later. The APT is expected to have an annual operating budget of at least $150 million.

In comparison, the FFTF may require up to about $400 million to begin tritium and medical isotopes production by 2002, and has a lower estimated operating cost of approximately $100 million per year.

Strengths and Advantages of the FFTF

The FFTF mission estimates that the reactor could begin medical isotope production by 2002, just as several new therapeutic radiopharmaceuticals are expected to enter the market. The FFTF has the capability to produce more than sixty different isotopes, including the high-end exotic isotopes that are expected to be key to nuclear therapy in the twenty-first century. Table 5-3 lists selected FFTF-produced isotopes and their potential uses in nuclear medicine therapy. The following list represents a subset from the total set of 30 isotopes under consideration for production at FFTF.

The FFTF is a 400 Megawatt (MW) reactor. The FFTF can:

- Produce isotopes of the highest specific activity in large quantities
- Help develop new nuclear medicine applications
- Produce a sizable quantity of tritium for national defense
- Dispose of weapons-grade plutonium as MOX fuel

Table 5-3

Diagnostic and Therapeutic Radiopharmaceuticals Market: Leading FFTF Isotope Candidates and Related Disease Indication (U.S.), 1997

Isotope	*Disease Indication*
Au-198	Ovarian cancer Prostate cancer Brain cancer
Bi-213	Prostate cancer Lung cancer Breast cancer Colorectal cancer Melanoma Ovarian cancer Lymphoma
Cd-109	Heart disease
Cu-67	Lymphoma Breast cancer Colorectal cancer Rheumatoid arthritis
Gd-153	Osteoporosis
Ho-166	Rheumatoid arthritis
I-125	Heart disease Prostate cancer
I-131	Brain tumors Breast cancer Liver cancer Colorectal cancer Melanoma Hodgkin's lymphoma Head and neck cancers Leukemia Neuroendocrine tumors Non-Hodgkin's lymphoma Neuroblastoma Thyroid cancer Hyperthyroidism Ovarian cancer Pancreatic cancer

Continued on next page

Table 5-3 (Cont.)

Isotope	*Disease Indication*
Ir-192	Breast cancer Prostate cancer Ovarian cancer Brain tumors Restenosis (heart disease) Uterine tumors
Lu-177	Restenosis Bone pain palliation
P-32	Leukemia Bone pain palliation Pancreatic cancer Polycythemia Head and neck tumors Hepatocarcinomas Rheumatoid arthritis Ovarian cancer
Pd-103	Prostate cancer Brain cancer Breast cancer
Pt-195m	Radiolabel for chemotherapy
Ra-223	Bone pain palliation Breast cancer Lung cancer Prostate cancer Ovarian cancer Colorectal cancer Melanoma
Re-186	Prostate cancer Thyroid cancer Colorectal cancer Lung cancer Breast cancer Ovarian cancer Bone pain palliation Rheumatoid arthritis

Continued on next page

Table 5-3 (Cont.)

Isotope	*Disease Indication*
Re-188	Restenosis Bone pain palliation Thyroid cancer Colorectal cancer Lung cancer Breast cancer Ovarian cancer
Sc-47	Bone pain palliation
Sm-145	Optical cancer
Sm-153	Leukemia Bone pain palliation Spinal cord tumors
Sr-85	Bone pain palliation Bone diseases
Sr-89	Bone pain palliation Prostate cancer Bone metastases Multiple myeloma
Y-91	Leukemia Breast cancer Lymphoma Colorectal cancer Hodgkins lymphoma Non-Hodgkins lymphoma

Source: Frost & Sullivan

The multiple functions that the FFTF can perform assure its financial viability. If the DOE chose the FFTF for tritium production, the reactor could undertake a dual mission of tritium production and medical isotope production. Built in the 1970s and in operation during the 1980s, the FFTF reactor still has at least 22 years of life after restart. This means that the reactor could be operating past 2020, thus playing an important role in tritium and medical isotope production.

Medical Research and Isotope Production

The FFTF is the largest DOE reactor. Thus, the FFTF can produce medical isotopes in the large quantities that the market is expected to demand. The high quality, as well as the high specific activity, of FFTF-produced isotopes makes them very reliable and attractive for nuclear medicine procedures.

Frost & Sullivan concludes that the FFTF can become the main U.S. source of high-quality medical isotopes. The reactor's size, as well as the quality of the isotopes it can produce, make it one of the facilities best suited to this function. While present isotope production is scattered among several much smaller DOE reactors, future demand for isotopes is expected to require the production capacities of a reactor the size of the FFTF and also the need for some backup reactors to meet stop-gap needs.

The state of nuclear medicine research in the United States is deplorable, a situation that should be reversed as quickly as possible. The FFTF's capabilities can allow the facility to become a major research center, particularly in nuclear medicine. This can be done at the same time that the FFTF initiates production of medical isotopes.

Frost & Sullivan contacted nuclear physicians who have used FFTF-produced isotopes. These physicians are completely satisfied with the quality of the isotope and dependability of the supply.

Given these capabilities, the reactor offers the DOE one of its best options for commercial radioisotope production in the United States. The FFTF is one of the safest U.S. reactors. It enjoyed a solid record of safety and availability during the decade that it was in operation. Since the FFTF only operated

for one decade, it is in very good condition. The FFTF's record during the decade of operation proves the reactor's value and low risk.

Tritium Production

The FFTF can produce a considerable amount of tritium for national defense. As the U.S. nuclear weapons arsenal ages and tritium decay continues, the FFTF can play an important role in replenishing this stockpile.

The dual mission approach is a working strategy developed and pursued by all parties concerned with the FFTF. Under this plan, the reactor would initially focus on tritium production to satisfy U.S. defense needs. Tritium is a vital component of nuclear weapons. It deteriorates over time and therefore needs to be regularly replaced. Half of the tritium in nuclear weapons is lost through radioactive decay every 12.3 years. Production of tritium at the FFTF would not increase the number of weapons. Rather, this tritium would be used to maintain existing weapons.

While previous DOE-commissioned reports have not rated the FFTF highly as a producer of tritium, this evaluation is being reexamined. The FFTF is capable of supplying a sizable amount of U.S. tritium needs. It could serve as a temporary tritium source until the national defense establishment identifies a more appropriate reactor for this defense mission. Observers of the FFTF expect tritium production to be switched to another facility around 2012. Using the FFTF as a temporary source of tritium would save billions of dollars which would otherwise be needed to build a new reactor for this purpose.

Disposal of Plutonium

The end of the Cold War left the United States with a massive stockpile of nuclear weapons. As a result, much of the plutonium stockpile is now excess. The United States is considering the disposition of this plutonium.

The FFTF is capable of disposing of weapons-grade plutonium as Mixed Oxide fuel (MOX). The FFTF could dispose of much of the United States' excess plutonium by making the plutonium useless for weapons purposes.

The DOE has continued to eliminate plutonium storage sites in the country. Rocky Flats, in Colorado, will be phased out. The materials stored there will be transferred to the Savannah River Site in South Carolina and the Pantex Plant in Texas. The Hanford Site will continue to store plutonium until a decision is made concerning disposition. The facility will either immobilize the plutonium in glass or ceramic, or use the plutonium as MOX fuel in its reactors.

The Fuels and Materials Examination Facility (FMEF) is part of the vast infrastructure for MOX fuel processing at Hanford. The FMEF was designed with several MOX fuel processing features:

- Designed to handle spent fuel and special nuclear material
- Analyzed for MOX fuel fabrication
- Twice the space needed for MOX fuel fabrication
- Designed with fully integrated safeguards and security systems

Weaknesses and Challenges for the FFTF

Interviews conducted by Frost & Sullivan for this study uncovered some very serious concerns held by the nuclear medicine industry regarding the FFTF. The major concerns are:

- High operating cost of the FFTF
- Large investment needed to restart the FFTF
- Skepticism about the dual-mission strategy in the nuclear medicine community
- Need to expand the packaging and transportation system for isotopes
- The DOE's control and influence over the FFTF
- Radioactive contamination at the Hanford facility

The main concern raised by nuclear physicians, radiopharmaceutical companies, and nuclear medicine research institutions is that the FFTF is too costly to operate. The DOE estimates that the annual operating cost of the FFTF would be approximately $100 million.

Since the DOE may require the FFTF to become financially self-sufficient, the high cost of operating the reactor needs to be addressed. Present isotope needs will not pay for the FFTF. However, market expansion can be expected to generate substantial demand for isotopes that would greatly favor the full operation of the FFTF.

Some of the nuclear physicians interviewed by Frost & Sullivan consider restarting the FFTF uneconomical in terms of 1997 demand. Furthermore, these respondents argue that the FFTF mission overestimates the present need for isotopes. Respondents feel that the FFTF's capability to produce several therapeutic isotopes (Sm-153, Lu-177, I-131, Ho-166) can be

easily matched by other U.S. reactors, such as BNL, MAC, ORNL, and MURR. They argue that if there is a shortage in the United States, isotopes could be easily obtained from foreign reactors.

Opponents of the FFTF fail to recognize that the FFTF mission is looking at future market opportunities for the reactor. Present market conditions do not warrant commercial isotope production at a facility of the FFTF's size. Yet, future isotope demands will most likely substantially surpass today's needs. With this market expansion in mind, the FFTF mission is pursuing the restart of the reactor.

While respondents unanimously agreed that no new reactor needs to be constructed to meet future demands, they are not at all sure that the FFTF is the only option among existing reactors. A large majority of respondents favor the MURR as a better-suited reactor than the FFTF, mainly because it is less costly to operate. They feel that since the MURR is already producing isotopes, the DOE should give that reactor more attention.

While some respondents expressed negative views on the FFTF, others feel that it is one of the best options available to the DOE. Respondents who foresee a future for the FFTF focus more on its capability to produce tritium than on production of medical isotopes. The FFTF, these supporters argue, has the potential to play an effective role in national defense. They do not consider the reactor the best choice for medical isotopes mainly because of the operating costs.

Some respondents are skeptical about the FFTF's ability to produce a wide variety of medical isotopes. While most respondents recognize that the FFTF can produce huge amounts

of high specific activity and ideal neutron energy isotopes, they expressed doubts concerning the variety of isotopes that the reactor is capable of producing.

Many nuclear medicine participants have not been informed of the variety of exotic isotopes that the reactor can produce. The FFTF mission has prepared a list of 70 isotopes that the reactor is capable of producing. This list should be widely distributed in the industry, specifically among nuclear physicians involved in therapeutic research.

The efficiency of the packaging and transportation system should be addressed by the FFTF mission. The establishment of an efficient packaging and transportation system is a key to the successful distribution of medical isotopes. Such a system would allow timely, reliable, and secure distribution. The FFTF lacks a packaging facility. The reactor is also hindered by the absence of a large airport in its vicinity.

The three Tri-Cities airports are small. Thus, the FFTF would have to ship isotopes through either Seattle or Salt Lake City. Respondents have expressed concern that shipping delays caused by inadequate transportation facilities could seriously reduce the potency of isotopes because of their short half lives.

MDS Nordion's success has greatly depended on the company's ability to build an efficient transportation system. Respondents are deeply concerned about the DOE's unwillingness to allow a private consortium to participate in managing the FFTF. Both Amersham and Mallinckrodt have tried to arrange participation, but the DOE has procrastinated and done little to gain private-sector confidence.

In a time of budgetary cutbacks, cooperation between the private sector and the DOE should be encouraged. The DOE's bureaucratic procedures are a challenge that the FFTF mission should work to overcome.

Experts in the nuclear medicine industry are concerned about the DOE's commitment to medical isotope production. The FFTF's previous mission was weapons production, which is more critical to the DOE and the Department of Defense than the production of medical isotopes. This meant that the FFTF's main role was to support defense. A primary focus on national defense is a concern to many nuclear medicine participants.

Many nuclear physicians do not believe that the DOE will ever end weapons production at the FFTF. They fear that weapons production could displace medical isotope production, making the FFTF an unreliable source of medical isotopes. Additionally, the primary role of the FFTF as a defense installation has negatively affected the environmental community's view of the reactor.

A large majority of respondents expressed hope that very little tritium, and eventually none at all, would be produced at the FFTF. Nuclear physicians were particularly adamant about relying on a reactor where the Armed Forces would be able to refocus the primary mission from medical isotope production to weapons manufacture. This nuclear medicine community does not accept this situation, nor does it understand why there has to be defense involvement in the eventual operation of the FFTF.

Frost & Sullivan recommends that the FFTF's safety and environmental record be shared with the general public. The American public is becoming increasingly sensitive to the

potential dangers of radiation contamination. Concerns over the disposal of nuclear waste have fueled the environmental movement.

The size of the FFTF may raise fears of contamination of the Columbia River basin. This is a valid concern which must be properly and openly addressed. The FFTF's excellent safety record demonstrates that although the reactor's size might raise environmental impact questions, it is a very safe facility. Increased production of medical isotopes at the FFTF will not increase radiation in the area to dangerous levels.

A recent radioactive accident at the Hanford Plutonium Reclamation Facility led to media discussion of environmental issues. The May, 1997, accident brought major news coverage to Hanford reporting the dangers of radioactive leaks. Frost & Sullivan believes that the Hanford facility must be as safe as possible for the FFTF to have a role in future medical isotope production. Without safety issues being properly addressed, the FFTF mission will have increasing difficulty gaining community support for restarting the reactor.

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Strategic Recommendations

FFTF Should Not Focus Solely on Medical Isotope Production

Having interviewed over 70 nuclear medicine physicians, industry participants, and government officials, Frost & Sullivan recommends that the FFTF mission consider producing isotopes for non-medical as well as medical uses. Non-medical uses of radioisotopes include:

- Industrial
- Government/national defense
- Electric power generation
- Academic research
- Food and instrument sterilization

Exclusive production of medical isotopes may limit the ability of the FFTF to pay for itself, at least in the short term. Isotope needs in food irradiation, national defense, academic research, and electric utilities should be considered. Frost & Sullivan believes that there is tremendous potential for the

FFTF reactor to enter the market as a supplier of radioisotopes within these applications as well.

Frost & Sullivan's nuclear medicine diagnostic market forecast projects that market will reach nearly $17 billion by 2020. The worldwide market is expected to exceed $34 billion in that year. Nuclear medicine therapy, in contrast, will not be as large. This is because nuclear medicine therapy is still largely in development, and it is not entirely clear that it will overcome the obstacles that it presently faces.

Although the prospects for nuclear medicine appear favorable, Frost & Sullivan believes that it would be a risk for the FFTF to tie itself too closely to therapeutic nuclear medicine when other industries also create market demand for radioisotopes.

Expanding the FFTF's client base would be a major achievement. The market for diagnostic and therapeutic medical isotopes is expected to thrive by 2010. Nonetheless, the FFTF should not rely exclusively on the likely growth of nuclear medicine. Thus, the FFTF mission should pay particular attention to non-medical markets. Failing to do so would seriously reduce the number of potential clients that the FFTF could supply.

FFTF Should Produce High-Value Therapeutic Isotopes

Frost & Sullivan has compiled a list of applications and radioisotopes that are currently in clinical research in the United States. Several radioisotopes, such as I-131 and P-32, are being researched for more than one application. These two

isotopes in particular are being investigated for cancer therapy. Nuclear medicine physicians are trying to match specific malignancies with the most effective radioisotopes.

Therapeutic radioisotopes are more expensive than diagnostic radioisotopes, hence a greater revenue generator. Nuclear medicine therapy uses much larger doses of radioisotopes for each procedure than nuclear medicine diagnostics does. For example, OncoScint, a tumor imaging procedure, uses 5 millicuries of In-111.

In contrast, Quadramet, a bone pain palliation therapy, uses 32 to over 100 millicuries, depending on the patient's weight. This makes nuclear therapy more expensive than a nuclear diagnostic scan and will create much higher demand for radioisotopes when more therapeutic applications become available.

For this reason, special attention should be given to the many nuclear therapy studies in progress. The FFTF reactor should focus on radioisotopes with greater market potential in nuclear therapy. The FFTF should be positioned to produce enough medical isotopes for nuclear medicine therapy as that field expands.

Existing Transportation System Should Be Improved in Order to Compete in the Twenty-First Century

Rapid transportation of isotopes to medical facilities is a necessity. MDS Nordion is particularly noted for its exceptional transportation system, built around proximity to the

international airports of Vancouver, Ottawa, and Belgium. The Missouri University Research Reactor (MURR) also has good access to major airports, which allows for quick transportation of the highly sensitive products produced at their respective facilities.

To compete, particularly as volume grows, the FFTF should further develop its existing packaging and transportation systems. The current infrastructure of the Tri-City area, while adequate to support current demands, would require trans-shipping products through the Seattle and Salt Lake City airports. The current system is functional, as demonstrated by the fact that more than 600 consecutive on-time shipments of Y-90 have been sent from Hanford to medical customers. However, it is recommended that the FFTF mission invest in expansion of the existing packaging and transportation system in order to make them able to handle a substantially larger volume of isotope products and shipments during the period 2002-2020. This should include exploration of possible private sector involvement in FFTF isotope packaging and shipping.

FFTF Mission Should Pursue Private-Sector Partnerships

Federal dollars for technological and medical research are becoming increasingly scarce. This is a grave concern among nuclear medicine participants. In the last year, the total budgets of Sandia, Oak Ridge, and Brookhaven, three important national laboratories, have been reduced by 4.5 to 11.2 percent.

The annual cost of operating the FFTF reactor is estimated by DOE officials to be about $100 million. It is

doubtful that the federal government will cover this entire cost after tritium production is phased out. Thus, it is imperative for the FFTF mission to find other ways to secure financial self-sufficiency.

National laboratories are increasingly willing to reach agreements with private-sector industry. This is beginning to alleviate the budgetary problems faced by some U.S. national laboratories. For example, corporations provided $27 million to Sandia National Laboratory (SNL) in 1996. SNL is expecting private financing to reach $35 million in 1997, and it could soar to $100 million by the year 2000.

In comparison, the total corporate financing received by SNL was $9 million five years ago. At Oak Ridge (ORNL), which is managed by Lockheed Martin Corporation, the same policy seems to be equally helpful. ORNL is actively pursuing more corporate cooperation agreements to secure reliable funding as federal dollars decrease.

MDS Nordion and the Canadian government have a similar agreement. In fact, the funds to build the new reactors, Maple I and II, were granted to MDS Nordion by the federal government of Canada.

A similar agreement covering the Tri-University Meson Facility (TRIUMF) is in effect. This Canadian national lab is located on the campus of the University of British Columbia and is operated by three local universities. It is supported by the National Research Council of Canada, which grants TRIUMF $C 30 million a year. TRIUMF operates a large cyclotron and produces a variety of radioisotopes.

MDS Nordion has a 30-year technical support agreement with TRIUMF, which makes MDS Nordion the sole commercial distributor of the isotopes produced at this facility. Corporate agreements such as TRIUMF and SNL have will provide these facilities with increased sources of private financing. There is no reason why the FFTF mission should refrain from actively pursuing similar corporate sponsor agreements.

Environmental Contamination Issues Should Be Addressed

During 1997, the Hanford facility, where the FFTF is located, received a vast amount of negative coverage by the national news media. This is a result of an accident that happened at the Hanford facility's Plutonium Reclamation Facility in May 1997. Reporters have questioned the overall radioactive safety record at Hanford, a concern that the FFTF mission should not ignore.

Environmentalism can be expected to remain a major issue in the United States because a large segment of the public is concerned about ecological issues. Environmental concerns are likely to develop into a major obstacle for the restart of the FFTF reactor if accidents continue to happen at Hanford. This issue has forced the shutdown in 1997 of some operations at BNL and Los Alamos National Laboratory.

To separate itself from the safety issues at Hanford, the FFTF mission must stress the reactor's safety record during the decade of operation in the 1980s. The FFTF has a good, solid safety record that can dispel the contamination concerns expressed in coverage of the May, 1997, accident.

The accident at Hanford, although it seems to have been quickly contained and not associated with a reactor, can potentially damage the reputation of the FFTF reactor in the eyes of the public. A respondent aptly stated this to be "guilty by association." More immediately, contamination issues could alienate federal authorities from supporting the FFTF mission.

Environmental concerns, and the simple mention of radioactivity, can turn public opinion against the FFTF. The world has witnessed the seriousness of radioactive contamination, particularly at Three Mile Island, BNL, and Chernobyl in the former Soviet Union. This is a very serious issue which the Hanford facility and the FFTF mission should address. Failing to do so may result in an insurmountable obstacle to restarting the FFTF.

Ongoing Community Involvement Should Continue

The support of the local community to the FFTF mission should be pursued by the Hanford facility and the FFTF team. Restarting the FFTF would turn Hanford into a major national research facility and one of the largest employers in the Tri-City area.

Hanford should raise awareness of its potential for creating jobs and contributing to public revenues. If nuclear medicine diagnostics and therapy expand to the forecast levels, the FFTF may become the nation's largest supplier of radioisotopes. The substantial economic potential can be translated into better jobs and a healthier economy for the area.

Assurance of the safety of the FFTF reactor is needed to win public support. This can only be achieved by continuing the

on going education and awareness campaigns undertaken by members of the FFTF mission. Legitimate concerns about nuclear contamination and waste disposal should be addressed to win support from local, state, and federal officials and from the public.

Concerns About Cost-Effectiveness Should Be Addressed

Some nuclear medicine industry participants believe that restarting the FFTF would be uneconomical. This may be true given the current market for radioisotopes, but the concern should not be today's market environment. Rather, the issue is the future expansion of nuclear medicine diagnostics and of nuclear medicine therapy. Taking this into consideration, restarting the FFTF does not appear to be uneconomical.

The production of tritium for national defense needs at the FFTF facility will make the reactor an economical option for the DOE. Additionally, the expected phase out of the tritium mission at the FFTF will coincide with the expanded demand for medical isotopes in the twenty first century.

This point should be made to the nuclear medicine industry. Market demand for radioisotopes is likely to catch up with the FFTF's capacity over the next decade or two as the need for radioactive isotopes grows, both for medical and non-medical uses.

Nuclear Medicine Industry Uneasy About FFTF's Dual Mission Focus

The FFTF mission wants the reactor to become a leading production site for weapons-grade tritium while also producing medical isotopes. This is known as the dual mission. The FFTF mission expects that tritium production would be shifted to an alternative facility around 2012. This coincides well with the projected increase in demand for medical isotopes. After phase-out of tritium production, medical isotope production is likely to generate sufficient revenues to support the FFTF.

The fear in the radiopharmaceutical industry is that production of isotopes would take second priority to tritium production at the FFTF. However, this issue is not unique to the FFTF. Any facility that the DOE might restart would likely have to pursue a dual mission to justify its operating cost until demand for isotopes grows.

The nuclear medicine community needs to be reassured about the DOE's commitment to medical isotope production at the FFTF. The FFTF mission has to gain the support and confidence of the nuclear medicine community. The cooperation from future customers such as nuclear physicians and radiopharmaceutical companies should be sought by the FFTF mission in its efforts to restart the reactor.

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Appendix

Table A-1

Nuclear Therapy Research (U.S.), 1997

Disease Indication	*Radioisotope*
Bone Pain Palliation	Sr-89, Sm-153, Sn-117m, Re-186, Ra-223, P-32, Sc-47
Bladder Cancer	Ta-182
Brain Tumor	Cf-252, Sm-153, Y-90, Au-198, Ir-192, I-131
Breast Cancer	Re-186, Y-90, Y-91, Ir-192, Re-188, P-32
Cervical Cancer	Cf-252
Colon Cancer	Y-91
Colorectal Tumors	Y-90, Cu-64
Gastrointestinal Adenocarcinoma	Y-90
Heart Disease	Ir-192, P-32, Lu-177
Hemophilia	Dy-165, Ho-166, P-32
Hodgkin's Disease	Y-90, Y-91, I-131
Hyperthyroidism	I-131
Leukemia	Y-90, Y-91, I-131, P-32, Sm-153, In-111, Bi-213
Liver Cancer	I-131, Y-90
Lymphoma	I-131, Y-90, Y-91
Melanoma	Cf-252, I-131
Multiple Myeloma	Sr-89
Non-Hodgkin's Disease	I-131, Y-90, Y-91
Optical Tumors	Sm-145, P-32
Ovarian Cancer	Re-188, Ir-192, Y-90, Au-198, P-32

(Continued on next page)

Table A-1 (Cont.)

Disease Indication	*Radioisotope*
Pancreatic Cancer	P-32
Polycythaemia Rubra Vera	P-32
Prostate Cancer	Re-186, I-125, Ir-192, Pd-103, I-131, Au-198, Sr-89, P-32
Pulmonary Fibrosis	Ga-64
Rheumatoid Arthritis	P-32, Dy-165, Ho-166, Re-186, Sm-153, Er-169, Au-199, W-188, Y-90
Small-Cell Lung Cancer	Y-90, Y-91
Thyroid Cancer	I-131, Re-188, I-125
Uterine Cancer	Ir-192, P-32

Source: Frost and Sullivan, 1997