NEWSLINE

Future of Nuclear Medicine, Part 3: Assessment of the U.S. Therapeutic Radiopharmaceuticals Market (2001–2020)

This section 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.

Nuclear medicine experienced sluggish market growth during most of the 1990s. This results from cutbacks in health care 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.

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. 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 P-32 chromic phos-

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

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

Note: This material was reprinted from *FFTF Medical Isotopes Market Study (2001–2020)* [1997] with permission of Frost & Sullivan, Mountain View, CA, and Battelle Pacific Northwest National Laboratory, Richland, WA.

phate approved for the treatment of polycythemia rubra vera (a bone marrow disease involving the overproduction of red blood cells). However, sales of this product have 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*.

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 noncancerous 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 health care. 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.

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.

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

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
- Polycythemia rubra vera

The four isotopes are I-131, Sr-89, Sm-153, and P-32. The success of nuclear therapy in treating thyroid-related [diseases] 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. Table 3-4* exhibits bone pain palliation radiopharmaceuticals awaiting FDA approval.

Nonetheless, the above-stated products are not the only ones in commercial use worldwide.

Therapeutic Radioisotopes Under Development

The United States is the center of current therapeutic nuclear medicine research. Work is under way 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

*Note: Table 3-3 is omitted from this reprint of selected sections of Chapter 3 of the Frost & Sullivan report.

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

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 health care 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:

- Iodine-131
- Rhenium-186
- Yttrium-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. Table 3-5 exhibits a list of therapeutic radiopharmaceuticals that are expected to enter the market by the year 2000.

Frost & Sullivan shares this view. At least 90 nuclear therapy trials are under way 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

TABLE 3-6
Therapeutic Radiopharmaceuticals Market: Revenue Forecasts (U.S.), 2001–2020

Year	Revenue ($ 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

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.

MARKET DRIVERS

Cost-Effectiveness of Nuclear Therapy Can Result in Significant Savings

Nuclear medicine therapy has the potential to save billions of U.S. health care 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 dis-

eases 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. health care 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 health care. 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 health care system and may feel overburdened. 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 health care 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 complementary 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 health care 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 that 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

U.S. nuclear medicine physicians are concerned about the unreliability of the supply of isotopes. This issue affects both the therapeutic and the diagnostic sides of nuclear medicine.

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. 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. 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 ongoing 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.

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.

Overview of Research Programs

A number of research programs to identify isotopes with potential uses in nuclear medicine therapy are under way. 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.

I-131 has been very successful in fighting thyroid cancer and hyperthyroidism, yet it also has potential in treating other diseases. 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

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

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. 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 diseases 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
	Head and neck cancers
	Leukemia
	Neuroendocrine tumors
	Hodgkin's lymphoma
	Neuroblastoma

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.

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

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.

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

Demand Side Overview

Research reactors around the United States 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 [National Engineering Laboratory]; Massachusetts Institute of Technology; and Georgia Institute of Technology offer 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, excluding marketing costs. This causes companies developing new drugs serious financial concerns.

Regulatory Approval

The cost of producing a new therapeutic radiopharmaceutical is increased by FDA and NRC regulations. Companies developing new radiopharmaceuticals 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.

Workforce Requirements

(Continued from page 13N)

requirements. In this context, the results of the benchmark model may help nuclear medicine leaders plan future nuclear medicine training programs, just as similar models may assist other specialties in forecasting their own training needs.

Yet in an environment of MCOs and cost containment, the inclination may be to further reduce the number of all specialists—including nuclear medicine physicians—over the course of the next few years. Moreover, the tendency of MCOs to restrict access to imaging procedures may result in delayed diagnosis of specific diseases with obviously negative results for patient outcomes. As the complexity of procedures increases, higher levels of training will be required, and those physicians meeting the more complex training criteria are expected to dominate that particular domain of nuclear medicine. MCOs may react by requiring increased qualifications for performing specialized procedures, and organizational subspecialties of nuclear medicine—such as the American Society of Nuclear Cardiology—may well grow. In fact, nuclear cardiology procedures have increased by approximately 19% since 1993 (*8*).

Planning and research are necessary to meet these challenges. This study on the effects of managed care is part of the planning process in that it may suggest strategies to meet the altered manpower requirements imposed by the changing health care environment. As for nuclear medicine research, rapid changes in technology and the availability of new imaging agents and new procedures inevitably mean that nuclear medicine physicians can create procedures and appropriate sequences of testing that will provide optimum diagnostic accuracy, and this too is expected to better meet the needs of the patient as well as improve cost-effectiveness.

REFERENCES

1. *Physician's Managed Care Report*. Dec. 1995:143.
2. *Managed Care Stats and Facts*. Jan. 8, 1996:2.
3. Weiner JP. Forecasting the effects of health reform on U.S. physician workforce requirements. *JAMA* 1994;272:222–230.
4. Clouse JC, Rogers M, Carretta RF, et al. Future nuclear medicine physician requirements. *J Nucl Med* 1996;37(5):14N–18N.
5. *Current population reports, 1993*. Washington, DC: U.S. Bureau of the Census; 1993.
6. Hilts SV, Pollycove M, Carretta RF, et al. The SNM manpower survey report. *J Nucl Med* 1992;33(11):51N–60N.
7. Vanden Brink J, et al. *TMG news*. Des Plaines, IL: Technology Marketing Group; Fall 1996.
8. Hughes C. Healthcare industry forecast: shifting winds, partly sunny. *Medical Imaging* 1997;12(1):28–37.

BIBLIOGRAPHY

AAMC data book: statistical information related to medical education. Washington, DC: Association of American Medical Colleges; 1994.

Bureau of Health Professions. *Eighth report to the President and Congress on the status of health personnel in the US*. DHHS publication HRS-POD-92-1.Washington, DC: U.S. Department of Health and Human Services; 1992.

(Continued on page 30N)