WHC-EP-0890

Hanford Isotope Project Strategic Business Analysis Yttrium-90 (Y-90)

Prepared for the U.S. Department of Energy
Assistant Secretary for Environmental Management

Westinghouse
Hanford Company Richland, Washington

Management and Operations Contractor for the
U.S. Department of Energy under Contract DE-AC06-87RL10930

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Economic Transition Center
Tri-City Industrial Development Council

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EXECUTIVE SUMMARY

The purpose of this analysis is to address the short-term direction for the Hanford Yttrium-90 (Y-90) project. The demand for this isotope is currently limited, but is projected to increase if Food and Drug Administration (FDA) approval for cancer therapy is obtained. The demand projections for this analysis are based on the cancer therapy potential.

Other potential uses for the isotope are being explored. A research project for using Y-90 in treating Kaposi's sarcoma, related to AIDS, is being evaluated in California. The isotope is being used in Europe to treat arthritis. A similar project for this country is being considered. These could increase the demand for Y-90.

Hanford is the sole DOE producer of Y-90, and is the largest repository for its source in this country. The production of Y-90 is part of the DOE Isotope Production and Distribution (IP&D) mission. A significant portion of the United States requirement for Y-90 is being satisfied by foreign sources.

Hanford is one of the nation's key suppliers of high-grade Y-90 for cancer research. Hanford Y-90 is being supplied to nearly a dozen hospitals, research facilities, and suppliers around the United States. The current research using Y-90 has been very promising, and pending the results of additional clinical trials there are indications that the demand for it will increase dramatically over the next few years.

The Y-90 is "milked" from Strontium-90 (Sr-90), a byproduct of the previous Hanford missions. The use of Sr-90 to produce Y-90 could help reduce the amount of waste material processed and the related costs incurred by the clean-up mission, while providing medical and economic benefits.

The cost of producing Y-90 is being subsidized by DOE-IP&D due to its use for research, and resultant low production level. It is possible that the sales of Y-90 could produce full cost recovery within two to three years, at two curies per week. Preliminary projections place the demand at between 20,000 and 50,000 curies per year within the next ten years, assuming FDA approval of one or more of the current therapies now in clinical trials. This level of production would incentivize private firms to commercialize the operation, and allow the government to recover some of its sunk costs.

Some of the additional benefits of the Y-90 project can be:

Transition of Hanford resources (materials, facilities, personnel, technology)

Leveraging of resources through partnerships with industry

Enhanced U.S. industrial competitiveness, reduction of the U.S. dependence on foreign sources and potential sales to foreign nations

There are a number of potential barriers to the success of the Y-90 project, outside the control of the Hanford Site. The key issues include: efficacy, Food and Drug Administration (FDA) approval and medical community acceptance. The research being conducted using Y-90 as a basis for cancer therapy must be projected to be medically and cost effective before private firms will continue to invest in the human clinical trials.

FDA approval is necessary before the production of Y-90 is significantly increased. This can be a very costly and long process. Medical community acceptance is also required for success. The physicians and technicians must accept the therapy and use it before it can become successful. See Sections 3.3 and 3.4 for more details.

There are at least three other sources for Y-90 available to the U.S. users, but they appear to have limited resources to produce the isotope. Hanford is the only supplier with adequate resources (Sr-90) to produce thousands of curies per week, at this time. The cost and difficulty to acquire the necessary Sr-90 could eliminate most, if not all, of the competition.

Continued growth of the Hanford Isotope Project could result in a new industry in the Tri-Cities. This could assist in the area's economic diversification and promotion of the research capabilities which are located on the Hanford site. There is a potential that pharmaceutical and health care firms will locate close to the primary source of their products. Washington State University has expressed considerable interest in expanding their radio-pharmaceutical education program in the local area to support and take advantage of Hanford isotopes.

Several companies have communicated interest in entering into agreements with Hanford for the processing and distribution of Y-90, including some of the major pharmaceutical firms in this country.

Decisions & Actions

Certain decisions and actions will be required to pursue the commercialization of the Hanford Y-90 project, assuming that is the direction that Hanford decides to take.

1. Continue processing and distribution of Y-90 to customers

2. Promote and expand the current user base

3. Evaluate and enhance existing process

4. Grow the Y-90 market so that the Y-90 project will be self-sufficient (full cost recovery) within two to three years

5. Initiate commercialization efforts now for the Y-90 operation, so that it will be completed within the next three to five years

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1.0 INTRODUCTION

This analysis addresses the short-term direction for the Hanford Yttrium-90 (Y-90) project. Hanford Y-90 is currently being provided to various research entities throughout this country. It appears to have potential in cancer therapy, based on the success of current research and human clinical trials (see Attachment A). The demand for Y-90 is estimated to be between 20,000 and 50,000 curies per year within the next ten years, assuming that one or more of the proposed therapies using this isotope is approved.

The future of the Hanford Y-90 project depends heavily on the success of the human clinical trials being conducted to determine the efficacy of potential cancer therapies using this isotope. Food and Drug Administration (FDA) approval, and medical community acceptance, will be necessary for the Y-90 demand to be as projected.

There are a number of factors of which the Hanford Site has control that will determine the success of the Y-90 project. The activities that must be considered by the DOE Headquarters (HQ) and Richland Operations Office (RL), and its contractors are discussed in this analysis.

Business partnerships must be established with the prospective customers of Hanford isotopes in the near term to assure that Hanford is perceived as a viable and reliable isotope source. This will require the commitment of DOE (HQ and RL) to maintain the isotope operations at Hanford until it is feasible to transfer the resources and capabilities to the private sector.

There is considerable support for this activity from the local community, due to its positive impact on: humanitarian efforts (disease therapy, health, etc.), economic diversification, resource transfer and education.

This analysis provides the current status of the isotope project, and its near term direction. The projection of Y-90 requirements is based on market studies, discussions with potential customers, and the best estimate of the Hanford personnel involved in this project. The market research study provided a conservative estimate of the demand, but private discussions with knowledgeable (industry, medical and scientific) personnel indicate that the expectation is much higher. A range was therefore provided for the expected demand.

The Tri-City Industrial Development Council (TRIDEC) sponsored market research study is included as Attachment D.

The revenue and cost projections are also based on these sources. Revenues are based on the best estimate of market expectations. The costs are based on current data, and projected expansions.

2. BACKGROUND & CAPABILITY

Radioisotopes are used in a broad range of applications in medicine, industry, agriculture, environmental, and scientific research. In 1991, the last year for which data are available, the total free market in isotope sales volume was about $350 million dollars for isotopes alone. The radioactive materials market in the U.S. in 1991 was:

a. $257 billion in total industry sales (gross output)

b. 3.7 million jobs

c. $11 billion in corporate profits

d. $45 billion in tax revenues to local, state, and federal governments

Medical products are the largest segment of the radioisotope market, and are also the fastest growing segment of the total market. A major driving force will be the new technologies for cancer related radioimmuno-diagnoses and radioimmuno-therapies. The radioimmuno-diagnosis technologies will also extend into other areas of disease diagnoses such as heart disease and arthritis. The U.S. radiopharmaceutical market for 1995 is estimated to be more than $3 billion dollars and is steeply rising.

DOE Isotope Production and Distribution Program

In August of 1994 DOE distributed the National Isotope Strategy which restates DOE's mission to supplying key isotopes in order to promote further advances in the manufacturing and the health care industries. That document describes the DOE plans for the production and distribution of isotope products and services. The Department's mission as stated in that document is:

"The Department of Energy will continue to produce and distribute certain radioisotopes and enriched stable isotopes for research or development purposes and medical diagnosis and therapy. The Department will distribute, sell, loan, or lease such isotopes. Any charges for distributed isotopes will provide reasonable compensation to the Department, will not discourage the use of such isotopes or the development of sources of supply independent of the Department, and will encourage research and development. The goal of producing and distributing these isotopes is to meet our national priority of meeting U. S. research needs and supporting our health care system."

"The Department of Energy will also continue to produce and distribute other radioisotopes and enriched stable isotopes for medical diagnostics and therapeutics, industrial, agricultural, and other useful applications on a businesslike basis. This is consistent with the goals and objectives of the National Performance Review. The Department will endeavor to look at opportunities for private sector to cofund or invest in new ventures. Also, the Department will seek to divest from ventures that can more profitably or reliably be operated by the private sector."

2.1 HANFORD

Hanford's involvement with non-defense isotope production began in the 1970's but did not become significant until 1989, when the DOE isotopes program was totally restructured by Congress. A key objective of this program was full cost recovery with emphasis on private sector production. After five years of operation under this program, DOE's expectations have not been realized and foreign dominance has increased.

There are a number of factors which contribute to Hanford's potential as a key player in the medical isotope industry.

Availability of facilities (hot cells, analytical laboratories, etc.)

Scientific and engineering expertise in isotope production, separation, processing, analysis, packaging and shipping

Regulatory license/approval, administrative and technical procedures and expertise to handle large quantities of radioactive materials

Stockpile of radioisotope materials which can be converted to useful medical isotopes, produced by the defense production and research missions

Highly-motivated personnel who are committed to the effort of delivering isotopes for disease therapy and developing an isotope industry locally

Hanford has been designated by the Department of Energy as their source for two major isotopes: Yttrium-90 (Y-90) and Cesium-137 (C-137). The Y-90 is "milked" from the abundant supply of Strontium-90 (Sr-90) located on the site. There is a large quantity of Cs-137 left over from the research and defense activities which can be provided to the private sector. A parallel strategic business analysis has been developed and published for Cs-137.

2.2 YTTRIUM-90

The future commercial use of Y-90 is very promising. Hanford has been selling its Y-90 to a variety of customers around the country for several years. Several cancer research institutions have expressed interest in this Y-90 for use in their development of radioimmuno-therapeutic materials. Pending demonstrated successes in clinical trials and approval by the Food and Drug Administration, the market for Y-90 could increase.

Y-90 can be generated at the level of thousands of curies per week at Hanford. The potential exists for Hanford to be the major supplier worldwide for Y-90 labeled radiopharmaceuticals for the treatment of leukemia, lymphomas, Hodgkin's disease, and other forms of cancer.

Using current technology, facilities, and expertise developed at Hanford, high-grade Y-90 is being supplied to nearly a dozen hospitals, research facilities, and suppliers around the United States in support of promising clinical trials on human cancer patients.

A primary market area for isotopes will therefore be the treatment of several types of cancer with monoclonal antibody or other similar technologies carrying Y-90 to cancer cells in patients. Commercialization of the process is a primary objective, with products that include:

a. Y-90 labeled peptides, proteins, and monoclonal antibodies; and

b. Y-90 sold directly to hospitals and research facilities

Hanford has sufficient supplies of Sr-90 to satisfy virtually all potential requirements for Y-90.

Hanford Resources to Produce Y-90

The processing of Y-90 is performed by Hanford personnel in the 325 Building, using a one-room (hot cell) laboratory. Additional efforts, such as packaging and testing are performed in separate facilities in the 325 and 222S Buildings. Y-90 production is governed by applicable DOE, NRC, state and federal regulations.

The current availability of Y-90 appears adequate in meeting the projected needs. Tank 105 in the 324 Building at Hanford hold several thousand gallons of a solution containing about 15,000 curies of Sr-90. It will also contain approximately 15,000 curies of Y-90 at radioactive equilibrium (achieved after holding about 16 days). The desired amount of Y-90 can separated by using existing technology, facilities and equipment.

The theoretical maximum amount of Y-90 which could be separated annually from the tanks' contents would be 340,000 curies. The practical amount of Y-90 which could be recovered is about 25% or 85,000 curies per year. There should be a significant increase in the recovery percentage with refinements to the process. Because of the 29 year half-life of Sr-90, this supply could be sustained at gradually lower production rates for about 60 years.

An additional 30,000 curies of Sr-90 is available from Tank 107 in the same building. The extraction of this Sr-90 is more difficult than that in Tank 105 due to the iron and alpha emitting contaminants in Tank 107. The process could be performed if the isotope is needed, but at a higher cost. There are also approximately 600 WESF capsules containing more than 23 million curies of Sr-90 in a solid fluoride form at Hanford. This additional source could be used to support the Y-90 production, if needed.

3.0 MARKET DESCRIPTION AND ANALYSIS

The most significant potential market for Y-90 is in cancer therapy. There are numerous forms of cancer therapy being used, but it appears that Y-90 may replace or complement much of the current practice.

3.1 RADIOPHARMACEUTICAL MARKET

A survey performed by Market Intelligence Research Corporation was conducted for the U.S. Radiopharmaceutical Market in 1989. This survey projected that cancer therapeutics are very much in the beginning of a period of high growth rate. The early successes of clinical trials treating several types of cancer are very promising. While the ramp-up in demand for monoclonal antibody (MAb) cancer treatment was predicted in 1993, present clinical trials now indicate a 1996-1998 time frame. A more current study will be completed in the fall of 1995.

The National Cancer Institute estimated that the direct medical cost of cancer was $35 billion in 1990. The market for cancer therapeutic agents is expected to exceed $5 billion in 1993, with monoclonal antibodies reaching over $1/2 billion. About one in three Americans (85 million people) now living will eventually have cancer.

3.2 YTTRIUM-90

The current market for Y-90 is limited to research and human clinical trial quantities, but the demand could increase. The continued success of the research and human clinical trials will determine the rate of increase. The demand for Y-90 continues to increase as the number of trials and different forms of cancer being researched increase. The isotope is also being considered for research in the treatment of other diseases, such as rheumatoid arthritis. (see Attachments A and C for details)

Expected Future Market for Y-90

The initial success in using Y-90 is with lymphoma. Successful development of a product for solid tumor treatment, such as lung, breast, or colon cancer would require on the order of 1000 Ci/wk for each type of cancer. Given the recent promising results in clinical trials this list of potentially treatable cancers could expand. The following displays the number of new cases of cancer in the U.S. each year, which could possibly be treated with Y-90.

Type	New Cases/yr	Deaths/yr
Small Cell Lung	43,000	38,000
Breast	183,000	46,000
Colorectal	149,000	56,000
Lymphoma	53,000	22,750
Ovarian	24,000	13,600

Assuming 50,000 to 60,000 new cancer patients were treated annually (1000+ per week), with doses averaging 300 millicuries (mCi)/treatment with 3 treatments each, the weekly isotope demand would be in the range of 1000 Ci/week. A more conservative estimate places the demand at 200 to 400 Ci/week, assuming only the treatment of lymphoma is approved. The demand could also be considerably higher if several of the larger cancers can be treated by Y-90.

Potential Requirement for Y-90

The table below shows the anticipated growth rate in the demand of Y-90 estimated for a potential cancer therapy. The key driver for market expansion is the availability of MAbs for major cancer types. The companies involved must demonstrate to the FDA that a suitable source of radiolabeled MAbs is in fact available and demonstrably capable of meeting FDA requirements in amounts, quality, and reliability.

YEAR	Amounts (Ci/wk)
1995/96	0.5 to 1
1997/98	1 to 2
2000	50
2005	200 to 1,000

3.3 COMPETITION

There are a number of potential competitors to Y-90 for use in cancer therapy. The first set include the traditional means for combating cancer: surgery, radiation, chemotherapy and immunotherapy. The second are the various radioisotopes which are now beginning to be applied in the fight against cancer. A third set includes the new options being researched, such as, cryogenics and genetic engineering. These are too new to evaluate their true potential at this time.

Traditional Therapy

Surgery is the oldest form of cancer therapy. It is used with a wide range of cancers, for both diagnosis and treatment. It is ineffective with small cell lung cancer, lymphoma and leukemia. The costs of surgery can be very expensive (up to $50K), if hospitalization is required.

Radiation therapy may be defined as radiotherapy, X-ray, cobalt treatment or irradiation. It is used with or in lieu of surgery. About one-half of all cancer patients receive radiation therapy. It could have numerous negative side effects: kills healthy cells, causes cancer, hair loss, etc. It is usually very expensive ($25K to $50K).

Chemotherapy is the use of a drug or combination of drugs to disrupt cancer cell's ability to grow and multiply. It can be used alone, or in combination with surgery or radiation therapy. Chemotherapy is initially one of the least expensive forms of cancer therapy, but it has side effects which can lead to complications and additional costs. The complications include hair loss, indigestion and a reduced immune system.

Immunotherapy uses the patients' own tumor cells to try to stimulate the patients' own immune system to kill them. There have been some limited successes with this approach, usually when other therapies have failed.

Radioisotopes

Radioisotopes, including Y-90, are being used to: fight cancer where there are no other viable therapies, or to replace or supplement the other therapies (eg. surgery). Research indicates that this form of therapy will have fewer side effects, and will be less expensive than most other therapies.

Currently Iodine-131 (I-131) is the only FDA approved radioisotope for therapy of thyroid cancer, and the relief of pain from bone cancer. Research is being conducted using I-131 for non-Hodgkin lymphoma and leukemia. The basic problem with I-131 is that it is not considered user friendly. It generally requires hospitalization and special handling due to its longer half-life (8 days compared to Y-90's 64 hours), gamma emission (Y-90 is basically pure beta) and tendency to vaporize.

There are several other radioisotopes being researched for potential as cancer therapies. The leading candidates include: Samarium-153, Phosphorus-32, Iodine-125, and Palladium-103. Others being studied include: Rhenium-186, Lutetium-177, Scandium-47, Copper-67, Tin-117 and Y-91. Y-90 appears to have the most promise for commercialization at this time.

3.4 POTENTIAL BARRIERS

There are several potential barriers to the success of Y-90 for cancer (and other diseases) therapy which are outside of the control of the Hanford Site. The key ones are:

Efficacy (is Y-90 really the basis for an effective therapy for a wide variety of cancers?),

Food & Drug Administration (FDA) approval, and

Medical and insurance communities' acceptance of the new therapy.

Efficacy

There are a number of research projects being conducted to determine Y-90's efficacy in a variety of therapies, primarily cancer. The isotope is being tested with a variety of delivery vehicles (eg. monoclonal antibodies). They are being tested with a variety of cancers, and the most success has been shown against lymphoma. The efficacy of Y-90 will determine whether or not FDA approval will be pursued by the researchers and the drug manufacturers.

Preliminary indications are that Y-90 will be effective against at least lymphoma, and probably other forms of cancer. This is based on phase I and II human clinical trials. Phase III is the most critical and costly to perform.

FDA Approval

FDA approval is based on the successful completion of phase I, II and III of the human clinical trials. The cost to move a new drug from inception to the market can be as high as $150 million, including: preliminary research, human clinical trials, education/promotion and production. This may eliminate a number of very promising new drugs. The conduct of the trials may last for more than ten years, so the research companies must be very confident and well funded to pursue FDA approval.

Phase I of the human clinical trials is primarily concerned with the safety of the new drug. It typically takes one year to complete, but may take longer depending upon the initial results.

Phase II addressed the patients's response to the drug. This phase normally takes from one to three years. There are a number of variables being tested in this phase, so it can also take considerably longer.

Phase III is typically the most difficult, time consuming and costly. It compares the new drug with existing forms of treatment. This phase will take two to eight years to complete. The number of patients involved range from one hundred to over one thousand. The cost of phase III requires considerable funding, likely with significant investment from a major corporation.

The FDA approval may take six months to two years to obtain after the results of the human clinical trials are submitted for review. Successful completion of the trials may not result in FDA approval. (see Attachment B)

Medical and Insurance Communities' Acceptance

Even after FDA approval, the new therapy is not guaranteed success. The medical community must accept the new therapy before it becomes widely used. Physicians and technicians are more comfortable in prescribing standard therapies. Surgeons will have some reluctance in recommending radioisotope therapy over surgery, because surgery is what they know and with which they have experience.

The medical community, and especially radiotherapists, will need to be educated and convinced of the value of using radiolabeled monoclonal antibody therapy for cancer therapy. There will be a delay until fears and prejudices are overcome. Radioisotopes such as Y-90 will become widely used if they are successful in treating the disease, and if they are cost effective.

Another factor which influences the medical community's acceptance of a new therapy is the insurance companies' willingness to pay for that therapy. The insurance companies usually need to be convinced of the medical and cost effectiveness of the new therapy, before they are willing to commit to pay for it. This can create a delay in the widespread use of the new process.

3.5 OTHER SUPPLIERS

There are at least three other suppliers of Y-90 available to this country's users: Amersham, Nordion and DuPont. Amersham and Nordion are foreign companies. Each of the four suppliers, including Hanford, provide about 10+ curies per year of Y-90 to U.S. customers for a total of about 50 curies per year. Prices for Y-90 appear to be about the same from all sources. Hanford is considered one of the best suppliers by its customers due to the purity and reliability of its product.

It appears that each of the three other sources can produce a few curies (<10) per week at this time. Hanford is currently the only source which has the necessary Sr-90 to produce thousands of curies of Y-90 per week. There are Russian sources that could provide the necessary Sr-90, but it will be difficult to import the isotope into this country at the needed quantity. There is also the question of the reliability of delivery, quality and timeliness of the Russian sources.

The site's readily available supply of Sr-90, combined with the world recognized expertise of the Hanford scientists, makes Hanford the best potential supplier of large quantities of Y-90. The commercialization of the Hanford process should create a very cost competitive situation, since the necessary source (Sr-90) is already in inventory and does not need to be procured. Hanford will likely be this country's source of choice as the requirements for Y-90 increase.

3.6 ADDITIONAL OPPORTUNITIES

A potential demand for Sr-90 has been identified. Hanford has more than 20 million curies of Sr-90 in solid fluoride form. There are also small quantities of other isotopes that are in sufficiently pure form to be useful to the customers. These may require additional processing for customer applications.

Y-90 could be the first step in establishing a medical isotope industry in the Tri-Cities. Successful use of the Hanford Y-90 to assist in the therapy of cancer (and other diseases) could attract various sectors of the medical industry to the Tri-Cities. This will obviously be dependent upon FDA approval. Other factors are:

Establishing a commercial radiopharmaceutical firm locally

Attracting ancillary medical products manufacturing firms

Establishing nuclear medicine educational programs (WSU - TC)

Establishing a radioisotope cancer therapy center in the Tri-Cities

Expanding the use of other Hanford isotopes (eg. Cs-137, alpha emitters)

4.0 STRATEGIES

The strategies involved in attaining the goals of the Y-90 project can be divided into three categories: market identification and development, production expansion and commercialization. The desired end state of the project is to create an isotope industry locally, which will also result in the reduction of Hanford waste and transfer of Hanford resources.

4.1 MARKET IDENTIFICATION & DEVELOPMENT

Research projects typically require millicuries (mCi) per week. Cancer therapy projects using the monoclonal antibodies (MAbs) and/or other technologies may require thousands of curies per week.

The potential Hanford market for Y-90 is divided into three parts:

1. Medical research (cancer, heart disease, and childhood diseases)---the isotope demands are typically tens to hundreds of mCi's per week.

2. Clinical trials---the market demands can range as high as several curies/wk, nominally a scale of ten greater than research needs.

3. Cancer/Disease Therapy---the demand could exceed 1,000 curies/week in the next ten years, once efficacy of a cancer treatment has met all of the FDA requirements, and the therapy has widespread acceptance.

The current strategy is for step 3, Cancer Therapy, to be commercialized for all pertinent medical isotopes. Hundreds of thousands of cancer treatments will be performed annually, and a substantial number could include Y-90.

The market for Hanford Y-90 will continue to grow with increasing numbers of research projects using this isotope, the number of patients in the various stages of human clinical trials, and the successes of these trials. More and more researchers are discovering the potential of Y-90, and that Hanford has the capability to supply large, high-quality quantities of the isotope. Hanford's relationship with its Y-90 customers has been very good.

A key to the expansion of the Y-90 market is partnerships with private firms. These can take a variety of forms, but the Cooperative Research and Development Agreement (CRADA) concept is very useful in initiating such relationships. CRADA's can be formed with minimal capital investments.

New markets for Y-90 are being explored, such as for the treatment of Kaposi's sarcoma and arthritis. Contacts are being made with the researchers in these diseases. There is a potential for conducting research with arthritis sufferers in the Tri-Cities. Attachment C describes some of the potential in this area.

4.2 PRODUCTION EXPANSION

The expansion of the Hanford Y-90 production facilities will depend on the demand. The current process can be readily expanded to meet the near-term requirements. The current facility used for the processing of Y-90 can accommodate a market demand for approximately 10 curies per week. A modification of the facility is likely to be necessary within the next three years to meet the increase in demand. The cost is estimated to be about $100,000 to increase the capacity to 50+ curies per week. This cost would be covered by the increased sales of Y-90.

The long-range demand for Y-90 is expected to be in the 100 to 1,000 curies per week range. This will require a considerable expansion to the existing facility, including the addition of several hot cells and larger handling space. It is anticipated that a new or renovated facility will be required, and that the private sector will be involved at this stage. There is an estimate of $1 million to $2 million for this activity, but it may be less if an existing facility is modified.

4.3 COMMERCIALIZATION

The Department of Energy (DOE-HQ), its Richland Operations Office (RL) and the Hanford Site contractors will need to remain directly involved in the isotope program, at least for the near term. They must provide the base for the continued development of the Hanford resources to a point where private industry can and will become the controlling functions.

The government should not compete with the private sector. Once the economic viability of the isotopes has been demonstrated, the resources should be transferred to private firms. There are a number of issues which must be addressed before this can happen, including: transfer mechanism, costs and licensing. Private industry should be able to provide the needed isotopes to the end users in a more cost effective manner than government. Table 1 displays the phases for commercialization.

The strategies for commercializing the Y-90 project at Hanford will include:

1. Interact regularly with the commercial isotope suppliers and users to determine their needs and to build trusting relationships.

2. Develop agreements with customers to meet their unique requirements.

3. Identify and resolve barriers to the transfer of necessary resources: technology, base materials, facilities, etc. Liability questions need to be resolved regarding waste disposal, leasing/purchasing existing contaminated facilities and licensing of technology.

4. Seek partnerships with private firms to transition the Y-90 processing from the Government to the private sector. There are several alternatives, including: exclusive marketing, commercialization of the Y-90 production or a phased approach. The initial step likely will be to contract with a firm for the conversion of the Y-90 radiochemical to a Y-90 radiopharmaceutical.

Exclusive Marketing

Several companies have suggested that they assume the exclusive marketing role for the Hanford Y-90. They have considerable experience and marketing networks which could increase the Hanford share of the market, and help sell the current excess supply of Y-90. The companies would take a share of the revenue in exchange for their activities.

The problem with this concept is that it does not add to the economy of the Tri-Cities, since the company's existing marketing force (outside the local area) would provide the service. The additional cost for an outside firm to market the Y-90 could possibly reduce DOE's net revenue, even with increased sales.

Production Commercialization

This is the ultimate goal of the Hanford Y-90 project, but there are no known companies which are willing to take the risk needed to commercialize today. The future of cancer therapies using Y-90 are promising, but there is no guarantee that there will be FDA approval.

The companies want to wait until there is more indication that the therapies will be successful before making a major investment. They would be willing to take over operations if the DOE would assume the financial risk, but there is no incentive for the DOE to do so.

A commercial venture operating under the regulations of the Nuclear Regulatory Commission (NRC), instead of the DOE, would be significantly more cost effective. This is an issue that will need to be addressed in pursuing the commercialization of the isotope.

Phased Approach

The most viable option appears to be the implementation of a phased approach. This would likely begin with a private firm contracting with the DOE for the conversion and distribution of Y-90 radiopharmaceuticals. This would increase the sales for Hanford, and the increase in price would help offset the firm's costs.

The conversion would involve the testing, certification, packaging and shipping of the Y-90. A "clean" facility will be necessary to allow for the conversion from radiochemical to radiopharmaceutical. This facility does not currently exist in the Hanford Y-90 processing area.

Other phases could be implemented, with the final phase being the total commercialization of the process. The private firm would purchase or lease the Sr-90 "cows" and perform the full process. This would probably require the licensing of the PNL separation process, and include the hiring of site personnel to perform the necessary tasks.

Table 1

YTTRIUM-90 COMMERCIALIZATION PHASES

PHASE I TODAY	PHASE II 1 - 3 YEARS	PHASE III 3 - 5 YEARS	PHASE IV < 10 YEARS
- IP&D subsidized	- Full cost recovery	- Full cost recovery +	- Significant profit
- <500 mCi/wk sales	- 2 Ci/wk sales	- 10 to 50 Ci/wk sales	- 200 + Ci/wk sales
- Research level of production[1]	- Research level of production[1]	- Enhanced production[2]	- Commercial production[3]
- Identify & pursue new applications (eg. arthritis)	- Expand application base/Initiate commercialization	- Develop and implement commercialization[4]	- Fully commercialized
	- Continued success of human clinical trials	- Approaching FDA approval	- FDA approval of one or more Y-90 applications
- Requires continued IP&D/RL/contractor commitment[5]	- Requires continued IP&D/RL/contractor commitment[6]	- Requires RL and contractor commitment	- Requires RL lease/sale of "cows" and licensing of separation process (or alt.)
- Revenue $6K/wk Cost $12K/wk	- Revenue $20K/wk Cost $14K/wk	- Revenue $30 to $150K/wk Cost $20 to $80K/wk	- Revenue $300K to $1M/wk Cost $150 to $400K/wk

1 Current single hot cell/"cow" operation

2 Multiple "cows" and expanded operation (<$100 K Hanford investment)

3 New/modified facility w/some automation ($2 M private investment)

4 Potential commercialization or negotiations for commercialization

5 Requires: IP&D continued funding and support, RL commitment to provide necessary facilities and raw materials, contractor commitment to provide necessary technical/administrative personnel

6 Revenue from sales will offset IP&D funding for Y-90

5.0 SUCCESS FACTORS

The success of the Y-90 project at Hanford depends upon a number of factors, some common with any business venture and others uniquely related to the government. The factors which are outside of the control of the Hanford Site are described in Section 3.0. The ability for Hanford to be received as a viable provider of medical isotopes relies on three other critical factors:

DOE HQ/RL commitment to the project, at least until it can be commercialized

Continued availability of the necessary Hanford resources

Contractor commitment to the project, including commitment to cost and schedule

5.1 DOE HQ AND RL COMMITMENT

The medical isotope project cannot continue to exist without support and commitment from DOE, HQ and RL. Funding and support are required from the Isotope Production and Distribution (IP&D) Office, since the project is not currently self-sufficient. Isotopes are produced and distributed at the various DOE sites based on direction, charter and funding provided by that headquarter's function.

RL's commitment to the isotope project is required to help assure the current and potential customers of Hanford's isotopes that Hanford will remain a reliable source for them. There have been numerous instances where DOE has been viewed as less than reliable for the delivery of products and services to private industry. The customers must feel that Hanford is a reliable source, otherwise they will seek the isotopes or their replacements elsewhere. Hanford has earned the reputation as being one of the best providers of isotopes, based on its performance in delivering Y-90.

Medical isotopes, especially where there is a life or death situation, are very critical to the users. The isotopes must be delivered on time, in the quantity and quality required. A reliable, cost competitive source must be maintained for continued interest by the current and future users.

5.2 AVAILABILITY OF HANFORD RESOURCES

Part of DOE's commitment must be the availability of Hanford resources, at least until commercialization can occur. These resources include raw materials, facilities, technology and personnel. It is anticipated that for the near-term, Hanford will provide the necessary isotopes. Commercialization will occur when private industry is convinced of the economic viability of the operations. The private firms will continue to require certain resources, such as raw material, even after commercialization.

The clean-up of Hanford is putting increasing pressure on the decommissioning of facilities, especially in the 300 Area. The PNL laboratories where Y-90 is being produced are located in that area. The production/processing of medical isotopes can be moved to other facilities, but the move must be planned to occur without interruption of the deliverables. Duplicate facilities will be required for a short period of time to help assure the reliability of delivery, thus funds must be available for this transition.

There needs to be a long-term availability for the technology and raw materials from which the isotopes are produced. The technology may and should be transferred to the private sector. The raw materials may or may not be transferred to them. The nature (long half-life, high radioactivity) of the source materials may require that DOE or other governmental agencies maintain ownership, and lease them to the private parties involved.

5.3 CONTRACTOR COMMITMENT

The Hanford Site contractors (currently PNL and WHC) must commit to support the continued operation of the isotope activities to help assure the long-term success of this venture. They must become more commercially oriented to better attract and serve customers for these isotopes. The contractors must continue to be responsive and reliable as the quantity and diversity of products are distributed throughout the nation, and potentially the world.

Cost and schedule commitments are critical in the commercial world, especially where they can impact the well being of an individual. The contractors must recognize these needs and maintain a reputation for meeting these commitments. The customers cannot be charged additional costs due to contractor errors, or suffer schedule slides due to these problems.

The long-term goal is to commercialize those isotope productions which are viable. Obviously some of the activities will never reach this stage, and may remain under the direction and control of the government. The contractors must commit to assist private industry in the transfer of the Hanford resources necessary to make commercialization a reality.

6.0 FINANCIAL ANALYSIS

The Isotope Production and Distribution (IP&D) Program within the Nuclear Energy organization of DOE-HQ directs and funds this activity. The Program is committed to produce and distribute isotopes for research and development, medical diagnosis and therapy, agricultural, industrial and other applications which are in the best interest of the nation.

IP&D selected the Hanford Site to produce Y-90 because of its capabilities to produce a high quality supply of this valuable isotope. IP&D recognizes the great potential of this isotope for the therapy of cancer and other diseases.

6.1 PRODUCTION COST ESTIMATES

Y-90 Cost Estimates

The current Y-90 process produces approximately one curie per week, but sales are in the hundreds of millicuries. Lower production levels are not possible due to the configuration of the process. Hanford could sell the excess Y-90, assuming a market, without any significant increase in costs. IP&D Program provides funding to offset production costs not covered by the sales of Y-90. The current operations costs are approximately $12,000 per week.

It is projected that the processing cost for Y-90 at the 50 curie per week level will be less than $2,000 per curie. The full cost for the processing of Y-90 will be more than covered by its sales at this production level.

The production cost for Y-90 is anticipated to continue to reduce as the quantity increases. The cost should be well below $1,000 per curie, once the production level exceeds 200 curies per week. This should occur within the next six to eight years, based on the market projection from medical industry sources. The actual costs will be determined by the facilities used and the level of private involvement at that time. It is fully expected that commercialization of the isotope process will have occurred.

6.2 REVENUE ESTIMATES

The revenue estimates provided are based on data provided by market analysis and information provided by current and prospective Hanford isotope customers.

Y-90 Revenue Estimate

The price for Y-90 is $15.75 per millicurie for quantities greater than 100 millicuries. Currently the revenue from the sales of Y-90 is about $200,000 per year.

The projected revenue from the sales of Y-90, assuming two curies per week and the current price, could be up to $1.5 million. The actual revenue may be higher or lower, based on quantity and a potential reduction in price. This will be sufficient to cover the production costs, and provide recovery of some of the government's sunk costs.

The sales of Y-90, at the 50 curie per week level, could reach $7.5 million per year at $3,000 per curie, which is the estimated acceptable market price. The price will be determined by the actual cost for the production and the market, but it probably won't be much more in order to remain competitive with other suppliers. This should allow for a cost recovery of about $1 to $2 million per year to the government for sunk costs and contribution to the Isotope Production and Distribution Program.

The longer term projection, assuming 200 curies per week, could exceed $15 million per year. This is based on a sales price of about $1,500 per curie, which is the anticipated market price (10% of today). It is probable that the operation will be commercialized by that time.

Ultimately the sales price per curie could be less than $1,000, assuming a demand of 500 to 1,000 curies per week.

6.3 FUNDING REQUIREMENTS

There will be some funding requirements to expand the Y-90 processing line. It is planned that these costs will be offset by revenues or other savings, however if they are not, other funding sources will be sought.

Y-90 Process Expansion

The current Y-90 process can be expanded to the 10 to 50 curies per week level with minimal expansion costs, on the order of $100,000. These costs will be offset by the increased sales within the expansion year. Increasing production beyond this level will require some investment.

A new facility costing at least one to two million dollars would be required to increase the production level to more than 100 Ci/week, assuming that total commercialization has occurred. The cost could be less if DOE maintains the production of Y-90. The investment should be recouped within a year or two.

7.0 DECISIONS AND ACTIONS

1. Continue processing and distribution of Y-90 to customers

DOE-NE (IP&D) is currently providing direction and funding support for the processing of Y-90. This needs to continue since the sales of do not fully cover the processing and distribution costs. The future prospects of Y-90 for cancer therapy and other medical applications appears very positive, so DOE support is justified.

The Hanford Isotope Program Office is doing a good job of responding to and supporting the research community. Excellent relationships have been established and should continue to be maintained to assure Hanford's positive position. There appears to be continued growth in demand by current and future customers.

2. Promote and expand the current user base

Future commercialization of the Hanford Y-90 project requires that the process attain full cost recovery and have the potential for significant profit. This will require the expansion of the current user base. There are a number of activities which can support this growth, some of which are:

- Develop partnerships (eg. CRADA's) to support unique requirements
- Develop partnerships for bulk (> 1 Ci/week) purchases, with customer providing distribution
- Identify and pursue other potential uses of Y-90 (eg. arthritis)
- Use community resources (eg. TRIDEC) to advertise and promote Hanford isotope capabilities
- Examine the potential for a commercial partner to convert the Y-90 radiochemical to a Y-90 radiopharmaceutical

3. Evaluate and enhance existing process

The current operation and equipment used to produce Y-90 is basically research oriented. The process has been enhanced in recent years, but there has been no investment in enhancing the operation. Changes are necessary to help assure that the processing of Y-90 can be performed reliably and cost effectively as the quantities are increased. Some recommended steps are:

- Evaluate current process, including facilities and equipment
- Develop and implement production plans to assure reliability of the process with larger requirements

4. Grow the Y-90 market so that the Y-90 project will be self-sufficient (full cost recovery) within two to three years

It appears that with continued growth in the sales of Hanford Y-90 that full cost recovery should be attainable in the next two to three years. This depends on continued success of the human clinical trials. Increased revenues will allow for the additional expenditure of funds on the operational aspects of the Y-90 processing. It should also increase the commercialization potential for this isotope. Most of the necessary activities are covered in Recommendation 2.

IP&D, RL and Hanford contractors will need to continue supporting the efforts for the processing and marketing of Y-90. IP&D support will still be needed, even after the project no longer requires funding. This support will help assure the emphasis on the isotope within DOE.

5. Initiate commercialization efforts now for the Y-90 operation, so that it will be completed within the next three to five years

The successful commercialization of the Y-90 operation will require considerable planning, planning which needs to start now. Community involvement and support will be necessary to help attract a private firm to locate in the Tri-Cities to produce and sell Y-90 radiopharmaceuticals.

The nature and success of the Y-90 commercialization will have an impact on the future of a potential isotope industry in the local area. It can be the genesis of that industry, or it could terminate the potential before it begins. Future research and development, education and training, a potential therapy center in Tri-Cities, and associated medical activities all need to be considered in planning for the commercialization.

Identification of potential commercialization partners has been initiated. The details of commercialization will depend on the selected partner(s). Some of the questions that will need to be addressed include:

> Who? Which prospective partner will provide the most benefit to the community, as well as the government?
>
> What resources will be needed? Will these be transitioned from the government, or will they be private?
>
> How will the technology transfer occur? What will be included in the licensing of the process?
>
> How will the "cows" be owned? Should the government maintain ownership and lease the cows, or sell them to the commercial partner? Are there any major liability issues?

The next step should be the issuing of an RFI (Request for Interest) from private firms that would like to help commercialize the Hanford Y-90 project.

Attachment A

The Y-90 Project

Hanford produces and sells small amounts of Y-90 to customers across the United States for a variety of health-related purposes primarily for use in human cancer clinical trials. This program has been operating for more than 4 years and has established itself as a very reliable supplier of high-quality, high-purity Y-90. Both the purity and reliability are very important for the medical institutions dealing all too frequently with life and death situations with humans in clinical trials.

Some of the recent customers using Hanford-produced Y-90 include:

CANCER THERAPY

a. University of Texas, Houston, M.D. Anderson Cancer Center---Clinical trials on Hodgkin disease. Eighty patients were treated for Hodgkin lymphoma with Y-90 labeled MAbs. Thus far, 80% of them have responded positively to the treatment. These patients had failed to respond to standard treatment procedures prior to entering these programs. All were treated as outpatients. M.D. Anderson is now establishing protocols with the FDA to treat brain, ovarian, and breast cancers.

b. University of Cal. at Davis---Clinical trials with breast cancer.

c. University of Nebraska---Human Studies of lymphoma

d. National Institute of Health, Bethesda---T-cell lymphoma, T-cell leukemia

e. NeoRx, Seattle---Small cell lung cancer

f. IDEC Pharmaceuticals---lymphoma

g. University of Colorado---Patient studies of breast cancer

ANIMAL STUDIES

h. Immunomedics---Animal studies of cancer

OTHER SUCCESSFUL STUDIES USING MAbs LABELED WITH OTHER RADIOISOTOPES

i. Fred Hutchinson Cancer Research Center, Seattle---84% remissions in B-cell lymphoma

j. Fred Hutchinson Cancer Research Center, Seattle---very positive preliminary results for acute leukemia

k. Intraperitoneal ovarian cancer at several institutions

MONOCLONAL ANTIBODIES (MAbs)

The results of a recent clinical trial on humans at the Fred Hutchinson Cancer Research Center in Seattle were published in the October 21, 1993 issue of the New England Journal of Medicine. This trial was performed as part of a larger program to determine the efficacy of the radiolabeled MAbs technology in the treatment of B-Cell lymphoma. The results of the trial indicate that 16 of 19 humans showed complete remission, an 84% remission rate, while the remainder showed some positive response.

The use of cancer-specific MAbs targets the delivery of the radioactive material to the cancer cells where it preferentially kills the cancer cells in situ. There is some damage to healthy cells, but not on a scale that is experienced in chemotherapy and whole-body radiation therapy. These latter two treatments are much more debilitating than the MAbs technology. There are business-sensitive variations of the MAbs technology now emerging, but the general principle of the specific delivery of lethal amounts of radioactivity to cancer cells in situ remains applicable.

Other clinical trials being conducted in hospitals and universities around the United States are showing similar promise on other types of cancer. The studies performed in Seattle used MAbs labeled with Iodine-131. For a variety of reasons Y-90 is gaining in favor as a preferred isotope by some physicians in such studies. These include: more specific delivery of radiation as beta particles, higher energy and dose rates, recent successes with Y-90, greater safety to health care workers, and lower costs. About 20% of the ongoing human clinical trials with MAbs involving radioisotopes for cancer treatment now use Y-90.

Currently, the Hanford Isotopes Programs provides Y-90 to several of the hospitals and universities who are conducting these trials. This material comes from existing process equipment designed for the separation of Y-90. Hanford currently sells hundreds of millicuries per week for medical and research applications.

YTTRIUM–90
RADIOCHEMICAL

PRODUCT INFORMATION

PHYSICAL DATA

Half Life	–	64.0 hours
Decay Mode	–	β^- with 2.28 MeV max

PROCESS DATA

Chemical Processing	–	Extraction into HDEHP (di(2–ethylhexyl)phosphoric acid)/ stripped with HNO_3 and purified
Assay	–	Inductively Coupled Plasma Spectroscopy (ICP)

PRODUCT SPECIFICATION

Chemical Form	–	^{90}Y as chloride in 0.05 M acid
Chemical Purity	–	< 100 µg/Ci Ca^{2+} < 40 µg/Ci Zn^{2+} < 30 µg/Ci Al^{3+}, Cu^{2+} < 20 µg/Ci Fe < 20 µg/Ci for all other detectable cations
Specific Activity	–	Carrier free
Activity Concentration *	–	> 0.5 Ci/ml
Radiochemical Purity *	–	> 95% Y as Y^{3+}
Radionuclide Purity *	–	< 2.5 µCi of ^{90}Sr/Cl ^{90}Y No other radionuclides detectable

** Activity and purity specifications are at shipment*

Availability:	Delivered weekly
Services:	Autoclaving and Pyrogen Testing, upon request
Packaging:	Acid washed borosilicate vials with Teflon or FEP faced butyl rubber closures in millicurie or curie units

Please note that this material is not certified as a radiopharmaceutical

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Attachment B

HUMAN CLINICAL TRIAL PHASES
FDA APPROVAL

There are four phases of FDA Human Clinical Trials, after the basic research has been completed. Phase IV is conducted after FDA approval, and sales have been initiated. The phases are:

Phase I - Testing drug to determine its safety

Small number of hopeless cases, determines maximum safe dose
Takes 6 to 18 months

Phase II - Testing drug to determine patient response

20 to 50 patients, measures response to treatment
Takes 1 to 3 years

Phase III - Comparing drug to other treatments (efficacy)

100 to 1,000+ patients, compares results (eg. longer life)
Can last from 2 to 8 years

Phase IV - Post marketing surveillance

There is no set time frame for any of the phases. They may last from a few months to several years, depending upon the progress of the researchers. FDA sets their priorities based on the IND (Investigational New Drug), the application which describes the drug and its potential application(s).

A New Drug Application must also be completed prior to FDA approval. This can be developed during the initial phases. It includes the following information:

Where the drug is to be manufactured

Who within the supplier is the responsible individual

What the format of the drug will be (capsule, powder, fluid, etc.)

How the blood or platelet testing will be conducted

What is the consequences of overdose

What is the chemical spectrum of the drug

How is the drug going to be advertised, what warnings, etc.

Attachment C

LOCAL ARTHRITIS RESEARCH POTENTIAL

Radioisotopes, including Y-90, have been used in research and treatment of arthritis in Europe. Some use of Y-90 for this application has begun in Canada. There are currently no known application of radioisotopes for arthritis in this country. Discussions have been held with local medical personnel, researchers currently using Y-90 for cancer applications and various national organizations. It appears that a potential exists for the initiation of some research using Y-90 for potential arthritis treatment in the Tri-Cities.

The steps have been initiated or need to be initiated to pursue this opportunity include:

Identification of local resources which may be used for this research

Hospital, medical centers and WSU TC

Local rheumatology support organizations

Identification and commitment of a local physician to perform the necessary research

Identification and commitment of a local patient base

Commitment of DOE IP&D to support the research (contribution of Y-90)

Continued dialogue with Dr. H. Vriesendorp, M. D. Anderson Cancer Center, who suggested and supports the concept

Obtain information on the activities in Europe and Canada regarding the use of Y-90 for arthritis therapy

Obtain FDA approval to conduct human clinical trials

Creation of a CRADA or other form of partnership between Hanford and the private sector

Determination of necessary procedures and testing

Identification and securing of necessary funding sources (eg. NIH, Arthritis Foundation)

The potential for conducting the full research in the Tri-Cities is limited due to the lack of a sufficient patient pool. Consideration is being given to the concept of teaming with a research institution for this activity.

Attachment D

YTTRIUM-90 MARKET STUDY

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STUDY OF THE

MARKET FOR

YTTRIUM-90 IN

CANCER THERAPY APPLICATIONS

for

Tri-Cities Industrial Development Council
Kennewick, WA

FINAL REPORT

August 7, 1995

JOYCE
& ASSOCIATES

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I. BACKGROUND

The Westinghouse Hanford Company is the recognized sole supplier of Yttrium-90 under the US DOE's Isotope Production and Distribution Program. Derived from hazardous waste, Y-90 is pure enough to offer commercially. Although demand for this isotope is on the increase, sources of supply are few, with many users being forced to purchase from suppliers outside the USA. There is clear potential for building a sizable business in the Tri-Cities, with two benefits: the creation of jobs in the local community, and a reduction in the cost and liability of storing radioactive waste on site. TRIDEC, in partnership with WHC, would therefore like to acquire an understanding of the market for Y-90, and has commissioned a market study to provide that understanding.

Phase I of the study demonstrated a clear opportunity for Y-90 in cancer therapy. This report examines that opportunity in depth.

II. OBJECTIVES

The overall objectives are to characterize the demand for Y-90 and to determine what Hanford would have to offer to compete. Specific objectives are:

1. Identify market segments and applications for the Y-90 isotope.
   - Medical

2. Characterize the current and future needs of customers and potential customers, both technical and commercial, for example:
   - Curies required per capsule, per shipment
   - Purity/form isotope is supplied in.
   - Price
   - Delivery
   - Customer support
   - After-sales support

3. Identify competitors to an intended Hanford isotope supply business.
   - Offshore suppliers (e.g., Amersham)
   - Competing radioactive isotope (e.g., I-131)
   - Competing technologies
- Profile key competitors and identify strengths and weaknesses

4. Determine the basic health of the industry.
   - Supply side
   - Demand side (e.g., profitability of commercializers of isotope technology such as NeoRx)

5. Identify and profile organizations which could be strategic partners with WHC in the supply of Y-90.
   - Current competitors (e.g., Nordion)
   - Potential users (e.g., NeoRx)
   - Other companies that could partner with WHC to process and ship isotopes in a non-DOE environment
   - Possible investors in a Tri-Cities-based business unit

6. Size the market, with focus on areas of attractiveness to Hanford.
   - Currently
   - Over a 5- to 10-year time frame
   - For North America primarily
   - International markets, for applications in which the domestic market is too small to be attractive

7. Identify the drivers that will cause the market to grow and project market size 10 years out.

8. Identify barriers, risks, and liabilities associated with WHC's participation in that market.
   - Risks, accidents, disposal, safety
   - Any concerns about WHC as a supplier, Hanford as a site

9. Identify, overall, the best opportunities for a Hanford isotope business.
   - By market segment
   - By application
   - By isotope
   - Short-term and longer-term

III. METHODOLOGY

The first phase of the study consisted of preliminary interviews across all segments and applications. From that work, cancer therapy emerged as the primary focus for Y-90.

This report describes the findings resulting from in depth interviews and investigation into the cancer therapy applications for Y-90.

Distribution of respondents are shown below. The appendix includes the complete respondent list.

Respondents by Category :

Users	35
Suppliers	11
Others	08
Total	54

IV. FINDINGS

STAGING

Staging - describes severity of a patient's cancer.

- Many systems used. Information conveyed is:
  - early stage(s) - untreated primary tumor,
  - middle stage(s) - gradual increase in size leading to lymph node involvement,
  - late stage(s) - spread to distant sites.

Staging helps

- determine prognosis,

- make decisions about treatment.

Clinical trials

- Organized studies using informed volunteer patients.
- Required for FDA approval.
- Carried out in phases.

Phase I - safety

- Small number of hopeless cases,
- Finds best way to give Y-90,
- Determines maximum safe dose,
- Can involve significant risk,
- Takes 6 to 18 months.

Phase II - response

- 20 to 50 patients with one type of cancer.
- All other therapies have failed.
- Tumor responds if:
  - it gets substantially smaller,
  - symptoms disappear,
  - improvement remains for at least a month after treatment ends.
- Trial successful if 20% or more of patients respond to treatment.
- Takes 1 to 3 years.

Phase III - Compare to standard treatments

- Patients are not hopeless cases.
- Uses hundred to thousands of patients.
- Patients chosen by chance to receive either the standard treatment or Y-90.
- Compares Y-90 patients to standard patients. Look for:
  - longer life,
  - better quality of life,
  - fewer side effects,
  - fewer cases of cancer returning.
  - less expensive treatment
- Trials can be lengthy (2 to 8 years)
  - larger numbers of patients required,
  - since patients still have hope, recruiting more difficult,
  - life expectancy and quality of life difficult to measure in short term.

EFFECTIVENESS/APPROVAL

- Y-90 can be considered effective without "curing" a patient's cancer.
    - many cancers have no known cure, or a very limited cure rate. Y-90 is effective if it:
        - extends life expectancy,
        - improves the quality of life.

- FDA or local Institutional Review Board (IRB) pre-approves trial plan for each phase.

- FDA reviews results as phases are complete.

- Phase III Data is submitted to FDA panel of experts.

- Final approval process
    - 6 to 18 months following Phase III completion
    - panel recommendation for approval.

CANCER THERAPY ACCEPTANCE

- Cancer treatment very conservative.

- Surgery, radiation, chemotherapy, nuclear medicine well established, often within rigid organizational lines.

- New treatments, if they show any promise at all, are given an opportunity to be used on hopeless cases.

- Widespread acceptance requires
    - a dramatic breakthrough
    - new or additional business outlets for the manufacturers, distributors, and practioners in already existing fields; e.g.
        - laser surgery picked up by medical device manufacturers, surgical supply houses, and surgeons.
        - new chemotherapy drug produced by existing pharmaceutical company, sold through existing channels, and is used by oncologists already prescribing cancer drugs.

"Who is going to prescribe Y-90 once it is approved? That is a very interesting question - it is all very political. Sorting this out is going to be a major issue for the companies who plan to sell Y-90 on a commercial basis. One thing for sure is that if Y-90 works and provides a new billable treatment, everyone is going to want it." - Nina Kortyleysezz, Univ of NE

INSURANCE/REIMBURSEMENT

- Medicaid, Medicare, private insurance companies and health maintenance organizations dominate payment for cancer treatments.

- Reimbursement essential for routine use of any drug or treatment.
    - steps to reimbursement
        - FDA approval
        - luminary use
        - publication of results in peer reviewed journals
        - conference presentations
        - insurance company evaluation of cost and efficacy; determines permitted use/amount reimbursed

- Cost of treatment has major impact on reimbursement and acceptance by healthcare community.

- If new treatment effective and inexpensive, acceptance can be rapid.

- If effective and expensive, or inexpensive but marginally effective, treatment will undergo much tighter scrutiny.
    - be withheld until less expensive treatments have been tried - limits patient pool available for new treatment.
    - be withheld until equally effective, more familiar treatments have been tried - limits patient pool.

- Bone marrow transplant; "TAXOL" - recent advances that have been used sparingly because of cost and questions of effectivity.

"Insurance companies usually resist paying for a new treatment. If it is expensive, then it has to go to the end of the line and wait for the standard, less expensive treatments to be tried first." - Amy Factor, Immunomedics

- FDA approval necessary but not always sufficient for acceptance by insurance companies.

- Additional endorsements normally required:
  - luminary,
  - professional societies,
  - sometimes additional studies to replicate findings.

- Assuring reimbursement is major marketing effort.
  - headed by company sponsoring trials.
  - normally begins simultaneously with start of Phase III trials.

Y-90 TARGET CANCERS, PROFILES

SMALL CELL LUNG CANCER

New cases per year in US - 43,000

Deaths per year US - 38,000

Prognosis - 5 Year Survival Rate: 20%

- Limited stage disease - 10%-30%
- Advanced stage disease - 1%-2%

Treatment

- Surgery and radiotherapy usually ineffective.
    - limited stage disease - combination chemotherapy and chest irradiation.
        - gives 4-5 fold improvement of survival time over untreated patient.
        - advanced stage disease - chemo and radiation does not improve over chemo alone except to relieve symptoms.

Studies underway

- High dose chemo
- Bone marrow transplantation
- Monoclonal Antibody

Y-90 Opportunity

- Small cell lung cancer resistant to all therapies.
- If, at all helpful, Y-90 will be used.

BRAIN CANCER

New cases per year in US - 11,000

Deaths per year - 9800

Prognosis - 5 year survival rate: 20%

Treatment

- Staging does not impact treatment.
- Surgery, if possible.
- Radiation to shrink tumor prior to surgery, or if surgery not possible.
- Chemotherapy sometimes combined with radiation.
- Alternatives if surgery, radiation, chemo, fail:
  - •• ultrasound - success not yet determined
  - •• tissue culture
  - ••• immunotherapy

Studies underway

- Various combinations of drugs

Y-90 Opportunity - Because of poor prognosis, Y-90 will be tried for

- Efficacy
- Lower treatment costs than expensive surgery and radiation.

BREAST CANCER

New cases per year in US - 183,000

Deaths per year in US - 46,000

Prognosis - 5 year survival rate: 72%

Treatment

- Early stages:
  - mastectomy is standard.
  - radiation - promising for early stage disease.
    - supplemented with limited surgery and/or temporary iridium implants.
    - studies suggest that radiation therapy may prove as effective as mastectomy.

- Later stages:
  - chemotherapy used in addition to mastectomy and radiation if cancer has spread
  - hormone therapy
  - bone marrow transplant - investigational

Y-90 Opportunity

- Replacement for or in combination with chemotherapy on metastasized cancer

- If inexpensive and very effective possibly replace radiation and surgery to reduce cost and psychological trauma.

COLORECTAL

New cases per year in US - 149,000.

Deaths per year in US - 56,000.

Prognosis - 5 year survival rate: 48%

Treatment

- Early and middle stages:
  - surgery
    - leads to cures in about half of cases.

- Middle stages:
  - chemo and immuno therapy under investigation

- Late stages:
  - chemotherapy
    - used in combination with surgery and radiation.
    - pain relief
    - used to kill cancer cells that may have spread after penetration of bowel wall by tumor.
    - 20% of patients who have metastasized colorectal cancer respond to chemotherapy.
  - immunotherapy - under study.
  - radiation therapy
    - pain relief
    - still being studied. Often used to shrink tumor before surgery, or as follow-up to kill remaining cells.

- Replacement for or in combination with chemotherapy and radiation if being used to treat metastasized cancer.

LYMPHOMA

New cases per year in US - 53,000

- Hodgkin's - 13,250
- Non-Hodgkins - 39,750

Deaths per year in US - 22,750

Prognosis - 5 year survival rate

- Hodgkin's - 68%
- Non-Hodgkin's - 43%

Hodgkin's treatment

- Early stage:
  - radiation
  - chemotherapy
- Advanced stage or recurrent:
  - chemotherapy

Non-Hodgkin's (aggressive form)

- All stages:
  - intensive chemotherapy
  - sometimes localized radiation
  - studies underway
    - bone marrow transplantation for patients who have become resistant to chemotherapy

Non-Hodgkin's (indolent form)

- Very slow growing
- Some patients receive no treatment
- Some receive chemo and/or radiation

Y-90 Opportunity -

- Surgery ineffective, prognosis poor, metastasis common.
- If effective, Y-90 can become treatment of choice.

PROSTATE

New cases per year in US - 200,000.

Deaths per year in US - 38,000

Prognosis - 5 year survival rate: 64%

Treatment

- Early stage:
  - surgery primary treatment
  - radiation gaining importance
  - brachytherapy

- Late stage:
  - hormone therapy
  - surgically inhibit testosterone
    - drugs
    - infuse estrogen chemotherapy if hormone has failed
    - immunotherapy under investigation

Y-90 Opportunity

- Can become important treatment in late stage cases of metastasis.

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OVARIAN

New cases per year in US - 24,000.

Deaths per year US - 13,600.

Prognosis - 5 year survival rate: 34%

Treatment

- Early stage:
  - surgery primary treatment
- Late stage:
  - chemotherapy

Y-90 Opportunity

- Except in earliest stages, prognosis poor.
- If Y-90 effective, can replace or be combined with surgery and chemotherapy.

Drug Development Process

"Approval by the FDA is no guarantee of acceptance by the medical community. Cytogen's "OncoScint" is dead. Surgeons and oncologosts found it didn't do anything more than what they already had." - Kim Kiyma, Syncor

"Be neither the first nor the last to adopt a new technology." - Doctor's proverb - Becky Bottino, NeoRx

Clinical trials

- Phase I, II comparatively simple, often covered by research grants.

- Research goals can be independent of commercialization

"Many trials include colorectal or ovarian cancers. These are solid tumors, but there are so many antibodies available to take Y-90 to these sites that even though they aren't the best choice for medical results, they are very convenient from a researchers point of view." - Nina Kortyleysezz, Univ of NE

- Phase III
  - significant trigger point
  - minimum of 100 patients; can run into thousands.
  - 2 years minimum; can be 8 years.

Commercialization effort

- Begins with Phase III start.
- Attracts luminaries.
- Presentations to:
  - professional societies,
  - insurance companies,
  - FDA panels
- Brings manufacturing on line in compliance with FDA regulations.
- Resolves all issues regarding:
  - packaging,
  - pricing,
  - distribution.
- Begins marketing effort
  - physician education
  - pre-sell insurance companies.
  - promotional effort
    - advertising
    - trade shows
    - company sponsored physician seminars

Market Introduction costs - $150M.

- Most of development costs start with beginning of Phase III trials.
  - requires high level of certainty before continuing.
  - requires corporate sponsorship.

Financing

- Drugs involving new technologies usually begin in small venture capital funded companies.

- Only after successful Phase I, Phase II, and at least initial portions of Phase III, will major corporations become involved.

- Funding deal can take many forms
  - complete company buy out
  - product buy out
  - royalty agreement for product manufacturing/marketing.

- After funding, drug must constantly compete for corporate resources.

Mainstream acceptance

- FDA approval necessary.
  - FDA approval is permission to compete, no guarantee to win.

- Reimbursement essential.
  - without reimbursement, drug will not gain widespread use.

- Drug must benefit medical practice
  - surgeons will view Y-90 as competitive
  - oncologists, nuclear oncologists, nuclear medicine will need to sort out ownership.

- Y-90 will probably be first radioisotope therapy.
  - no precedent
  - no clear ownership
  - efficacy outside of research setting not known

- Y-90 will not be standard
  - physicians will be wary of:
    - patient harm
    - exposure to liability

- First treatments take place in teaching, research centers on patients having little chance of recovery.

- Experience with drug will determine how fast acceptance spreads into mainstream practice and patient population covered.

- 5 to 10 years required for use on broad based population by non-research physicians.

Parallel activities

- Development of new or additional method of drug administration - e.g. aerosol in addition to injection
  - greatly reduced cost of development and trials
  - extends life of patent protection

- Facilitate use of "off-branding"
  - physicians permitted to prescribe approved drug for indications other than tested in formal trials.
  - advantages:
    - offers hope to otherwise hopeless cases.
    - speeds widespread use of drug.
  - risks:
    - may not benefit patient.
    - possibility of unknown side effects.
    - physician vulnurable to malpractice.
    - little chance of reimbursement.

Summary - new drug from animal trials to mainstream use

- $150 million

- 15 years

- major commitment

"Radiopharmaceuticals cost as much to develop as any other drug. Do we put $150 million in Y-90 to treat prostate cancer (200,000 patients), or $150 million into Prozac (20 million patients)? Most drug companies don't put their money into radioisotopes." Kim Kiyma, Syncor.

MARKET PENETRATION

Cancers treated

- Experts differ:
  - "Lymphoma, leukemia, some lung cancer will be the cancer sites most suitable for Y-90. There has been no success with any radioisotopes on solid tumors." - Bob McGuire, Cytogen
  - "Y-90 is overkill on lymphoma. We think solid tumors are far better choices than lymphoma or leukemia." - Sandor Erdlyi, Nordion
  - "We know I-131 doesn't work on solid tumors and we don't think Y-90 will." - Steve Glen, Coulter
  - "The only thing definite right now is that Y-90 seems to definitely affect solid tumors." - Alan Fritzburg, NeoRx
  - "Lymphoma and leukemia are the best candidates for Y-90. No solid tumor has ever been cured using any radioisotope." - Jorge Carrasquillo, NIH
- Initial target: lymphoma
- Secondary targets: leukemia, lung
- Other solid tumors: unlikely; will require breakthrough therapy.
  - solid tumors generally treated by surgery.
  - solid tumors have shown little response to radioisotopes.

Stage

- In all cases Y-90 will begin with end stage patients.
  - prudent medicine.
  - reduces exposure to malpractice.

- As history of efficacy established, will move toward earlier stages replacing less effective and/or more expensive treatments.

Physician speciality

- Surgeons will not be involved.

- Oncologists and radiation oncologists will be the prescribing physicians.

- Nuclear medicine can play various roles depending on hospital organization.
  - manage patients under direction of oncologist.
  - treat patients directly after referral by oncologist.

- "Oncologists and radiation oncologists will use Y-90. Nuclear medicine may possibly be involved actually handling the material. Surgeons will not be involved." - Bob McGuire, Cytogen

COMPETITIVE THERAPIES

Surgery

- Oldest form of cancer therapy.
- Used for treatment and diagnosis.
- Performed as out-patient, doctor's office, clinic, or full hospitalization procedure.
- Expense can be high depending on hospitalization required
- Minimal side effects.
- Risks well understood and managed.
- Cosmetic impact can be severe.
- Primary cancer treatment for:
  - breast
  - colorectal
  - prostate
  - ovarian
  - brain cancer when possible

- Ineffective with:
  - small cell lung
  - lymphoma - all kinds
  - leukemia

- Studies on-going for refined or new techniques.
  - laser
  - ultrasound
  - micro
  - cryogenic

- Cost - $5K to $50K

Radiation

- Also known as radiotherapy, X-ray, cobalt treatment, or irradiation.

- Primary therapy with Hodgkins; depending on stage, used on all major cancers

- Half of all cancer patients receive radiation therapy.

- For some patients, it is only treatment needed.

- Used:
  - before surgery to shrink tumor
  - after surgery to stop growth of any cancer cells that remain
  - in lieu of drugs or surgery
  - reduce symptoms in advanced patients: shrink tumor, relieve pressure, control bleeding or pain

- Risks:
  - kills healthy cells
  - causes cancer

- How given:
  - externally with X-ray machines as an out-patient treatment
  - internally with radioactive implants - requires several days in hospitals
  - typical routine is
    - 5 treatments/week; 20 minutes/treatment; 5 weeks
    - 1-2 weeks later "booster" treatment daily for 5-10 days with X-ray machine
    - alternate "booster" can be radioactive implants for 2-3 days

- Side effects:
  - fatigue, skin problems, loss of appetite, hair loss in local area of treatment

- Cost: $25K to $50K
  - several specialists
  - complex equipment
  - 5 days a week for several weeks

Chemotherapy

- A drug or combination of drugs to disrupt cancer cell's ability to grow and multiply.
- Over 50 drugs presently approved.
- Primary therapy with lymphoma; depending on stage can be used on all major cancers
- Used locally (e.g. skin cancer) or systemically
- Administered orally, intravenously, or by injection into muscle.
- Can be used alone, or in combination with surgery and/or radiation therapy.
- Can be administered at home, as an out-patient in a clinic or hospital, or in doctor's office.
- May be daily, weekly, or monthly.
- May be given in a start and stop regimen to give the body a chance to recover.

- Side effects include hair loss, indigestion, reduced immune system.

- Risks - complications due to infections caused by weakened immune system.

- 1% chance of killing patient.

- Cost:
  - least expensive of standard treatments
  - rare instances of drugs costing to $2000 per dose
  - nominally drugs cost $20 to $50 per dose
  - drugs typically cost less than 5% of overall treatment

Bone Marrow Transplantation

- Treatment for:
  - routine - leukemia and lymphoma
  - experimental - variety of advanced cancers including breast and lung

- Requires a donor and hospitalization of donor.

- Usually tried after chemotherapy and radiation have been used.

- Patient must have immune system suppressed and radiation to kill leukemia cells.
  - infection a problem
  - bleeding
  - damage
  - two-way rejection can occur -
    - patient can reject donor's marrow (patient rejection)
    - marrow can reject patient (host rejection)
- Risk:
  - 5% - 10% chance of killing patient

- Bone marrow transplant is treatment of choice for some stages of leukemia and lymphoma, however:
  - it is complex
  - it is only available in certain speciality centers
  - it can have life threatening complications
  - it is expensive

- Cost
  - $100K - $250K

Tissue Culture

- When other therapies are failing.
- Used as adjunct to chemotherapy.
- Sample of patients tissue taken to try to find drugs that kill the cancer cells.

Immunotherapy

- Used when other therapies are failing.
- Used as adjunct to standard therapies.
- Uses patients own tumor cells to try to stimulate patients own immune system to kill them.
- Used on various cancers including:
  - brain
  - colorectal
  - prostate

Hormone Therapy

- Used when other therapies are failing.
- Used as adjunct to chemotherapy.
- Try to cause patient hormones to discourage tumor growth.
- Used on various cancers including.
  - breast
  - prostate

Hyperthermia

- Experimental, used on soft tissue cancers.
  - requires solid tumor target: neck, breast
- Disrupts cellular reproductive cycle.
- Technique intensive, requires hospitalization.
- Studies on-going in limited number of sites.
- Future outlook - unknown, has been slow to progress due to lack of commercial interest.

CURRENT TREATMENTS

Cancer	Stage	Primary	Secondary	Prognosis
Lung	early 5 year	chemo and chest radiation		none 10%-30%
	late	chemo	radiation for pain	5 year 1%-2%
Brain	all	surgery if possible	radiation, chemo, ultrasound,	5 year 20% tissue, immuno
Breast	early	surgery	radiation	5 year 72%
	late	chemo, hormone, bone marrow		

Cancer	Stage	Primary	Secondary	Prognosis
Colorectal	early, middle	surgery	Chemo and/or radiation	5 year 48%
	middle	chemo	immuno	
	late	chemo	immuno radiation	
Hodgkin's lymphoma	early	radiation, chemo		5 year 68%
	late	chemo	no treatment	
Non-Hodgkin's lymphoma, aggressive	all	intensive chemo	radiation, bone marrow	5 year 43%
Non-Hodgkin's lymphoma, indolent	all	no treatment	chemo, radiation	5 year >90%

Cancer	Stage	Primary	Secondary	Prognosis
Prostate	early	surgery	radiation, brachy	5 year 64%
	late	hormone	chemo, immuno	
Ovarian	early	surgery		5 year 34%
	late	chemo		

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STAGE AT DIAGNOSIS

Distribution of various cancer diagnoses by stage.

		----------Stage at Diagnosis----------			
Cancer	Total	early	middle	late	unknown
Lung	100	22	30	36	12
Breast	100	63	27	6	4
Prostate	100	58	15	15	12
Colorectal	100	41	35	18	6
Average	100	46	27	19	8

SELECTED TREATMENT COSTS

Treatment costs per cancer patient in $000.

Cancer	Source	Hosp	Phy	Drugs	Other	Total
Lung	M	20	8	1	4	33
	K	29				38
Breast	M	34	13	4	6	57
	K	19				42
Prostate	M	35	11	4	5	55
	K	20				36
Colorec	M	41	11	2	5	59
	K	41				60
Ovarian	M					
	K	51				77
Lymphoma	M					
	K	41				59
Average		33	11	3	5	51

Notes:

1. M - Medicare data; K - Kaiser Permanente data

2. All data in 1990 dollars adjusted by the 1994 cost of living index.

3. Additional cost information:

   - surgery - radical prostatectomy - $18K-$20K
   - radiation - early stage prostate - $13K-$17K
   - seed implant - early stage prostate - $9K-$11K
   - radiation - lymphoma - S12K-$20K
   - radiation - small cell lung cancer - $5K-$10K
   - chemotherapy drugs - small cell lung cancer - $6K

Y-90 PRICING

Competitive pricing

- Expert consensus:
  - cost of treatment important
    - drives acceptance of new drug by physicians
    - drives acceptance by insurance companies
  - Y-90 will compete against existing chemotherapy approaches
  - $1000 total treatment cost for Y-90 will make attractive; foster acceptance

"Absolutely, without a doubt, you have to consider the cost of the treatment. We don't just look at effectiveness." - Mitch Sugarman, Kaiser Permanente

"Cost always matters. It is an important part of any treatment." - Nina Kortyleysezz, Univ of NE

"Sometimes in trials, costs are ignored. But once a treatment goes into mainstream practice, cost is certainly looked at." - Lisa Vandenburg, Univ of WA

"Surgery, chemotherapy, and radiation are well entrenched. Y-90 is going to have to demonstrate a dramatic improvement to replace them, especially if Y-90 costs more to use." - Sandor Erdlyi, Nordion

"A single $1000 treatment cost would be very attractive, but if many treatments are required, $500 to $1000 is the range it has to be in" - Alan Carpenter, DuPont Pharma

"To be competitive with other treatments, our Y-90 radiochemical cost has to be around $100-$200 per treatment." - Becky Bottino, NeoRx.

"Based on what we see now, $1/mCi is the target price for Y-90 when it's commercialized" - Alan Fritzburg, NeoRx.

Isotope pricing

- Total kit will include Y-90 radiopharmaceutical, antibody, packaging.

- Radiochemical Portion Acceptable At 30% Of Total Kit Cost - $300

- Dosage and number of treatments important.

- Expert opinion divergent.
  - dosage:
    - 500 mCi - Alan Carpenter, DuPont
    - 200 mCi - Alan Fritzburg, NeoRx
    - 100-150mCi - Steve Glen, Coulter
    - 40-50mCi - Nina Kortylesezz, U of NE

  - number of treatments:

"If it doesn't cure after one treatment, it's not going to." - Steve Glen, Coulter

"Murine antibodies will only permit one treatment. If suitable MCA's are found, many treatments could be used" - Nina Kortyleysezz, Univ of NE

"Probably three treatments per patient per year" - Vern Alvarez, Cytogen

"I think multiple treatments will be used" - Alan Carpenter, DuPont

"Each patient will require a dose every two or three monnths." - Huibert Vriesendorp, MD Anderson Cancer Center

- At two treatments, 100mCi per treatment, use per patient will be 200mCi.
  - $300/200mCi = $1.50 per mCi

Effect of In-111

- Use of In-111 will add cost to treatment.
  - possibly double cost of treatment
  - may require lowering Y-90 isotope cost

"Imaging may be required by the FDA for approval, but it won't be a problem in actual use. If we have to use Indium it will mean another $1500-$2000 per treatment." - Bob McGuire, Cytogen

"The use of In-111 could double the cost of the treatment." - Nina Kortyleysezz, Univ of NE

Summary

- Hanford's price attractive
  - in Phase I, II trial quantities to facilities able to complete radiopharmaceutical processing and certification
- Hanford's offering not as attractive
  - to facilities unable/unwilling to complete pharmaceutical processing
  - as quantities increase at Phase III and beyond

- Competition, need for acceptance, use of In-111 all drive cost.

- $1/mCi is target range for commercialization for isotope only, not including the MAb, etc.

COMPETITIVE ISOTOPES

Isotope - I-131

Use - Only FDA approved radioisotope for therapy. Thyroid cancer, relief of pain from bone cancer.

On-going studies:

- Work being done at UW and Fred Hutch for for non-Hodgkins lymphoma, and leukemia.

- Coulter sponsoring trials at Univsities of Colorado, Washington, Michigan.

Issues:

- Considered non-user friendly.
- UW studies require lead lined room.
- Relationship between therapùtic effects of I-131 and antibodies not clear. (dosage insufficient for sterilization; not known why cancer cells die)

"The (treatment) expense is enormous. No one in the industry thinks it will ever be accepted even if the FDA does approve it." Becky Bottino, NeoRX

"I-131 has been around for years, too long really. It's cheap, it's convenient, but its probably never going to be used much more than it is now." Sandor Erdlyi, Nordion.

Competitive rank - 1

Isotope - Y-90 (microspheres)

Use: treatment of liver cancer.

On-going studies - Nordion plans to begin Phase III in Canada. No known US studies

Issues:

- Reports of patient deaths caused by leaching Y-90 in early trials. Said to now be solved.
- Nordion has exclusive worldwide rights for Theragenics microsphere technology.
- Y-90 microspheres approved only in Canada, and only for patients who have exhausted all other therapies.
- Nordion plans to enter US only after successful marketing in Canada and Europe. At least 5 to 10 years in future.

Competitive Rank - 2

Isotope - Sm-153 (Samarium)

- Use: relief of pain from bone cancer
- On-going studies - Cytogen nearing Phase III completion
- Competitive Rank - 3

Isotope - Sr-89

- Use:relief of pain from bone cancer
- On-going studies - reported to be nearing FDA approval, or already approved.
- Competive rank - 3

Isotope - P-32

- Use: treatment of ovarian cancer
- On-going studies - Research
- Competitive rank - 3

Isotope - I-125

- Use: prostate; slow growing tumors
- Number of on-going studies
- Competitive Rank - 3

Isotope - Palladium 103

- Use: fast growing tumors
- Number of on-going studies
- Competitive rank - 3

Other Isotopes

- Not seen as competitive to Y-90.
- Rhenium 186, bone cancer pain
- Strontium-90, bone cancer pain
- Lutetium-177
- Scandian-47
- Cu-67
- Tin-117
- Y-91

Y-90 STATUS AS OF 6/95

Hodgkin's lymphoma

- Trials - Phase I, II
- Sites/sponsors
  - MD Anderson
  - Coulter
  - Univ of CO trials discontinued. Unknown if will restart.

Non-Hodgkins lymphoma

- Trials - Phase I
- Sites/sponsors
  - IDEC
  - Univ of WA
  - Immunomedics
  - U Neb trials stopped until more money available
  - NIH start new Phase I in six months

Leukemia

- Trials - Phase I, II
- Sites/sponsors
  - NIH
  - Kettering

Small cell lung

- Trials - Phase I
- Sites/sponsors
  - NeoRx

Colorectal

- Trials - Phase I
- Sites/sponsors
  - Immunomedics
  - NIH
  - Univ of NE

Breast

- Trials - Phase I
- Sites/sponsors
  - Hope, Los Angeles

Prostate

- Trials - Phase I, II
- Sites/sponsors
  - Cooper Hospital
  - Stanford
  - Cytogen will complete Phase II; III doubtful

Ovarian

- Trials -.
- Sites/sponsors
  - Cytogen cancelled Phase I trials

Arthritis

- Trials - Phase I, II
- Sites/sponsors

  Shedoke McMaster, Ont, Canada - treatment for pain. Not known when or if will be completed.

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Y-90 SUPPLIERS

- Amersham
  - believes about 50 Ci per year being sold into research trials in US
  - Amersham share - 10 Ci
  - European portion not reported but believed small

- Nordion
  - capacity 500 Ci per year
  - 50 Ci per year shipped to research trials
  - US shipments 10-15 Ci per year
  - does not believe Europe is a significant part in current Y-90 marketplace

- DuPont Pharma
  - believes 50 Ci per year being sold into research trials in US
  - capacity 50-100 Ci per year
  - US portion 10-15 per year

- Hanford
  - US shipments 10 Ci per year

- Total US shipments reported as 40-50 ci/ year.

- Production capacity exceeds shipments for all suppliers.

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Y-90 USAGE PROJECTIONS

Dosage/treatments

- Small cell lung cancer and solid tumors - NeoRx, Nordion
  - uses proprietary "pre-targeting" technology to deliver large doses to tumor site
  - 200 mCi per dose
  - 2-3 treatments per patient

- Lymphoma, possibly leukemia and lung cancer - all others
  - 50 to 150 mCi per dose
  - 1 to 3 treatments per patient

Clinical trials

- Phase III can be 10X - 20X more expensive than Phase II; can be 2-3 times more lengthy.

- Phase III only done with corporate sponsorship.

- Corporations focus Phase III trials on one cancer at a time.
  - research vs commercial orientation
    - good research models not necessarily best commercial models

Forecast assumptions

- Phase I trials - 40 patients, 1 year
  - 10 patients/site; 4 sites
- Phase II trials - 140 patients, 2.5 years
  - 35 patients/site; 4 sites
- Phase III trials - 600 patients, 4 years
  - 150 patients/site; 4 sites
- FDA approval - 1 year after Phase III data
- Completion of Phase I and Phase II trials on all tumor sites.
- Only lymphoma going into Phase III and commercialization.
- Three sponsors follow lymphoma into Phase III trials.
- All cancers:
  - 100 mCi/dose
  - 2 doses/patient
  - $25/mCi - Phase I, II quantities
  - $10/mCi - Phase III quantities
  - $1.00/mCi - commercialization quantities

RESEARCH FORECAST*

Lymphoma,all types

	96	97	98	99	00	01	02	03	04
Cases/yr.	80	172	264	276	484	692	900	900	600
Ci/yr.	16	34	52	56	96	138	180	180	120
$/mCi	25	25	25	25	20	15	10	10	10

Small cell lung, colorectal, prostate, ovarian, breast, and brain cancers:

	96	97	98	99	00	01	02	03	04
Cases/yr.	240	276	276	276	---	---	---	---	---
Ci/yr.	48	54	54	54	---	---	---	---	---
$/mCi	25	25	25	25	---	---	---	---	---

Totals

	96	97	98	99	00	01	02	03	04
Cases/yr.	320	448	540	552	484	692	900	900	600
Ci/yr.	64	88	106	110	96	138	180	180	120
$/mCi	25	25	25	25	20	15	10	10	10
$M/yr.	1.6	2.2	2.7	2.8	1.9	2.1	1.8	1.8	1.2

If leukemia and small cell lung cancer carried through Phase II

	96	97	98	99	00	01	02	03	04
Total	1.8	2.6	3.0	3.2	2.8	4.2	3.6	3.6	2.4

* Trials on-going or planned

Commercialization Forecast

Scenario A

- Only lymphoma treated
- Y-90 becomes primary treatment, commencing with late stages.
- Full market penetration (90% of all new cases) takes 10 years

	Year									
	04	**05**	**06**	**07**	**08**	**09**	**10**	**11**	**12**	**13**
Cases/yr. (X000)	2.5	5.0	10	15	20	25	30	35	40	45
Ci/yr. (X000)	0.5	1	2	3	4	5	6	7	8	9
$M/yr.	0.5	1	2	3	4	5	6	7	8	9

Scenario B

- If leukemia & small cell lung cancer reach commercialization:

	04	**05**	**06**	**07**	**08**	**09**	**10**	**11**	**12**	**13**
$M/yr.	1.2	2.3	4.6	6.9	9.2	12	14	16	18	21

Note: Radiochemical grade Y-90 differs from radiopharmaceutical grade Y-90 by the need for testing for sterility and endotoxins. The pricing shown in the research and commercial forecasts reflects Hanford's radiochemical price.

R&D Companies

- View themselves as the developer and maker of the targeting agent (MCA).

- All plan to partner with manufacturing and/or marketing companies to take product into healthcare.

CUSTOMER PROFILES

CYTOGEN

- Number of employees: 130

- Profitability: Start-up, loss operation

- Stability
  - Stock has shown poor performance overall.
  - FDA approved OncoScint diagnostic imaging product for ovarian and prostate cancers has had slow market acceptance.

    "OncoScint is dead. Surgeons and oncologists found it didn't do anything more than what they already had." Kim Kiyma, Syncor

  - Company has had layoffs to restructure and conserve capital.

- Product focus
  - Y-90 part of company's new effort to expand its market presence into therapeutic rather than only diagnostic.
  - Y-90 has not lived up to expectation and may be dropped.

Status of Y-90 trials:

- Phase I human trials
  - have seen little success with solid tumors.
  - ovarian trials have been cancelled.
  - finishing Phase II prostate. Likely will not continue.
  - Future Y-90 trials, if any, will concentrate on lymphoma, possibly leukemia.

- Strategy

  - Originally to develop and commercialize diagnostic products for ovarian, colorectal, and prostate cancer.

  - New plan is to acquire nuclear oncology products that have highest sales potential and are nearest to commercialization.

  - In 1993 acquired from Dow Chemical Co. exclusive US license for Samarium (Sm-153) - radiopharmaceutical for treatment and alleviation of pain from bone cancer.
    - Second Phase III trial nearing completion.
    - Has signed letter of intent with DuPont to manufacture and market Samarium..

  - Cytogen will remain R&D company in nuclear oncology. Plans to be the maker of the MCA targeting agent. Use partners for manufacturing and marketing.

IMMUNOMEDICS

- Number of employees: 80

- Profitability: Start up, loss operation

- Product focus:
  - Primarily in cancer imaging agents
    - ImmuRAID-CEA - colorectal: nearing completion of Phase III trials. FDA and international approval dates unknown.
    - ImmuRAID-LL2 - lymphoma
    - ImmuRAID-AFP - liver
  - Cancer therapy agents
    - ImmuRAIT-LL2 - lymphoma
    - ImmuRAIT-CEA - colorectal

- Immunomedics supplies MCA. End user combines the isotope (Technetium-99) with MCA.

- Te-99 supplied by other source - Dupont, Nordion, Amersham.

- Interest in Y-90 comes from speculation and need to be involved if other clinical trials prove successful.
  - Y-90 being compared to I-131 and rhenium-188 for suitability for colorectal, breast, and lung cancer.

- Status of Y-90 trials:
  - Early Phase I trials

- Strategy:
  - Conserve cash, priority on getting approval for colorectal imaging agent.
    - MCA imaging kits primary product line.
    - Conduct and/or monitor large number of Phase I trials watching for additional opportunities in cancer imaging or therapy using various promising isotopes.
    - Rely on others for radiopharmaceutical manufacturing and marketing.

- Number of employees: 80

- Profitability: start up: loss operation

- Stability : unknown, but looking to "deep pockets" partner (DuPont) to help finance continued development of their product.

- Product focus:
    - Primary - OncoTrac - lung cancer imaging kit.
    - Secondary
        - Avicidin - lung cancer therapy
        - Biostent - cardiology

- Status of Y-90 trials
    - 30 patients in Phase I - trials at Virginia Mason and Stanford.
    - Expects to start Phase II in 3-6 months.
        - trials for small cell lung cancer.
    - Other patients looked at. Possible that NeoRx may shift or expand focus in next several months to other cancers:
        - breast, colon, ovarian.

- Strategy
  - When Phase III trials begin, NeoRx would like to see Y-90 transferred to a private company at Hanford for completion as a radiopharmaceutical
  - Commercial success through manufacturing and marketing partnerships for NeoRx developed cancer imaging and therapy products.
    - Boehringer-Ingelheim - worldwide manufacturing and marketing Oncotrac imaging outside US
    - DuPont - marketing rights for Technetium-99
  - Get OncoTrac FDA approved to provide income.
  - Continue to pursue corporate partnerships for manufacturing, marketing, and financing product development.
  - Concentrate on developing "pretargeting" method of radioisotope delivery. Believe this will give them access to solid tumor therapy via large Y-90 doses.

- Issues
  - Has found Hanford difficult to deal with in developing joint agreements.
  - Believes Y-90 interesting but no sense of urgency in industry. "People have waited too long for MCA and isotope therapy to bear fruit. These are no longer hot areas. People are jaded. MCA and isotopes will have to prove themselves." Alan Fritzburg, MD, NeoRx

COLTURE PHARMACEUTICAL

- Number of employees - 3000

- Stability - Considered major supplier and a standard in its industry.
  - diagnostic kits and supplies

- Product focus:
  - primary effort of I-131, planning Phase III trials.
  - Y-90 secondary; backup and informational only

- Status of Y-90 trials
  - Phase I trials, lymphoma
  - not known if trials will continue.

- Strategy
  - Set up small R&D group to work with radioisotopes
  - Develop targeting agents that can be sold as kits to combine with radioisotopes for cancer therapy.
  - Combine with partnerships for manufacturing and marketing of the kits/radioisotopes.
  - Concentrate on I-131 for lymphoma first
  - Possible secondary efforts
    - I-131 - breast cancer
    - Y-90 - lymphoma, breast cancer

IDEC

- Number of employees - 160
- Stability - Competitors report unstable.
- Product focus - Antibody kits for cancer diagnostics and therapy
- Status of Y-90 trials - Phase I trials underway for non-Hodgkins lymphoma. Trials on-going for 4.5 years, expect at least another 4-5 before completion. Y-90 is only isotope they are involved with.
- Strategy - Plan to supply antibody kits. Expect hospital to obtain Y-90 from separate source and combine themselves. Except for research, IDEC will not purchase Y-90 themselves.

Y-90 SUPPLIERS

Nordion

- Have purchased rights to microsphere technology from Theragenics.
- Completing trials with microspheres.
- Decision to continue with Y-90 not yet made.
- Possible they will drop program.
- Plan no activity in US until success seen in Europe.
- Do not consider Y-90 to have a significant role in cancer therapy.
- Weak partner for Hanford

Amersham

- Has initiated discussion with Hanford
- Interest in Y-90
- Has own sources of Y-90
  - claims production facilities
- Views Y-90 technology as difficult
  - interested in Hanford technical expertise
- Has strong presence in US
- Good potential partner for Hanford

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Dupont Pharma

- Strong interest in Y-90
- Combined with Merck to provide major pharmaceutical presence in US
- Has made significant investment in automated radiopharmaceutical production facility
- Views Hanford as source of Y-90 and expertise
- Strong partner for Hanford

Syncor

- Number of employees - 3000
- Profitability - gross profit of $66m on sales of $320m for 1994
- Product - radiopharmaceutical distribution; packaging patient specific dosages as ordered by customer.
- Markets - hospital and clinic based nuclear medicine departments
- Key accounts - numerous accounts making up 65%-70% of radiopharmaceutical business in the us
- Direction - remain dominant in radiopharmaceutical distribution. Possible expansion of "compounding" business - purchasing radiochemical directly from isotope supplier and producing radiopharmaceutical under direction of pharmaceutical company.
- Apparent strategy - wait and see on results of commercialization of Y-90. If commercialized will distribute for radiopharmaceutical company and/or deal directly with Hanford as a compounder.
- Issues - Syncor has 117 local sites across the US. Most accounts are within 2 hours shipping time of Syncor. Problem is not one of half-life, but one of regulation. Must comply with all state and federal regulations regarding handling and shipping of radioisotopes.

DRIVERS/BARRIERS/RISKS

Drivers

- Cancer reputation/prognosis - Because cancer such a devastating disease, Y-90 will be accepted if possible.

- Efficacy - Cures very rare in most cancers. Y-90 cures will generate unusually high interest in medical community.

- Insurance - Cures reported in lymphoma. Reduces cost of otherwise lengthy treatment. Will enhance reimbursement.

- New billable procedure - Will add to health care giver income stream, particularly if used as adjunct to existing therapies.

- Cost - lack of side effects and small number of treatments required will encourage use as an out-patient procedure.
  - hospitalization 65% of cancer treatment cost; out-patient procedure very positive impact on cost reduction.
  - Y-90 very attractive; use and acceptance encouraged.

- Chemotherapy/radiation already treatments of choice for lymphoma.
  - Y-90 will be readily understood.
  - reduces physician education.

- Sponsors
  - Five companies dedicated to developing therapeutic radioisotopes; working with Y-90.
  - Suppliers, manufacturers, marketers, and distributors exist now for radioisotopes; Y-90 will fit within current infrastructure.

Barriers

- Commercialization - key barrier; reason so little development actually takes place in radioisotopes.

- Cost of drug development is independent of market need.

- Phase III trials require corporate sponsorship because of time and cost. Cytogen, Immunomedics, NeoRx, Colture, IDEC all small, can only pursue one cancer at a time. Slows commercialization.

- Wait and see attitude - Y-90 not as promising as once thought. Now seen by many as incremental improvement in cancer treatment.
  - "Y-90 doesn't show the promise it once did. It will never be a big seller." - Rod Huggins, Nordion
  - "Except possibly for lymphoma and leukemia, it's unlikely that Y-90 will be a primary treatment." - Robert Sharkey, Immunomedics
  - "Radiopharmaceuticals is a small market. Less than 10 new products have been approved by the FDA in the last 6 or 7 years. Almost all are for diagnosis." Kim Kiyma, Syncor
  - "Radiotherapy has been unsatisfactory overall. Many trials have been conducted with little result. The main problem is toxicity." - Becky Bottino, NeoRx

- FDA
  - Y-90 approval exacerbated by
    - No Phase III trials yet started.
    - backlog in FDA approval bureaucracy.
    - little or no precedent for therapeutic radioisotopes.
    - "FDA doesn't even know how to spell radiation, much less know what to do with it." - Diana Renton, Theragenics Corporation.
    - "It received a bad reputation because of unwise use a few years ago. Now the FDA is approaching Y-90 very carefully in MCA cancer trials. -Dr. Van der Heiden, Mallinckrodt.

- Lack of Y-90 imaging ability.
  - May require use of In111 in conjunction with Y-90.
  - Impact on trials, approvals, not known.
  - If required will certainly increase cost, perhaps by as much as $1500-$2000 per treatment.

- Reimbursement - essential - will depend on cost, efficacy, luminary endorsement.
  - insurance companies will welcome a "cure", will look less favorably on a treatment that only increases cost of patient's dying.

- Price
  - must be in the $1/mCi range.

- Reliability of supply
  - Is not a problem in research phase.
  - Essential for commercialization.

- Liability, risks, accidents, disposal, safety, training
  - Not viewed as a problem by R&D companies.
  - Existing distributors, suppliers, manufacturers feel all issues manageable.

Risks

- Two different schools of thought; large difference in potential market.
  - lymphoma - 53,000 new cases/yr
  - solid tumors - 610,000 new cases/yr

- Lack of imaging ability means that Y-90 may have to be used in conjunction with Indium 111 -

  - " Indium is priced at $400/dose. That's considered very expensive. Y-90 can't be more expensive than Indium 111." Amy Factor, Immunomedics.

  - "Indium 111 may be required by the FDA for approval, but it won't be a problem in actual use. If it is required it will mean another $1500 to $2000 per treatment". Bob McGuire, MD, Cytogen Corporation.

- Political climate - Y-90 getting a lot of press. This may help drive early trials, but will have little positive impact on commercialization. It could have a negative impact if anything goes wrong.

HANFORD POSITION

Positives

- Expertise
  - Hanford viewed as eminent in technical knowledge concerning production of isotopes
  - Amersham and DuPont both desire collaboration on technical matters.

- Production capability
  - no concerns over Hanford's ability to supply Y-90 in production quantities

- Focus
  - Hanford dedicated to Y-90 product
  - Nordion's commitment uncertain
  - Amersham, DuPont view Y-90 as one of several product possibilities.

- Price
  - Hanford has best pricing on $/mCi basis*
    - Hanford $15-$50
    - Nordion $50-$70
    - DuPont $75
    - Amersham $80

* other suppliers' prices are for radiopharmaceuticals

- Quality
  - Hanford regarded as having highest purity of Y-90
  - Both Nordion and DuPont have lost accounts due to quality problems

- Form
  - hydrochloric acid solution supplied by Hanford desirable

- Customer service
  - Hanford has excellent record on timely shipments
  - technical information supplied with shipments superior

- Recognition
  - Hanford widely known as Y-90 supplier
  - Hanford presently supplying approximately 20% of medical grade Y-90
- Hanford has opportunity to increase sales to Phase I and II trial sites.
  - with existing radiochemical offering
  - radiochemical market will decline as trials move towards Phase III

Negatives

- Concentration
  - high concentration of Hanford's Y-90 reported to create difficulty in precise dilution for medical applications
  - Amersham's 50 mCi/milliliter easier to use than Hanford's 2000 mCi/milliliter

- Sterility
  - Hanford does not test for sterility and endotoxins; creates additional work for researchers
  - Amersham and Nordion both do these tests for customers

- Shipment quantities
  - researchers need small quantities - 5 to 50 mCi
  - Amersham supplies in 20 mCi increments
  - Nordion supplies per customer request anywhere from 5 to 50 mCi
  - Hanford regarded as inflexible in this; creates difficulty and waste for researchers

- Shipment schedule
  - shipments of more than one day per week added convenience for customers but not essential

- Organization
  - perception that "government" is generically hard to deal with
    - organization chart confusing
    - beaurocracy cumbersome
    - uncertainty over stability of supply
  - privatization regarded as essential

- Marketing skills
  - Hanford not accustomed to pro-active selling
  - In response to telephone interview - "Always before I have had to call (Hanford) and place my order. You are the first one to ever call me. I am very happy to hear from you." - Fu-min Su, NeoRx

V. CONCLUSIONS

Market Segment

- Medical grade radioisotope

Applications

- Research - solid tumors, leukemia, lymphoma, small cell lung cancer

- Commercial
  - lymphoma - primary focus
  - leukemia, small cell lung cancer - secondary focus
  - solid tumors - highly unlikely to go to commercialization

Customer needs

- Packaging in 5, 10, 20, 50 mCi quantities
- Hydrochloric acid solution
- Lower concentrations - 50mCi/milliliter desired
- Testing for sterility, endotoxins performed by supplier
- Existing Hanford Y-90 purity, shipment reliability and technical support maintained
- Increasing shipments from one to two days per week desirable but not essential
- Essential to select supplier prior to start of trials; cannot introduce new supplier during trials
- Research pricing of $25/mCi very attractive.Could be increased if Hanford meets sterility/endotoxin requirement and offers more flexible packaging and concentrations
    - Hanford has opportunity to increase sales to Phase I and Phase II trial sites
        - with existing radiochemical offering
    - Radiochemical market will decline as trials move into Phase III and beyond
- Commercial pricing of $1/mCi very attractive
    - will encourage reimbursement and mainstream usage
    - possible to increase if Y-90 proves superior treatment
        - reduces overall cost of treatment
        - one-dose treatments

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Competitors

- Suppliers
  - Amersham, Nordion, DuPont

- Isotopes
  - I-131
    - Coulter and Alpha Therapeutics planning to start Phase III trials for lymphoma
    - most likely competitor for Y-90, but weak overall
    - regarded as difficult to use because of toxicity
    - considered to have little commercial appeal because of no apparent advantages in improved efficacy or reduced treatment cost.

- Y-90 microspheres and arithritis treatments limited to Canadian trials. No completion dates or FDA trials scheduled.

- All other isotopes viewed as research, investigational only. None considered serious competitors for Y-90.

- Technologies/treatments
  - surgery, external beam radiation well entrenched, successful in solid tumors. Y-90 must show dramatic benefit to make inroads
  - chemotherapy uses over 50 approved drugs, many inexpensive and suitable for out-patients.

- Y-90 will have difficulty replacing unless a clear benefit.

- Resources
  - Y-90 must compete for development funding against drugs and treatments that may have potential for much larger patient population

Health of Industry

- Overall weak
- Suppliers
  - all large
  - are not dependent on Y-90 for success
  - small venture funded R&D companies take early development risks.
- Nordion may leave Y-90 market
- Amersham, DuPont looking to various partnership possibilities
  - to spread technical risk
  - obtain backup Y-90 production
  - have assistance with marketing and distribution
- Demand side
  - Coulter Pharmaceutical well funded division of large well established medical laboratory supply company, but pursuing possible dead end with I-131.
  - IDEC and Per Immune (Organon Teknika) supply antibody kits for cancer therapy; view Y-90 as means to enhance kit market, but not dependent on it.
  - Cytogen, Immunomedics, NeoRx, all small, startup companies operating at a loss, very dependent on success of Y-90

Strategic partners

- Partnership with DuPont Pharma
  - Y-90 important to DuPont
    - Forecasting on order of 50K Ci/year when commercialized.
  - DuPont has made significant investment in new automated radiopharmaceutical manufacturing facility.
  - Experienced in pharmaceutical development, manufacturing, regulatory, and marketing issues.
  - Needs Hanford's expertise in radiochemical technical issues.
    - Many customer complaints regarding DuPont's quality; Hanford's considered excellent.
  - DuPont wants to work with Hanford
    - sign confidentiality agreement
    - visit DuPont in August or September for tour and dicussion on partnering.
    - sees Hanford as supplier of raw material, DuPont does finishing as radiopharmaceutical.
- Amersham Medi-Physics - Consider if deal with DuPont not satisfactory
  - values Hanford's technical expertise.
  - would rather purchase Y-90 than make.
  - see Hanford as supplier of raw material; Amersham provide pharmaceutical processing.
  - has already initiated contacts with Hanford.
- Nordion - Weak partner
  - wavering on commitment to Y-90.
  - focus is on Y-90 microsphere method.
  - plans to introduce in Europe before US.
- Syncor
  - focus is filling prescriptions. Weak in pharmaceutical manufacturing and marketing.

Market Size - Research Phase

- 45 Ci per year being supplied to US market currently.

- Approximately 64 Ci per year required for research trials on-going or planned for near term.
  - Hanford presently supplying approximately 20% of 1995 needs for research/clinical trials.
  - Amersham, Nordion, DuPont have remaining 80% of market.

- As Phase III trials peak around years 2002-2003, market increases to:
  - 180 Ci/yr - lymphoma only
  - 360 Ci/yr - lymphoma, small cell lung cancer, and leukemia

- Dollar markets for these two scenarios, respectfully:
  - $1.8M
  - $3.6M
  - as prices decline with volume

Market Size - Commercialization Phase

- Commercialization of Y-90 can produce US demand by 2014 of:
  - 9000 Ci annually for treatment of lymphoma
  - 21,000 Ci annually for treatment of lymphoma, small cell lung, cancer and leukemia.

- A range of $9M to $21M at $1/mCi

Market drivers, barriers, risks

- Drivers
  - commercialization
    - upside opportunity for radiopharmaceutical company to sell a $1000 treatment kit into a 50,000 to 120,000 patient annual market
    - $50M to $120M annual sales

- Barriers
  - $150M development cost
  - daunting FDA hurdles
  - need for reimbursement
  - long term physician education to gain widespread use of new technology

- Risks
  - no Phase III trials have been conducted
    - efficacy of Y-90 when compared to other treatments unknown
  - few Phase I and II trials completed
  - risks vary with cancer
    - lymphoma - low risk
    - leukemia and small cell lung cancer - moderate risk
    - solid tumors - high risk
  - possibility that In-111 may be required as an imaging agent
    - experts disagree
    - need for In-111 would increase cost of treatment and reduce market penetration
    - commercialization measured in decades
    - no means to forecast changes in FDA requirements, reimbursement issues, health care reform, or unforeseen impact of other medical advancements.

- Overall best opportunities
  - lymphoma therapy
  - partnership as supplier of Y-90 radiochemical to DuPont Pharma

VI RECOMMENDATIONS

Short Term: 1995-1998

- Maximize penetration of planned Phase I and Phase II trials:
  - with existing offering

Mid Term - 1998-2003

- Partner with radiopharmaceutical firm and achieve higher penetration at Phase III trials
  - partner becomes customer for Hanford's radiochemicals
    - candidate's preferred option
  - partner functions as the operator of the Hanford radioisotope site and as the radiopharmaceutical processor for Hanford's radiochemicals
    - candidate's less preferred option, but still viable

Recommended Actions

1. Maintain Hanford's existing offering.
   - pricing - $25/mCi for radiochemical
   - technical follow-up
     - data sent with each shipment
     - notification of any discrepancies or anticipated anomalies
   - shipment reliability
     - on-time delivery against schedule
   - customer service
     - prompt response to requests for shipment and information
2. Improve offering by meeting customer needs on:
   - offering less concentrated solutions
     - 50 mCi/ml preferred
   - doses in 5,10,20 and 50 mCi quantities

3. Increase marketing effort by proactive sales approach.
   - maintain close customer contact with existing accounts to assure Hanford as supplier on upcoming trials
     - minimum of monthly phone contact; increase as trials approach
     - investigate slowing or loss of orders to determine any corrective effort required by Hanford.

- Contact customer accounts
  - develop forecast for upcoming Y-90 trials
  - convert customers about to start new trials who can process Hanford's Y-90 radiochemicals.
  - Start by contacting:

    - Cytogen
      Princeton,NJ
      Bob McGuire, MD
      (609) 987-8200
      Suppliers: Amersham, Nordion

    - Immunomedics
      Morris Plains, NJ
      Gary Griffits, MD
      (201) 605-1330 ext 235
      Supplier: Hanford

    - NeoRx
      Seattle, WA
      Fu-min Su, PhD
      (206) 281-7001
      Supplier: DuPont

    - Coulter Corporation
      Miami, FL
      Steve Glen, MD
      (305) 380-2570
      Supplier: Amersham

- IDEC
  San Diego, CA
  Paul Chinn, PhD
  (619) 550-8536
  Supplier: Amersham, Nordion

- NIH
  Bethesda, MD
  Mark Rotman
  (301) 496-5675
  Supplier: DuPont, Hanford

- Burroughs Welcome
  Raleigh, NC
  John Hohneker
  (919) 315-8196
  Supplier: not yet chosen

- Per Immune (Organon Teknika)
  Rockville, MD
  Manny Subramanian
  (301) 258-5200
  Supplier: Amersam, Nordion, DuPont

- Alpha Therapeutics
  Los Angeles, CA
  John Walen, MD
  (213) 225-2221
  Supplier: Amersham

- Existing university based trial sites

- Establish contact with medical community through attendance at conferences sponsored by:

  American College of Radiology

  American Society of Therapeutic Radiologists

  American Board of Nuclear Medicine

  Society of Nuclear Medicine

  American Society of Clinical Oncology

  National Foundation of Cancer Research

4. Begin negotiations for privatization of Y-90 through contact at

   DuPont
   Alan Carpenter
   Director of Business Development
   (800) 362-2668 ext 8397

   Amersham
   Karen Stec
   Director of Business Development
   (800) 322-6334 ext 274

5. Pursue two options:

   - Partner is customer for radiochemical
   - Partner takes over Hanford's radiochemical production as well as completion of processing for radiopharmaceutical

6. Qualify partner for ability to commercialize the Y-90 radiopharmaceutical
    - sponsor trials
    - produce or have source of antibodies suitable for targeting lymphoma, small cell lung cancer, and leukemia
    - have experience and facilities suitable for manufacturing and packaging radiopharmaceuticals
    - influence luminaries and medical professional organizations
    - understand regulatory issues and facilitate approval by the FDA
    - establish reimbursement
    - conduct physician education
    - have distribution channels suitable for radiopharmaceutical products
    - have successful radiopharmaceutical marketing and sales organization
7. Maintain partnership through Phase III trials and commercialization efforts of Y-90 cancer therapies.

VII APPENDIX

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ISOTOPE SUPPLIER - PROFILE

Company: Amersham Corporation

Location: Arlington Heights, IL

Affilation/Ownership: Owned by Amersham International plc, Little Chalfont, Buckinghamshire, England

Key Contacts (name/title): Dr. Michael Langton, Technical Manager, Oncology; Dr. Richard Icholv, New Business Development Manager

Products: Isotopes

Markets:

- Industrial (supplied by Amersham Corporation)
- Medical (supplied by Medi+Physics)

Revenues:

- Sales in North America $240 M during the period April 1993 - March 1994 represent 47% of the total corporate sales. Corporate sales were up 20% from the previous year.
  - Industrial sector 15%
  - Health Care sector 37%
  - Life Science sector 46%

- Worldwide operating profit $68 M in 1994, up 72% from previous year, representing a combination of real profit growth and a 20.9 million dollar benefit from foreign exchange movements. Europe is still the strongest source of profits.

Facilities:

- Russian sources, British, German and French sources. Russia has been now for some time Amersham's major supplier of raw material isotopes.

Apparent Strategies:

- Focus on Life Science and Health Care sectors (represent 83% of sales)
  - Life Science is the largest and most profitable
  - Life Science business is a biotool business for genetic engineers and cell biologists
  - Acquisition of United States Biochemical Corporation in 1993, a major supplier of biochemicals and reagents

- Expand beyond nuclear medicine through innovative achievements in biotechnology: "We believe that the future lies increasingly with non-radioactive techniques, such as fluorescent labelling" *

- Extend presence in US via diagnostics and pain palliation business
  - 80% of Amersham's sales in the health care sector from diagnostics
  - Opened a new market in pain palliation with a Sr-89-based drug approved by FDA in June 1994 - importance of diagnostics may well be declining
    - Metastron

* Amersham Annual Report

- Acquisition of Medi+Physics in 1991 doubled Amersham's business in North America and provided access to the distribution channel. Amersham's three major branded radiopharmaceutical products launched since 1987 have benefitted from the network

- Shifting away from the role of a pure raw material supplier by incorporating design and management services, therefore gaining control over the procurement decisions

- Diversify beyond industrial isotope business into associated services
  - Gamma radiography inspection services - with new opportunities for expansion into non-radioactive, non-destructive testing
  - accuracy testing of radioactive measuring and detection equipment
  - environmental services

- Secure sources of isotopes by setting up strategic long-term partnerships with international suppliers
  - Harwell supplied Amersham through 1991, at favorable prices
  - joint venture with Russian Ministry of Atomic Energy
  - 15% stake in Nordion

Strengths/Weaknesses:

- An international company with strong position in the U.S. through the acquisitions of USB and Medi+Physics. FDA approved radiopharmaceutical products.
- Unpredictability related to the future stability of the main isotope source (Russia).

JOYCE
& ASSOCIATES

ISOTOPE SUPPLIER - PROFILE

Company: DuPont Corporation

Location: North Billerica, MA

Affilation/Ownership: Public company

Key Contacts (name/title):
Dr. Carmen Marchetti
Medical Products Department

Products: radiopharmaceuticals

Markets:
- Diagnostic imaging

- Together with Amersham and Mallinckrodt, DuPont Pharma controls 90% of the market for medical isotopes

Facilities:
- Y-90 produced in Wilmington, Delaware
- Present production capacity for Y-90 is 1-2 Ci/week

Apparent Strategies:

- Provide the client with a ready made medical product by controlling each step from the manufacture of cyclotron-based radioisotopes to the integration with pharmaceutical components and delivery of a ready-to-use product to customer

Strengths/Weaknesses:

- Domestic source of radioisotopes
- Control over the entire marketing channel

Key Issues:

- Interested in additional Y-90 production capacity on the West Coast.

- DuPont Pharma is responsible for the marketing of medical radioisotopes. Dupont Pharma is a joint venture between DuPont and Merck and it is not a public company

- DuPont gave up its share in NeoRx, but has still the marketing right for the Technetium-99-based imaging products developed by NeoRx