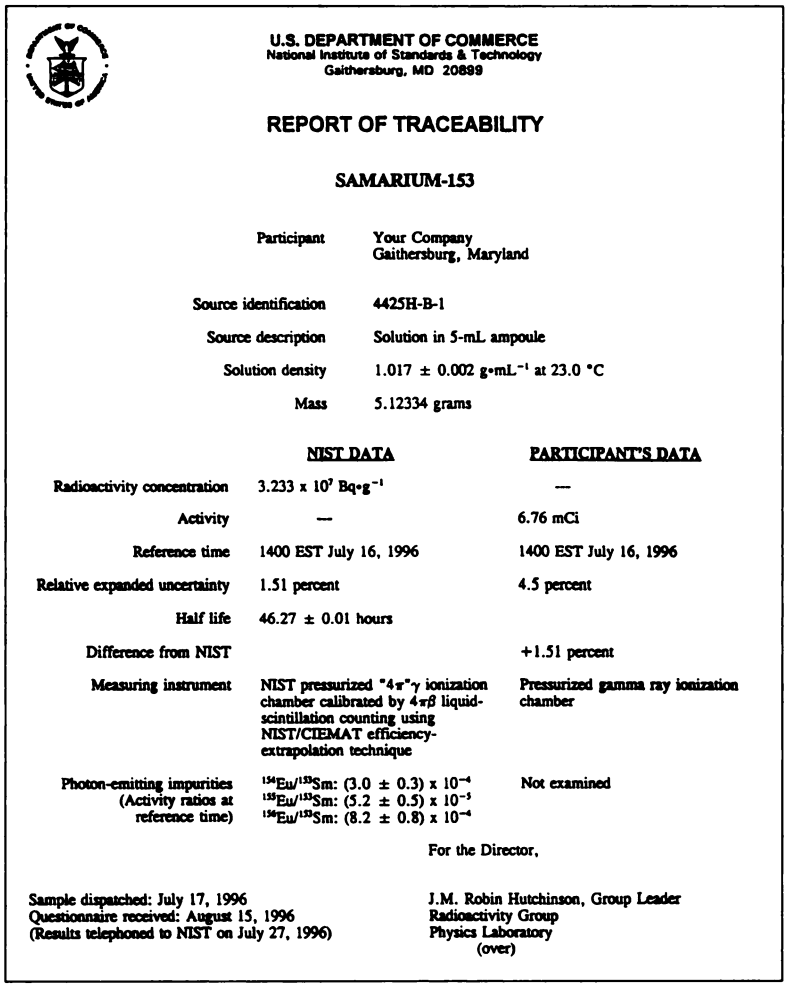
NEWSLINE

Radiopharmaceutical Measurement Assurance Program Provides Significant Cost Savings



U.S. DEPARTMENT OF COMMERCE
National Institute of Standards & Technology
Gaithersburg, MD 20899

REPORT OF TRACEABILITY

SAMARIUM-153

Participant	Your Company Gaithersburg, Maryland
Source identification	4425H-B-1
Source description	Solution in 5-mL ampoule
Solution density	1.017 ± 0.002 g•mL^{-1} at 23.0 °C
Mass	5.12334 grams

	NIST DATA	PARTICIPANT'S DATA
Radioactivity concentration	3.233 x 10^{7} Bq•g^{-1}	—
Activity	—	6.76 mCi
Reference time	1400 EST July 16, 1996	1400 EST July 16, 1996
Relative expanded uncertainty	1.51 percent	4.5 percent
Half life	46.27 ± 0.01 hours	
Difference from NIST		+1.51 percent
Measuring instrument	NIST pressurized "4π"-γ ionization chamber calibrated by 4πβ liquid-scintillation counting using NIST/CIEMAT efficiency-extrapolation technique	Pressurized gamma ray ionization chamber
Photon-emitting impurities (Activity ratios at reference time)	^{154}Eu/^{153}Sm: (3.0 ± 0.3) x 10^{-4} ^{155}Eu/^{153}Sm: (5.2 ± 0.5) x 10^{-5} ^{156}Eu/^{153}Sm: (8.2 ± 0.8) x 10^{-4}	Not examined

For the Director,

Sample dispatched: July 17, 1996
Questionnaire received: August 15, 1996
(Results telephoned to NIST on July 27, 1996)

J.M. Robin Hutchinson, Group Leader
Radioactivity Group
Physics Laboratory
(over)

Figure 1. Sample NIST traceability report, comparing participant's measurement with NIST data.

In an era of cost containment and reduced government services, a 1997 economic impact study conducted by the National Institute of Standards and Technology (NIST) Physics Laboratory and the University of North Carolina at Greensboro of the NIST Radiopharmaceutical Standards Program demonstrated that taxpayers are getting their money's worth from a program that ensures accurate measurements of the radiopharmaceuticals used to diagnose and treat disease.

Standard Reference Materials Program

The Measurement Assurance Program (MAP), a joint effort by NIST and the Nuclear Energy Institute (NEI), represents a successful collaboration between a government agency and industry to provide a much-needed, cost-effective service. The standards developed by NIST are sold to radiopharmaceutical manufacturers through the Standard Reference Materials (SRMs) Program, which provides samples of isotopes whose values have been measured with great precision and accuracy. The radiopharmaceutical companies use the SRMs to evaluate the accuracy of their own measurements and methodology.

Given the volume of nuclear medicine procedures performed yearly (about 10 million annually) at costs of between $500 and $750 per procedure, the lack of accurate measurements would necessitate repeat procedures and significantly increase costs to both patients and the radiopharmaceutical industry. The radiopharmaceutical standards program, which costs $2.4 million, produces benefits worth $236.2 million to patients and industry, a cost–benefit ratio of 97:1. According to Brian Zimmerman, PhD, research chemist, NIST, Gaithersburg, MD, the assumptions used in computing the benefits are conservative, so this ratio is probably low. Moreover, added Zimmerman, the economic data do not include improvements in the quality of life for the patients who benefit from accurate tests. The program is also important, Zimmerman noted, "because the existence of the program ensures patient safety by setting standards for radiopharmaceuticals, and it is instrumental in helping to bring new products to the marketplace."

Radiopharmaceutical Measurement Assurance Program

Formerly the National Bureau of Standards (NBS), NIST, an agency within the U.S. Department of Commerce, was founded in 1901 by congressional act to be the source of standards for physical measurement in the U.S. NIST's goals are to develop reference and definitive methods of analysis, certify and issue standards and ensure their effective use. As the only national standards entity with a dedicated nuclear medicine program, NIST achieves its goals by disseminating over 1300 different SRMs. NIST's Radioactivity Group produces about 60 SRMs. These 60 SRMs include the short-lived radioactivity SRMs used for nuclear medicine quality control and are known as the 4400 series (see box on page 22N) because their listings in the SRM catalog begin with the number 44.

In collaboration with the NEI, through an arrangement called the Cooperative Research Development Agreement, in which individual companies work directly with NIST researchers, NIST conducts two MAPs: one for radiopharmaceuticals and

Radiopharmaceutical Standards Established by NIST Since the Mid-1970s

Radionuclide	SRM no.*	Half-life	Last issued
Chromium-51	4400N	27.702 days	July 1992
Iodine-131	4401X	8.02070 days	January 1998
Tin-113-Indium-113m	4402C	115.09 days	October 1980
Strontium-85	4403B	64.84 days	April 1977
Thallium-201	4404T	3.040 days	June 1997
Gold-198	4405B	2.69517 days	August 1978
Phosphorus-32	4406O	14.262 days	October 1997
Iodine-125	4407V	59.408 days	December 1997
Cobalt-57	4408F	271.79 days	July 1995
Selenium-75	4409D	119.79 days	August 1981
Technetium-99m	4410W	6.01 hours	September 1997
Iron-59	4411B	44.503 days	January 1979
Molybdenum-99	4412W	65.94 hours	February 1998
Mercury-197	4413A	64.14 hours	May 1976
Iodine-123	4414C	13.27 hours	June 1980
Xenon-133	4415V	5.243 days	March 1998
Gallium-67	4416S	3.2612 days	April 1998
Indium-111	4417Q	2.8047 days	August 1997
Mercury-203	4418A	46.612 days	November 1976
Ytterbium-169	4419C	32.026 days	October 1986
Lead-203	4420B	51.873 hours	November 1984
Gold-195	4412A	186.098 days	December 1979
Chlorine-36	4422A	3.01×10^5 years	April 1980
Strontium-90	4423A	28.78 years	November 1995
Sulfur-35	4424A	87.51 days	October 1988
Samarium-153	4425C	46.27 hours	July 1997
Strontium-89	4426A	50.53 days	April 1995
Yttrium-90	4427A	64.10 hours	October 1994

*The letters at the end of the SRM number indicate the frequency with which the isotopes have been issued as SRMs. As the data in the last column show, many of the SRMs are no longer produced, for a variety of reasons: for example, low demand (e.g., ^{203}Hg, ^{59}Fe) because of the availability of radionuclides that are easier to use or deliver lower radiation doses to patients or, even if the radionuclide is still widely used (e.g., ^{123}I), the radiochemical used to produce the SRM would make it too expensive.

one for the nuclear power industry. The radiopharmaceutical MAP was started in the 1970s after a National Academy of Sciences report specified the need for national standards from NBS (as NIST was then known). At the time, there were numerous problems in the quality control of administered radiopharmaceuticals. In addition to a lack of calibrations for many radionuclides used in nuclear medicine, SRMs available at the time were often in the wrong physical form.

Participants in the radiopharmaceutical MAP, who represent all facets of the radiopharmaceutical industry, pay fees to the NEI to cover the costs of participation in the program as well as membership in the NEI. (The NEI ultimately uses these funds to pay NIST for the SRMs.) Participants meet once a year to determine which ten standards should be prepared. However, according to Zimmerman, the selection process is also determined by the emergence of new isotopes for which no standards exist, as well as a review of ongoing research in the literature. Ten different SRMs are produced annually, one per month, except for May and November. Those two months are known as open months, in which participants may submit samples for NIST verification of radionuclides that are not on the current schedule. High- and low-level SRMs are provided for all radionuclides except ^{99m}Tc.

When NIST has completed an SRM, it is sent to the participants along with a questionnaire, but the NIST measurement is not disclosed. The participants make their own measurements and report their results on the reporting form. There can be large discrepancies between manufacturers' readings and the NIST value. According to Zimmerman, the largest to date was ±25% (for ^{188}Re), but they have varied ±10% or as low as ±5% (for ^{99m}Tc). Once NIST receives the completed questionnaire (Fig. 1), a report is generated that compares the participant's measurement with the NIST measurement, providing traceability for the measurement.

NIST traceability is an important factor for radiopharmaceutical manufacturers. Before approving a product, the Food and Drug Administration (FDA) requires a NIST-traceable method for isotope standards, said Zimmerman. Zimmerman also noted that when a manufacturer is working on a final product, there needs to be a record of the impurities in the product, and NIST traceability certifies the radiochemical impurities. Said Simon Steingart, quality control manager, Amersham (Arlington Heights, IL), "the FDA requires traceability to some standard, and the NIST measurement meets this criterion." Steingart also noted that the NIST measurement is a key item in Amersham's product releases.

When all the questionnaires have been returned to NIST, a summary is generated that lists all the deviations—the companies are not identified—from the NIST measurement for all participants and the detector used to make the measurement. The summary also includes the average differences from the NIST measurement. Although these data are primarily used by manufacturers and institutions that develop isotopes, the low-level SRMs can be sold to the general public, and the proceeds from these sales are also used to support the program.

Economic Impact Study

NIST regularly evaluates the effectiveness of its programs, and in November 1997 it undertook an economic impact study of its Physics Labora-

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MURR

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set of radiolanthanides trying to find the one with the best chemistry and the best physical properties. The initial patients were dogs at the vet school. Then, of course, it went to people—first here at Columbia, and then elsewhere in the country."

Samarium-153 was approved by the Food and Drug Administration for use as a palliative agent for metastatic bone disease in the U.S. in March 1997. MURR continues to supply the raw irradiated product for manufacture into that agent. The work with ^{153}Sm has led to work with other bone agents. MURR recently began assisting with clinical trials using ^{166}Ho as a marrow ablative agent for multiple myeloma.

Indeed, because of its pioneering work in the field, MURR is well placed to take advantage of the rapidly expanding area of therapeutic nuclear medicine. "We're suffering from funding problems like anyone else, and we don't have the infrastructure support that some government labs do, but we've always tried to work well within our means," commented Ehrhardt.

MURR continues to look forward as the new millenium approaches. One project in development is a $25 million, 81,500-square foot building addition that will provide additional research laboratories and office space. Current emphasis, however, is on the renewal of MURR's Nuclear Regulatory Commission operating license, which expires in November 2001. Stone and Webster Engineering Corporation (Boston, MA) was hired to develop the plan and budget that will allow MURR to upgrade its infrastructure. These improvements will allow MURR to continue making strides in nuclear medicine and biomedical research well into the next century.

—Jeffrey E. Williams

Radiopharmaceutical Measurement Assurance Program

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tory (of which the Radioactivity Group is a component) because of the commercial importance of nuclear medicine procedures, the customer service aspects of the program and the program's longevity and track record—over 20 years of data on costs and benefits that could be monitored.

According to the study's results, both patients and industry receive tremendous cost savings from the program. For example, without NIST standards, the accuracy of radiopharmaceuticals would decrease by 10%–15%, resulting in the need to redo about 1% of most diagnostic tests because of doses that are too low or test results that are unreadable. The use of NIST standards results in estimated savings of $45 million yearly for diagnostic procedures. According to the study, patients also see savings for therapeutic applications as well. Without NIST standards, 3% of all therapeutic procedures (of which about 1 million are performed annually at costs of $1500 to $2500 per procedure) would have to be repeated.

Manufacturers also reap economic benefits by not having to develop standards and resolve measurement discrepancies. "The radiopharmaceutical MAP is an excellent, cost-effective program," said Steingart, "particularly in view of the results we receive. It would be difficult for the radiopharmaceutical community to conduct a similar program, the special equipment is expensive and it would require cooperation from all the manufacturers regarding standards." According to the study, it would take 5–10 years to establish a privatized radiopharmaceutical standards entity if NIST abandoned the MAP program, at a cost of about $1.3 million per year during the transition phase.

—Eleanore Tapscot

Scatter

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reimburse for nuclear cardiology, inflammation imaging and SPECT imaging in general. We are currently reliving those experiences with PET imaging, cerebral perfusion imaging, fusion imaging and the diagnostic and therapeutic use of radiolabeled antibodies and peptides. How many efforts by academic centers and industry have been aborted because of the lack of financial support and subsequent fear of the effect of failure?

Medicine and our specialty, nuclear medicine, frequently overcame past adversities and achieved its current successes. We must continue to believe in, and subsequently prove, the efficacy of our newly developed procedures and commit our personal and professional resources to achieve new successes despite the lack of vision of others who fail to see the value in the quality of health care provided by these procedures.

Stanley J. Goldsmith
Editor-in-Chief, *The Journal of Nuclear Medicine*
June 1998