97-2 Planning Report

Economic Evaluation of Radiopharmaceutical Research at NIST

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Economic Evaluation of Radiopharmaceutical Research at NIST

I. Introduction

Nuclear medicine is the branch of medicine that relies on radiation emitting substances, called radioisotopes or radionuclides, for the diagnosis or treatment of a disease or condition. The field of nuclear medical and biological research can be traced to the 1895 discovery by Wilhelm Conrad Roentgen of a ray that could penetrate the human body and display bone structures.[1] Soon thereafter, in 1896, Henri Becquerel demonstrated that uranium in its normal state gave off X-rays. Following these two path-breaking discoveries came the radioactivity discoveries by Marie Curie in 1897. Then, in 1925, Herrman Blumgart and Otto Yens used radioactive substances in human patients for the first time. In 1936, John H. Lawrence and Joseph Gilbert independently undertook the first therapeutic clinical applications of a radioactive substance to treat leukemia.

The use of radiochemicals or radiopharmaceuticals increased slowly during the pre-war period and then more rapidly in the decades following World War II. Finally, in the early 1970s, radiopharmaceutical manufacturers realized the importance of calibrations for the short-lived radionuclides being used in nuclear medicine. According to Golas [1996], in the early 1970s Standard Reference Materials (SRMs) were available in unsuitable physical forms and activity levels. Also, there were no standard methods for measuring the activity of a radionuclide, even ignoring the imprecise decay information that was available. As a result, no method existed for a pharmacy to assure the accuracy of the radiation in a prescribed dose.

In the early 1970s, there was not an established research program on radiopharmaceutical measurement at NIST [then the National Bureau of Standards (NBS)], or at any other federal facility. In 1972 the Atomic Industrial Forum (AIF) responded to industry needs and appointed a subcommittee of Manufacturers of Radioactive Reference Standards, with the objective of "… obtaining a high degree of consistency and reliability in commercially available radioactive reference standards and their accompanying Certificates of Calibrations" [Seidel and Hutchinson, 1976 (p. 1)].[2] The NBS was represented on this committee, as were all major commercial manufacturers of radiochemicals.

In 1973, following the formation of this subcommittee, a symposium was held at NBS to address the concerns of radionuclide manufacturers regarding the proposed standards. Speakers at the symposium emphasized the need for such standards, citing:

1. the lack of standards for about 75 percent of the more than 100 radionuclides then produced by industry;

[1] This information draws directly from Society of Nuclear Medicine [1996a].

[2] This committee became subcommittee N42.2 of the American National Standards Institute (ANSI).

2. the unusable physical form and activity levels of the few standards that were available; and,

3. the failure to have industry-wide adopted decay-scheme data upon which to base derived standard instrument calibrations.

It was also noted at the symposium that the lack of standards was an obstacle to both the assurance of accuracy in the administration of radioisotopes, and to the approval of new drugs by the federal Food and Drug Administration (FDA).

In response to industry-wide concerns expressed at this symposium, NBS entered into a cooperative research agreement[3] with the Atomic Industrial Forum (AIF) [now the Nuclear Energy Institute (NEI)]. "… whereby NBS will supervise and administer on behalf of AIF a measurements technology quality assurance program which caters more specifically to the needs of the radiopharmaceutical industry" [Collé, 1976 (p. 71)].[4] The NBS also entered into an interagency agreement with the FDA to "ensure the continuous availability of national radioactivity standards at appropriate levels of activity for use by the radiopharmaceutical industry, and thus to establish a degree of uniformity in the measurements throughout the industry" [Collé, 1976 (p. 71)].

Today, radiopharmaceutical Standard Reference Materials are produced within the Radioactivity Group of the Ionizing Radiation Division of the Physics Laboratory at NIST through a CRADA with NEI, and sold to the members of the NEI/NIST Radioactivity Measurement Assurance Program (MAP) and to the public. The purpose of this report is to document and quantify selected broad-based economic impacts associated with this program's research activities.

The report is outlined as follows. In Section II, the research activities of the Radioactivity Group are discussed in detail. In Section III, a conceptual framework for evaluating the economic effects of radiopharmaceutical research at NIST is described and evaluated. In Section IV, the findings from the economic evaluation are interpreted. Finally, concluding remarks are offered in Section V.

[3] Such agreements are now known as Cooperative Research and Development Agreements or CRADAs.

[4] Today, this program is known as the NEI/NIST Radioactivity Measurements Assurance Program.

II. Radiopharmaceutical Research at NIST

A. Incidence of Radiation Treatment

In 1996, over 3,900 hospital-based nuclear medicine departments in the United States performed over 10 million nuclear procedures; about 90 percent of these procedures were diagnostic and about 10 percent were therapeutic.[5] The number of such procedures has increased from 7.7 million just a decade ago. Experts expect these numbers to increase between 5 percent and 10 percent per year over the next 5 years.[6] Patients undergoing a nuclear medical exam receive a prescribed dosage of a radiopharmaceutical. These radiopharmaceuticals produce radioactive emissions specifically formulated to be collected temporarily in the organ being examined. Gamma cameras and PET scanners are used to detect and transfer these emissions to film or to a computer image for study.[7]

Data from the Health Physics Society [1996] show that in 1987, 26 percent of the 7,690,000 diagnostic tests conducted in the United States were bone studies, 18 percent were heart studies, and 17 percent were lung studies.[8]

If a patient receives too little radiation the procedure will often have to be redone, particularly for a therapeutic procedure. If the patient receives too much radiation, injury or death could result. In either case, there is an economic cost to imprecise measurement. It is therefore incumbent upon the nuclear pharmacist to deliver as close to the prescribed dosage as measurably possible, that is to ensure that the patient receives *x* amount of radiation, where *x* is measured in terms of number of atoms of the radioactive substance decaying per unit of time.

B. Research Mission of the Radioactivity Group

The Ionizing Radiation Division, one of six divisions in the Physics Laboratory at NIST, provides national leadership in:[9]

> "… fundamental research and measurement standards for all types of ionizing radiation, including X-rays, gamma rays, electrons, neutrons, energetic heavy charged particles, and radioactivity. The Division's

[5] Health Physics Society [1996]. See also, Institute of Medicine [1995].

[6] This forecast was provided by experts within the Radioactivity Group at NIST. See also Institute of Medicine [1995].

[7] Society of Nuclear Medicine [1996b].

[8] These are the most recent study-specific data available.

[9] Physics Laboratory [1996].

> extensive domestic and international collaborations in applied research help to make ionizing radiation effective in industrial and health applications and safe in the environment and the workplace.

The Radioactivity Group is one of three research groups within the Division. Its mission is to develop and maintain U.S. radioactivity standards and to confirm the standards internationally; to perform research on radioactivity decay scheme characteristics; to develop and apply radioactivity measurement techniques; and to disseminate results using standard reference materials, calibrations and testing services, and cooperative industrial measurement traceability programs.

This mission complements NIST's overall responsibilities. The NBS was established in the Treasury Department under the Organic Act of March 3, 1901:

> *Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,* That the Office of Standard Weights and Measures shall hereafter be known as the National Bureau of Standards … That the functions of the bureau shall consist in … the determination of physical constants and the properties of materials, when such data are of great importance to scientific or manufacturing interests and are not to be obtained of sufficient accuracy elsewhere.

The NBS was transferred to the Department of Commerce and Labor in 1903 and to the Department of Commerce in 1913.[10] All responsibilities were transferred to NIST when NBS was re-named under the Omnibus Trade and Competitiveness Act of 1988. As described in the United States Code, Title 15, Chapter 7:

> [The] National Institute of Standards and Technology [shall] enhance the competitiveness of American industry while maintaining its traditional function as lead national laboratory for providing the measurement, calibrations, and quality assurance techniques which underpin United States commerce, technological progress, improved product reliability and manufacturing processes, and public safety … [and it shall] prepare, certify, and sell standard reference materials for use in ensuring the accuracy of chemical analyses and measurements of physical and other properties of materials.

[10] Between 1903 and 1934 it was called the Bureau of Standards.

C. Research Activities of the Radioactivity Group[11]

To date, NIST has produced the 28 radiopharmaceutical standards listed in Table 1.[12] Also shown in Table 1 is the primary diagnostic use of each of the radionuclides.

A radiopharmaceutical standard produced at NIST is typically accurate to within ±1% at the one standard deviation level; that is all standards produced at NIST are calibrated within ±1% of the actual decay rate of the substance. Or stated alternatively, NIST's calibration error on these SRMs is ±1%. These calibrated SRMs are provided to the radiopharmaceutical manufacturing companies that belong to the NEI/NIST MAP for an approximate fee of $600.00 per vial.[13,14] The current members of the assurance program are listed in Table 2.

Not all radiopharmaceutical manufacturers are members of the MAP. Non-member companies can obtain standards from commercial laboratories for a similar fee; however, the standards produced and sold by commercial laboratories are less accurate than those produced at NIST. On average, commercial laboratories are within ±5% of the actual decay rate of the substance, but these laboratories are traceable to NIST.[15]

Ten SRMs are produced at NIST each year, one each month following a schedule agreed upon by MAP members. The months of May and November are so-called "open months." During these two months, members of the MAP can submit their own samples to NIST for calibration as long as it contains a radionuclide already standardized by NIST. This allows companies that produce radioactive substances to have calibrated samples of radionuclides that are important to them, but that are not on NIST's current production schedule to obtain traceability.

Table 3 shows NIST research costs related to the production of the radionuclide SRMs since 1990. While NIST initially became active in providing these SRMs in 1974, the cost data relevant to this study, as discussed below, begin with 1990. These cost data include all NIST capital, labor, and materials expenses.

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[11] This section draws directly from Golas [1996].

[12] Some of these standards are no longer produced or are produced only rarely for a user to verify response rates. The letter at the end of the SRM number indicates how many times the substance has been produced (e.g., A=1, B=2, and so on).

[13] In general, a vial is a standard NIST glass ampoule that contains 5 milliliters of solution.

[14] These revenues are divided between NIST and NEI; $108.00 to NIST to underwrite, in part, research and the production of the SRM, and $492.00 to NEI.

[15] This information was provided by experts within the Radioactivity Group at NIST, and it was verified during the interview stage of the study.

Table 1. Radiopharmaceutical Standard Reference Materials (SRMs) Produced at NIST

Radionuclide	SRM Number	Diagnostic/Therapeutic Use or Relevant Organ
Chromium-51	4400 N	Diagnosis of blood cell survival
Iodine-131	4401 V	Thyroid and other organs
Tin-113-Indium-113m	4402 C	[Replaced by Indium-111]
Strontium-85	4403 B	Bone studies
Thallium-201	4404 S	Cardiac studies
Gold-198	4405 B	Synovectomy, treatment for rheumatoid arthritis
Phosphorus-32	4406 N	In vitro traces/biotechnology
Iodine-125	4407 T	In vitro clinical chemistry
Cobalt-57	4408 F	Standard for calibration of imaging instruments
Selenium-75	4409 D	Biochemical tracer
Technetium-99m	4410 V	Imaging of multiple organs
Iron-59	4411 B	Hemoglobin studies
Molybdenum-99	4412 U	[Parent of Technetium-99m]
Mercury-197	4413 A	In vitro tracer studies
Iodine-123	4414 C	Thyroid and other organs
Xenon-133	4415 T	Lung imaging studies
Gallium-67	4416 Q	Gastrointestinal tract imaging
Indium-111	4417 P	Radioimmunotherapy
Mercury-203	4418 A	In vitro tracer studies
Ytterbium-169	4419 C	Brachytherapy
Lead-203	4420 B	In vitro tracer studies
Gold-195	4421 A	Tracer for new therapeutic agents
Chlorine-36	4422 A	Beta-particle standard
Strontium-90	4423 A	Beta-particle standard
Sulfur-35	4424 A	Cell kinetics and metabolism; biochemical tracer
Samarium-153	4425 B	Bone palliation agent
Strontium-89	4426 A	Bone palliation agent
Yttrium-90	4427 A	Radiolabelled antibody therapy

Source: Institute of Medicine [1995] and information provided by experts within the Radioactivity Group at NIST.

Table 2
Current Participants in the NEI/NIST Radioactivity Measurement Assurance Program

Bristol-Meyers Squibb Company
DuPont Merck Pharmaceuticals Company
Institute of Nuclear Energy Research (Taiwan)
Mallinckrodt Medical, Incorporated
Medi+Physics, Incorporated
Nordion International, Incorporated
Packard Instruments, Incorporated
Syncor International Corporation
U.S. Food and Drug Administration

Source: Golas [1996] and the Radioactivity Group at NIST.

Table 3. NIST Costs Related to the Production of Radiopharmaceutical SRMs (in $1,000)

Year	NIST Costs
1990	$210
1991	$218
1992	$218
1993	$265
1994	$226
1995	$384
1996	$364

Source: The Radioactivity Group at NIST.

III. An Economic Analysis of Radiopharmaceutical Research at NIST

A. The Conceptual Framework

The approach selected for evaluating the economic impacts associated with the research activities of the Radioactivity Group at NIST has been adopted from previous evaluations of other laboratory research programs at NIST and from evaluations of other public investments in infrastructure technology.[16] The actual NIST costs related to the production of radiopharmaceutical SRMs (Table 3) are compared to estimates of the economic benefits received by SRM users derived from a hypothetical counterfactual experiment. The experiment assumes that the first-level economic benefits associated with the Radioactivity Group's research can be approximated in terms of the additional costs that radiopharmaceutical manufacturers and patients would incur in the absence of NIST's research.

The hypothetical counterfactual experiment is used because this case study lacks comparable baseline observations. In other words, it is not the case that some members of MAP rely on NIST for only selected SRMs. Were that the case, then a comparison of diagnostic/ therapeutic efficiency could in principle have been conducted between calibrated and non-calibrated substances.[17]

It is important to keep in mind that this study focuses on only one part of the production and distribution chain—the radiopharmaceutical manufacturer. The radiopharmaceutical itself requires a radionuclide that is produced either in a nuclear reactor or a particle accelerator. Some manufacturers operate their own reactors or accelerators, but many do not. Therefore, the radionuclides must be purchased from other laboratories such as those operated by the U.S. Department of Energy or by universities. Once the radiopharmaceuticals are prepared at the manufacturer, they are shipped to the clinic or hospital. At this point, it is the responsibility of the radiopharmacist to dispense the bulk shipment into individual doses for the patients. Finally, the radiopharmaceutical is administered to the patient by the nuclear medicine technician. At each of these steps in the distribution chain, it is important to maintain good measurement and quality assurance practice because any errors introduced, especially early in the distribution chain, are quickly multiplied before the drug is given to the patient.

B. Survey Data and Analysis

Previous experience with the collection of information related to the economic benefits associated with NIST's laboratory research suggests that the most efficient, and presumably the most accurate means to collect data is through semi-structured, interactive telephone interviews. Accordingly, the Radioactivity Group identified a contact person in each of the seven manufacturing companies in the MAP listed in Table 2. In effect, this group defined the domestic industry of radiopharmaceutical manufacturers for this study.

[16] See Link [1996a, 1996b] and Link and Scott [1997].

[17] Data could not be obtained from manufacturers of radiopharmaceuticals that are not members of the MAP.

The radionuclide industry is of modest size. Based on data from the Department of Commerce's Bureau of the Census in its 1992 *Census of Manufacturers*, SIC industry 2835 is Diagnostic Substances. In 1992, the value of product shipments from this four-digit industry was $6,177.1 million. The five-digit SIC industry 28352, *In Vivo* Diagnostic Substances, had a value of product shipments of $1,051.8 million in 1992. The value of product shipments of *In Vivo* Radioactive Reagents (diagnostic and therapeutic), SIC 2835220, was $323.2 million in that year, and there were seven companies with shipments over $100,000.

Prior to the telephone interview, each identified participant was sent an electronic mail message from the Radioactivity Group introducing the study, soliciting participation in the study, and assuring confidentiality of individual responses. Each identified participant was asked to think about two general topics prior to the telephone interview. The first topic related to what their company would do under the hypothetical counterfactual situation where NIST ceased to produce SRMs. The second topic related to how the industry would adjust to such a situation and what the consequences would be.

Each identified manufacturing individual was interviewed. The following conclusions are based on these interviews.

1. Absent NIST's Radioactivity Group's involvement in SRMs, it would take between 5 and 10 years for some industry group or association to form and become accepted as a de facto standard setting body. The total (summed over the seven companies) expected transaction costs during this transition period would be at least $1.3 million per year. This amount represents the additional labor costs expected to be required on the part of manufacturers to resolve measurement disputes between manufacturers and customers, and the associated additional measurement equipment needed by manufacturers. The expressed expectation was that these costs would increase between 4 percent and 10 percent per year until a steady state situation was reached.

2. During this 5 to 10 year transition period, the level of accuracy at the manufacturing stage would decrease from the current ±3% to between ±5% and ±10% owing to the lack of accurate reference materials and measurement methods. At the hospital, the accuracy of dosages would fall from the current ±10% to at least ±15%.

3. Reliance on foreign national laboratories for SRMs has never been considered due to the measurement quality at NIST. Thus, no respondent could reasonably assess the likelihood that the industry would turn to a foreign national laboratory for SRMs in the hypothetical counterfactual situation.

These findings are summarized in Table 4.

Table 4. Summary of Findings from Interviews with the MAP Manufacturing Members

Hypothetical Counterfactual Situation	Range of Responses
Absent NIST's radiopharmaceutical research, how long would it take an industry group or association to form and become accepted as a de facto standard setting body?	Between five and ten years
During this five to ten year transition period, what would happen to the accuracy of radiopharmaceuticals at the manufacturing stage?	Accuracy would decrease from ±3% to between ±5% and ±10%
During this five to ten year transition period, what would happen to the accuracy of the radiopharmaceuticals administered by hospitals?	Dosage accuracy would decrease from ±10% to at least ±15%

The findings from these interviews with radiopharmaceutical manufacturers are, that should NIST's current efforts regarding SRMs be absent, an industry association would over a 5 to 10 year period evolve to replicate NIST's current role and level of accuracy in SRMs. During this transition period manufacturers would experience sizable transaction costs and patients would receive less accurate dosages of radionuclides. The economic costs to manufacturers during this transition period are estimated to be at least $1.3 million per year, to increase at a rate not less than 4 percent per year; and patient dosages of radioactive substances will fall by at least 5 percentage points, from ±10% to ±15%.[18]

To quantify, in dollar terms, the economic cost of decreased accuracy, the Radioactivity Group identified three recognized experts at renowned U.S. medical centers as candidates for telephone interviews. Each was interviewed, and as a group they expressed the following opinions:

1. A decrease in the accuracy of a radioactive substance from ±10% to ±15% would require that, on average, 1 percent of all diagnostic procedures be re-done due to too low a dosage (e.g., imprecise imaging) at an estimated average cost of between $500 and $750 per diagnostic procedure.

2. A decrease in the accuracy of a radioactive substance from ±10% to ±15% would require that, on average, 3 percent of all therapeutic procedures be re-done due to too low a dosage (e.g., ineffective treatment) at an estimated average cost of between $1,500 and $2,500 per therapeutic procedure.

3. The health implications (e.g., organ damage) of too high a dosage could not be estimated owing to the fact that such consequences would not be known immediately.

[18] Certainly, manufacturers and patients received benefits from NIST's research during the 1990 to 1996 period. However, as shown in Table 6, these benefits were not quantified owing to the counterfactual methodology adopted for estimating avoided costs if NIST were to cease its related research activity.

However, it is probable that substantial long-term economic costs would be associated with this type of misadministration.

Table 5 summarizes these economic benefits.

Table 5. Summary of Economic Benefits from Radioactivity Research at NIST

Category of Economic Benefit	Economic Benefit
Reduced transaction costs between radiopharmaceutical manufacturers and their customers	Saved $1.3 million
Increased accuracy of diagnostic procedures	Saved re-doing 1% of all procedures at an average cost of $500 to $750 per procedure
Increased accuracy of therapeutic procedures	Saved re-doing 3% of all procedures at an average cost of $1,500 to $2,500 per procedure

C. Calculation of Economic Evaluation Metrics

Table 6 replicates in the second column the NIST research costs from Table 3 from 1990 through 1996. The cost datum for 1997 is the 1997 budgeted cost amount; estimated costs (rounded) for 1998 through 2001 are based on a 5.5 percent annual increase, the actual increase from 1996 to 1997. The five year forecast period is based on the opinion of radiopharmaceutical manufacturers that, absent NIST, the industry would incur transactions costs and decreased accuracy for a period of five to ten years. For the sake of conservativeness, the lower bound of the forecasted range is used—five years.

The third column in the table contains manufacturers' estimates of the total industry cost savings from NIST continuing its SRM activity as estimated by the transaction costs (labor and equipment costs) that manufacturers would have had to incur in the absence of NIST's radiopharmaceutical research. The 1997 estimate of $1.3 million is a direct interview aggregate. The range of opinion on the growth rate of this amount was 4 percent to 10 percent per year. Again for the sake of conservativeness, the lower bound of the forecasted range is used—4 percent.

The fourth column contains the estimated value of the cost savings to patients from avoiding having to have procedures re-done because of an underdose of radiation. With respect to diagnostic procedures, the base estimate of 1 percent of 9,000,000 diagnostic procedures per year was used, valued at the lower-bound estimate of $500 per procedure. For therapeutic procedures, the base estimate of 3 percent of 1,000,000 therapeutic procedures per year was used, valued at the lower-bound estimate of $1,500 per procedure. Coincidentally, the estimate of patient costs avoided given NIST's research involvement is $45,000,000 for each procedure, or a total annual economic benefit estimate of $90,000,000. Based on expert opinion that the

number of such procedures will increase between 5 percent and 10 percent per year over the next five years, a conservative lower-bound rate of increase of 5 percent per year is imputed to the $90,000,000 estimate. Absent opinion on the annual rate of increase in procedure costs, it was assumed, again for the sake of conservativeness, that per procedure costs will remain constant over the next five years.

Finally, the fifth column in Table 6 contains total net benefits, defined, by year, to be the sum of manufacturer and patient benefits less NIST costs. Net benefits are negative in value in years 1990 through 1996 owing to the fact that economic benefits are not realized until 1997.

Table 6. Actual and Projected NIST Costs and Economic Benefits (in $000)

Year	NIST Costs	Manufacturer Benefits	Patient Benefits	Total Net Benefits
1990	$210	—	—	- $210
1991	$218	—	—	- $218
1992	$218	—	—	-$218
1993	$265	—	—	- $265
1994	$226	—	—	- $226
1995	$384	—	—	- $384
1996	$364	—	—	- $364
1997	$384	$1,300	$90,000	$90,916
1998	$405	$1,352	$94,500	$95,447
1999	$427	$1,406	$99,225	$100,204
2000	$450	$1,462	$104,186	$105,198
2001	$475	$1,521	$109,395	$110,441

IV. Interpretation of Findings

The data in Table 6 are used for the calculation of three evaluation metrics; an internal rate of return, an adjusted internal rate of return, and a benefit-to-cost ratio. Each of these is an

accepted metric for quantifying the net economic impact associated with a public research program like that within the Radioactivity Group.

A critical issue related to the calculation of the evaluation metrics is the choice of a base period and the choice of a terminal period for the analysis. The choice of the terminal period was discussed previously with regard to a five year forecast. However, some judgment must be exercised in determining the base period. The relevant question is the following: the current level of research expertise within the Radioactivity Group represents the culmination of previous efforts dating back to what year? Certainly, knowledge depreciates over time. Based on discussion with the Radioactivity Group, current economic benefits are traceable to research that began four to six years ago. Again, for the sake of conservativeness, a six-year period is used, and thus the cost data in Table 3 and Table 6 begin with 1990.

A. Internal Rate of Return

By definition, the internal rate of return (IRR) is the value of the discount rate, *i*, that equates the present value (PV) of a net benefit stream to zero. Mathematically, the IRR is the rate of discount, *i*, that satisfies the equation:

$$(1) \qquad PV = [(B_0-C_0)/(1+i)^0] + ... + [(B_n-C_n)/(1+i)^n] = 0$$

where (B_t-C_t) represents net benefits in year t, and n is the number of years under consideration.

Based on the net benefit data in the fifth column of Table 6, the calculated value of i for which PV=0 is 1.38 (rounded), implying an internal rate of return to NIST's investments in radiopharmaceutical research of 138 percent.

The internal rate of return estimate of 138 percent means that 1.38 (rounded) is the value of the discount rate that equates the present value (1990 as the base year) of net benefits to zero, or stated alternatively the present value of total benefits to the present value of costs.

Economists and policy makers generally use internal rate of return measures, for on-going or completed public-sector research projects, to estimate what is referred to in the economics literature as an approximation of the social rate of return. If 138 percent internal rate of return calculated above, is greater than the hurdle rate (generally accepted rate of return) experienced by NIST, then the radiopharmaceutical research program is surely worthwhile from a social perspective. This is especially evident when one considers that this internal rate of return is a conservative estimate, as discussed in Section V.

B. Adjusted Internal Rate of Return

It is not uncommon to misinterpret an internal rate of return measure as an annual yield similar to that earned on, say, a bank deposit. One invests, say $100, and then earns interest on that $100 each

year plus interest on the interest. That is not the case in an R&D project, in general, or in the case of NIST's radiopharmaceutical research, in particular.

Under an alternative set of assumptions, an adjusted internal rate of return (AIRR) can be calculated from the data in Table 6 to provide a rate of return that is more analogous to an annual yield (as earned on a bank deposit for example). It is important to re-emphasize that the AIRR is not the same as the IRR and that the AIRR is not directly comparable to the economics literature on social rates of return. Nevertheless, the AIRR remains an accepted evaluation metric.

If all net NIST costs are referenced to 1990 using a discount rate of 8.78 percent, the 1990 present value of NIST costs is $2,435,720. The discount rate of 8.78 percent is the sum of the Office of Management and Budget's [1992] recommended real rate of discount of 7.0 percent plus and inflation factor of 1.78 percent.[19] If all economic benefits (the sum of manufacturer benefits and patient benefits) are referenced forward to the year 2001 using the same rate, the 2001 present value of industry benefits is $596,138,530. The AIRR is the rate of return that equated a single NIST investment of $2,435,720 in 1990 to a single benefit estimate of $596,138,530 in 2001.

Thus, the annual compounded rate of return that corresponds to such an investment in 1990 culminating in 2001 equals 65 percent (rounded) based on the value of x that satisfied the following relationship:

(2) $\$2{,}435{,}720\ (1+x)^{11} = \$596{,}138{,}530$

C. Benefit-to-Cost Ratio

The third evaluation metric is a benefit-to-cost ratio (B/C). This ratio is, by definition the present value of all benefits to the present value of all costs, where the point of reference for both benefits and costs is the base time period, 1990. The relevant discount rate for the calculation of present value is again 8.78 percent. For the data in Table 6, the present value of all benefits equals $236,215,070 and the present value of all costs equals $2,435,720. Thus, the ratio of benefits-to-costs is:

(3) B/C = 97-to-1

It should be noted that the calculated IRR of 138 percent from equation (1) implies a benefit-to-cost ratio of unity. Rewriting equation (1) using summation notation:

(4) $PV = [\Sigma_{t=0 \text{ to } n} B_t/(1+\underline{i})^t] - [\Sigma_{t=0 \text{ to } n} C_t/(1+i)^t]$

[19] The Office of Management and Budget [1992] recommends using a nominal discount rate equal to a 7 percent real discount rate plus an inflation factor. The inflation rate of 1.78 percent is the Federal Reserve Board's published implicit price deflator for the past four quarters.

where *i* is the IRR that equated PV=0. When PV=0, then it follows that:

(5) $$[\Sigma_{t=0 \text{ to } n} B_t/(1+i)^t] = [\Sigma_{t=0 \text{ to } n} C_t/(1+i)^t]$$

or that the present value of benefits equals the present value of costs, or B/C=1. Thus, as is the case here, when B/C > 1 it implies that the IRR is greater than the social rate of discount used in the benefit-to-cost calculation.

V. Conclusions

NIST responded to the radiopharmaceutical industry's needs for standards as outlined by the Atomic Industrial Forum in 1973. Related research has been ongoing at NBS/NIST since 1974. This research, in the opinion of manufacturers and in the opinion of medical experts today has been invaluable. Quantitatively, the activities of the now Radioactivity Group are significantly benefiting society as measured by accepted evaluation metrics.

Three standard evaluation metrics were quantified in this study: an internal rate of return of 138 percent, an adjusted internal rate of return of 65 percent, and a benefit-to-cost ratio of 97-to-1. Each of these metrics was calculated under the most conservative set of assumptions possible. In every instance when experts expressed an opinion in terms of a range of values, the most conservative end point of the range was used. Also, there are certainly costs associated with both underdose and overdose misadministrations that go beyond the direct cost of readministering a dosage (in the case of an underdose). The benefits associated with these cost savings also have not been considered in this analysis. Were they to be considered, the estimated values of all three of the metrics above would increase. Still, when compared to the social cost of resources used to generate the economic benefits described herein—an 8.78 percent return on resource costs—the radiopharmaceutical research at NIST is without question valuable to society.

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