

## ● Physics Contribution

# NATIONAL RADIOACTIVITY STANDARDS FOR $\beta$ -EMITTING RADIONUCLIDES USED IN INTRAVASCULAR BRACHYTHERAPY

B. M. COURSEY, PH.D.,\* R. COLLÉ, PH.D.,\* B. E. ZIMMERMAN, PH.D.,\*  
J. T. CESSNA, B.S.\* AND D. B. GOLAS, M.S.†

\*Ionizing Radiation Division, Physics Laboratory, National Institute of Standards and Technology, Gaithersburg, MD; and

†Nuclear Energy Institute, Washington, DC

The uses of  $\beta$ -particle emitting radionuclides in therapeutic medicine are rapidly expanding. To ensure the accurate assays of these nuclides prior to administration, radioactivity standards are needed. The National Institute of Standards and Technology (NIST), the national metrological standards laboratory for the United States, uses high-efficiency liquid scintillation counting to standardize solutions of such  $\beta$  emitters, including  $^{32}\text{P}$ ,  $^{90}\text{Sr}/^{90}\text{Y}$ , and  $^{188}\text{Re}$ . Additional measurements are made on radionuclidic impurities, half lives, and other decay-scheme parameters (such as branching decay ratios or  $\gamma$ -ray abundances) using HPGe detectors and reentrant ionization chambers. Following such measurements at NIST, standards are disseminated in three ways: Standard Reference Materials (SRMs), calibrations for source manufacturers, and calibration factors for commercial instruments. Uncertainties in the activity calibrations for these nuclides are of the order of  $\pm 0.5\%$  (at approximately 1-standard deviation confidence intervals). © 1998 Elsevier Science Inc.

Radioactivity standards,  $\beta$  particles, Intravascular brachytherapy, Liquid scintillation counting.

## APPLICATIONS AND THE NEED FOR STANDARDS

Therapeutic nuclear medicine has seen rapid growth in the past few years in several areas: radioimmunotherapy, bone palliation, bone marrow ablation, and radionuclidic synovectomy. The resurgence of interest in what are often called “magic bullets” is a result of improvements in tissue-specific agents, such as monoclonal antibodies, and organ-specific pharmaceuticals, such as bone-seeking diphosphonates. The nuclides under consideration are mainly short-lived, high-energy  $\beta$  emitters (1,2).

All of these applications of course require an accurate assay of the injected radiopharmaceutical; U.S. and Canadian regulations dictate that the injected activity must be within  $\pm 10\%$  of the prescribed dosage. The therapeutic administration of radioactive by-product material in the United States is regulated by the U.S. Nuclear Regulatory Commission (3, 4). Radiopharmaceutical administrations are normally radioassayed by measuring a serum vial or syringe using a reentrant ionization chamber, such as those

manufactured by Capintec, Radcal, and Vinten (commonly called “dose calibrators”). For a given instrument, the potentiometer setting to obtain the correct activity for a particular radionuclidic source (given by the manufacturer as a calibration factor) depends on a number of critical variables: photon energy, vial geometry, sample volume, and density of solution. A de facto standard for these instruments in the United States is 5 mL of solution in a standard glass ampoule, such as those distributed by the National Institute of Standards and Technology (NIST). A response curve for  $\gamma$ -ray emitters in NIST ampoules in a Capintec (5) dose calibrator is given in Fig. 1. Chambers of this design are particularly sensitive in the low-energy region to small changes in geometry and vial thickness.  $\beta$ -Particle emitters generate bremsstrahlung, which has a large component at lower photon energies, so chamber response for a  $\beta$  emitter is also highly dependent on geometry and vial thickness.

Recent interest in the use of radioactive sources to prevent restenosis following percutaneous transluminal coro-

Presented at the symposium on Advances in Cardiovascular Radiation Therapy, Washington, DC, 20–21 February 1997.

The mention of commercial products throughout this article does not imply recommendation or endorsement by the National Institute of Standards and Technology, nor does it imply that the products identified are necessarily the best available for the purpose.

Reprint requests to: Dr. B. M. Coursey, Ionizing Radiation Division, Physics Laboratory, National Institute of Standards and Technology, Gaithersburg, MD 20899.

**Acknowledgments**—The authors express thanks to F. F. (Russ) Knapp, Jr., and Saed Mirzadeh at the Oak Ridge National Laboratory for supplying  $^{188}\text{Re}$ ; Sam Lott at NeoCardia for providing  $^{32}\text{P}$  sources; and Mary Anne Dell at Capintec for discussions on dose calibrators. They also thank their colleagues F. J. Schima, D. D. Hoppes, and M. P. Unterweger, the physicists at NIST who measure and evaluate nuclear decay scheme data for these radionuclides.

Accepted for publication 13 November 1997.

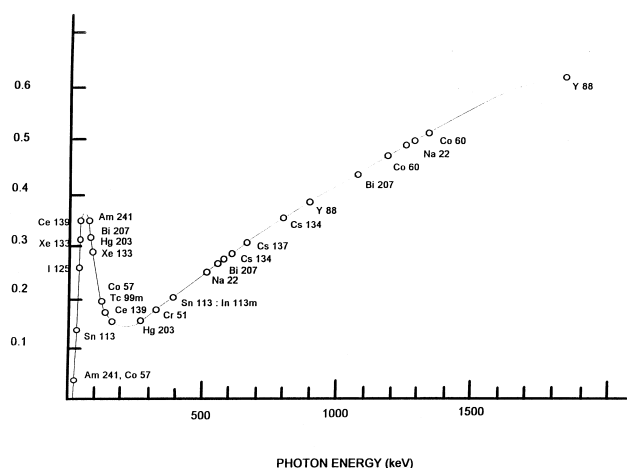


Fig. 1. Relative response curve for Capintec dose calibrator for various radionuclides as a function of energy (Capintec, 1997).

nary angioplasty (PTCA) procedures has led to clinical studies involving  $\beta$ -particle ( $^{32}\text{P}$ ,  $^{90}\text{Sr}$ ) and  $\gamma$ -ray emitting ( $^{192}\text{Ir}$ ) radionuclides. Quite a long list of nuclides is under consideration. Many of the candidate  $\beta$ -particle emitters for intravascular brachytherapy are the same ones used in therapeutic radiopharmaceuticals. The characterization of brachytherapy sources for dosimetric quantities (air kerma strength or surface-absorbed dose rate) is carried out in the NIST Dosimetry Group (6, 7) and will not be dealt with in this article. The present status of radioactivity standards and measurements for solutions of  $\beta$ -particle-emitting radionuclides, as illustrated with a few examples, is described in the following sections.

### THE ROLE OF NIST

The National Institute of Standards and Technology, formerly the National Bureau of Standards, was created by a Congressional act in 1901 to be the source and custodian of standards for physical measurements in the United States. As a part of its mandate, the responsibilities and goals of NIST are to develop and maintain national reference standards and definitive methods of analysis; to certify and issue suitable transfer standards; and to provide mechanisms that assure the quality of measurements being made in the United States. The latter responsibility and goal are largely accomplished through a variety of interlaboratory measurement assurance programs that are intended to ensure the effective use of standards and methods in the measurement community, and which will thereby help to achieve accurate measurements in the United States and throughout the world. To assist in reaching these objectives, the NIST Standard Reference Material Program distributes more than 1300 different Standard Reference Materials (SRMs) that have been developed and certified in the NIST laboratories, located in Gaithersburg, Maryland, and in Boulder, Colorado. Standards for therapeutic radionuclides in the United Kingdom are described elsewhere (8).

The Radioactivity Group of the Ionizing Radiation Division in the NIST Physics Laboratory produces about 60 of these SRMs. They are intended for the calibration of radioactivity-measuring instruments and for the monitoring of chemical and geochemical processes. A subset of these is the (usually) short-lived "radiopharmaceutical" SRMs intended for nuclear medicine quality control. The radiopharmaceutical SRMs are produced through a Cooperative Research and Development Agreement (CRADA) with the Nuclear Energy Institute (NEI) (9, 10). NIST has nearly 400 such CRADAs in which individual companies work directly with NIST researchers to achieve joint goals. The NEI is the commercial nuclear power industry's Washington, DC-based policy organization. Its main function is to support the nuclear power industry. NEI represents a broad spectrum of nearly 400 companies in the United States and overseas, and is involved with these measurement assurance programs only as a service to its member companies. The companies that were interested in starting these measurement assurance programs already belonged to NEI, and the organization provided a common, already-in-place infrastructure to hire people to work at NIST to provide the services that the companies desired.

The current participants in the radiopharmaceutical program are listed in Table 1. Together, the participants represent the entire spectrum of the radiopharmaceutical industry, from bulk radiochemical suppliers to radiopharmaceutical manufacturers, to a radiopharmacy that provides unit doses of radiopharmaceuticals in the form of filled syringes and capsules, and to hospitals for individual diagnostic tests and treatments. The U.S. Food and Drug Administration also participates through an interagency agreement with NIST.

The SRMs are provided to the manufacturers on a fixed annual schedule so they can plan and use these standards as part of their quality assurance process. They are supplied to the participants as "blinds"—that is, with the NIST-measured activity undisclosed. The participants perform measurements on the sources and report their results on a

Table 1. Current participants in NEI/NIST measurement assurance program for radiopharmaceuticals

Bristol-Meyers Squibb Company
New Brunswick, NJ
DuPont Merck Pharmaceuticals Company
North Billerica, MA
Mallinckrodt Medical, Incorporated
Maryland Heights, MO
Medi+Physics, Incorporated
Arlington Heights, IL
Nordion International, Incorporated
Kanata, Ontario, Canada
Packard Instruments, Incorporated
Downers Grove, IL
Syncor International Corporation
Chatsworth, CA
Food and Drug Administration
Winchester, MA

Table 2. NIST SRMs and calibrations for radionuclides used in radionuclidic therapy and intravascular brachytherapy

Nuclide	$T_{1/2}$	Primary radiation	Coincidence counting	Liquid scintillation	Ionization chamber	NaI $\gamma$ counting	HPGe spectrometry	SRM or calibration
$^{32}\text{P}$	14.28 d	$\beta$		✓				4406N
$^{89}\text{Sr}$	50.52 d	$\beta$		✓				4426A
$^{90}\text{Sr}$	29.1 a	$\beta$		✓	✓			4423A
$^{90}\text{Y}$	2.67 d	$\beta$		✓	✓			4427A
$^{117\text{m}}\text{Sn}$	14.00 d	$e^{-}, \gamma$		✓	✓	✓	✓	Calib.
$^{125}\text{I}$	60.1 d	$\gamma$	✓		✓	✓		4407U*
$^{131}\text{I}$	8.040 d	$\beta, \gamma$	✓	✓	✓	✓	✓	4401V
$^{153}\text{Sm}$	1.929 d	$\beta, \gamma$		✓	✓		✓	4425B
$^{166}\text{Ho}$	1.117 d	$\beta, \gamma$		✓			✓	Calib.
$^{169}\text{Yb}$	32.03 d	$\gamma$	✓		✓		✓	4419C
$^{186}\text{Re}$	3.777 d	$\beta, \gamma$		✓			✓	Calib.
$^{188}\text{Re}$	17.01 h	$\beta, \gamma$		✓			✓	Calib.
$^{192}\text{Ir}$	73.83 d	$\beta, \gamma$						Dosim. calib.

\* Dosimetry calibrations also exist for Model 6702 and 6711 brachytherapy seeds.

questionnaire supplied with the source. After the questionnaire is received at NIST, a report is issued which compares the participant's measurement with the NIST value, providing traceability for the measurement.

Table 2 gives a summary of the SRMs and calibrations that NIST has developed for many radionuclides used in therapy. The 4400 series SRMs are those developed for the NEI/NIST radiopharmaceutical program. In many instances (e.g.,  $^{125}\text{I}$  and  $^{192}\text{Ir}$ ), there is not a connection between the NIST dosimetry standard, in terms of a dosimetric quantity (air kerma strength in  $\text{Gy m}^2 \text{s}^{-1}$ ), and the NIST radioactivity standard, in terms of a radionuclidic quantity (radioactivity in Bq). Both at NIST and in the European Community, there is now a concerted effort under way to establish both dosimetry and radioactivity standards for the more common nuclides and source geometries.

## RADIONUCLIDIC STANDARDIZATION OF $\beta$ EMITTERS

Standardizations of  $\beta$ -emitting radionuclides by  $4\pi\beta$  liquid scintillation (LS) spectrometry are routinely performed by NIST using the Centro de Investigaciones Energeticas, Medioambientales y Technologicas (CIEMAT)/NIST method for efficiency tracing. This protocol (11, 12), originated by the CIEMAT and NIST, is one of the more commonly invoked methodologies for LS spectrometry efficiency tracing. The method uses various updated and revised versions of the CIEMAT-developed EFFY code (13, 14) to determine the detection efficiencies for cocktails of the traced radionuclide (under known and varying quench conditions) by following the experimentally determined efficiencies for closely matched cocktails of a  $^3\text{H}$  standard. Tritium ( $^3\text{H}$ ) is recommended to serve as the matched (in terms of cocktail composition and quenching) standard, since extrapolations to the low-energy portions of the  $\beta$ -particle spectra are more sensitive than those obtained with higher-energy standards. The critical importance of cocktail

matching, particularly for lower-energy  $\beta$  emitters, has been treated by Collé (15).

The principle of the method is to calculate the counting efficiency for a two-phototube LS counter from a simple model, which includes the electron detection efficiency of the counter (photoelectrons produced per keV deposited) and the theoretical  $\beta$ -particle energy distribution of Fermi:

$$\epsilon_c = \left\{ \int_0^{E_{\beta_{\max}}} P(Z, E) \times [1 - \exp(-E\eta Q(E)W(E))]^2 dE \right. \\ \left. \times \left\{ \int_0^{E_{\beta_{\max}}} P(Z, E) dE \right\}^{-1} \right\},$$

where  $P(Z, E)dE$  is the Fermi distribution function in the case of an allowed  $\beta$  decay;  $Z$  is the atomic number;  $E$  is the  $\beta$ -particle energy;  $\eta$  is a figure of merit, expressed in terms of the number of photoelectrons per keV;  $Q(E)$  is an ionization quenching function that is used to account for the differences in light yield for electrons as a function of energy (15); and  $W(E)$  is a wall correction term, taken here as unity.

Figure 2 shows three theoretically calculated  $\beta$ -particle spectra (as used for the efficiency tracing) for nuclides that have recently been standardized at NIST. These are the  $\beta$ -particle spectra,  $P(E)$ , in the equation above. For nuclides which have coincident  $\gamma$  rays, as, for example,  $^{188}\text{Re}$ , the actual measured electron spectrum includes contributions as well from photons and conversion electrons associated with the  $\gamma$  transitions. Since these events are in coincidence with a continuum of  $\beta$  particles having energies from zero to  $\beta_{\max}$ , the measured spectrum for  $^{188}\text{Re}$  looks essentially the same as that for  $^{90}\text{Y}$ .

In our laboratory, LS measurements are made with two commercial counting systems: System B—a Beckman LS7800 with two phototubes that function in a sum-coinci-

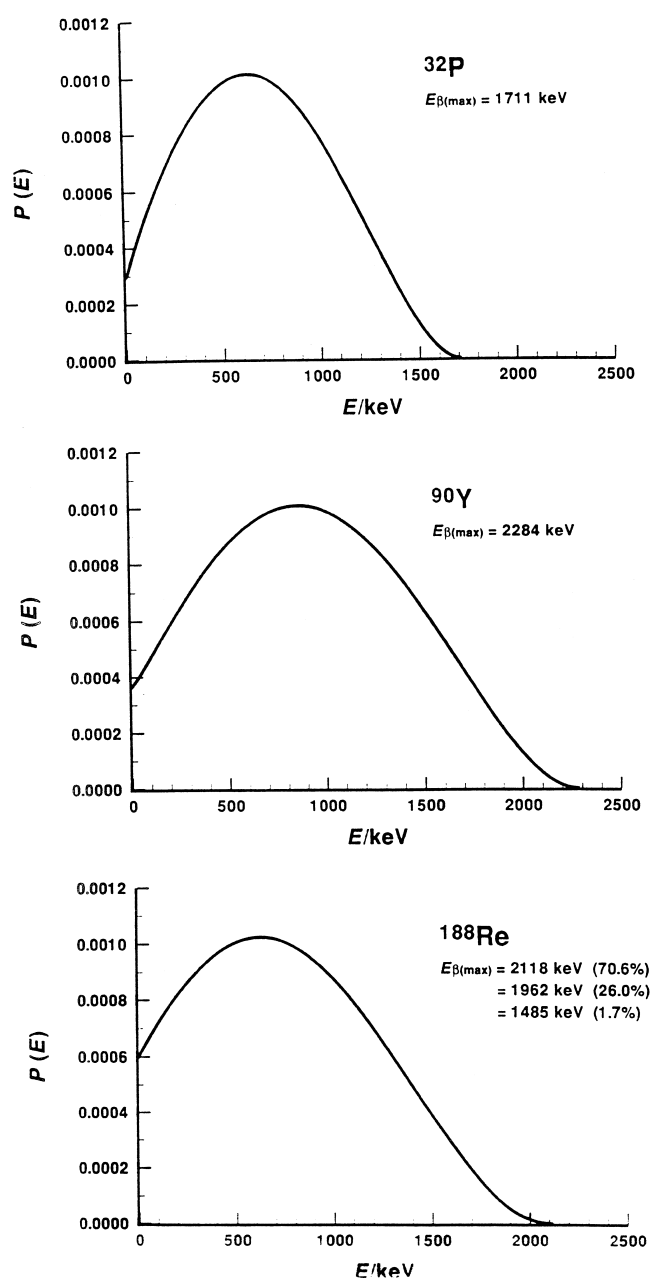


Fig. 2.  $\beta$  Spectra for three radionuclides as calculated with the Fermi distribution. The plots consist of the probability  $P(E)$  for a  $\beta$  particle of energy  $E$  as a function of  $E$  (in units of keV).

dence mode, a logarithmic pulse amplifier, and an external  $^{137}\text{Cs}$  source for quench monitoring—and System P—a Packard Instruments Model A2500TR, which is also a two-phototube sum-coincidence system, but it operates with linear pulse amplification and has a  $^{133}\text{Ba}$  external source for quench determinations. Descriptions of the operating characteristics, the instruments' respective performance, and use within this laboratory for various radionuclidic calibrations are available elsewhere (16).

In addition to standardizing the nuclides for activity by LS spectrometry, NIST also performs measurements of photonic emission rates with calibrated HPGe semiconductor detectors (17) primarily for radionuclidic impurity anal-

yses, and for half lives with a pressurized, reentrant ionization chamber (18).

The sources for such ancillary measurements are directly related gravimetrically to solutions standardized by liquid scintillation spectrometry. The NIST photon-spectrometry systems have in turn been independently calibrated using SRM 4275 (which consists of a radionuclide mixture of  $^{154}\text{Eu}$ – $^{155}\text{Eu}$ ,  $^{125}\text{Sb}$  (19), as well with other single radionuclides. As a result, measurements of the LS-determined activity coupled with those for photonic emission rates from the same sources can be used to extract useful nuclear parameters, e.g., decay-branching ratios.

It is important to accurately identify and quantitate radionuclidic impurities in radiopharmaceuticals that limit the useful shelf life of the product and lead to unwanted patient dose. At NIST, each radionuclide standard is assayed for impurities as soon as possible after receipt of material, to ascertain if there are any short half-life nuclides, and a second time after the samples have substantially decayed, to detect the long-lived impurities. Listings of impurities are made available on SRM certificates, which allow producers to (a) judge the effectiveness of their chemical cleanup, (b) consider the impact of impurities on their dose calibrator measurements, and (c) include accurate information on impurities on their package inserts for the radiopharmaceutical.

### EXAMPLES OF RECENT NIST STANDARDIZATION ACTIVITIES: $^{90}\text{Y}$ , $^{32}\text{P}$ , AND $^{188}\text{Re}$

Following are three examples that illustrate the methods used to standardize high-energy  $\beta$  emitters at the NIST, and the use of these standardized solutions to characterize radionuclide calibrators for use in radioassays prior to therapeutic administration.

#### Yttrium-90

The uses of  $^{90}\text{Y}$  in radionuclide therapy have been expanding for the past several years. Promising areas for clinical applications of radiolabeled monoclonal antibodies include the treatment of lymphoma (20). Clinical trials have also been conducted for  $^{90}\text{Y}$ -impregnated glass microspheres for use in treatment of liver cancer (21). In about 1986, the Oak Ridge National Laboratory (ORNL) began large-scale production and distribution of  $^{90}\text{Y}$  for therapeutic uses (22). NIST developed (23) a 5-mL ampoule standard for ORNL to use with their Capintec radionuclide calibrator, and this standard setting was used in specifying the amounts distributed to customers. At the same time, NIST calibrated several Capintec chambers in the radiopharmacy and research laboratories at the U.S. National Institutes of Health (NIH). For the Capintec instrument potentiometer settings are recommended by the manufacturer for a number of radionuclides. The Capintec setting “48  $\times$  10” gave the correct readout in millicuries, at least for the five chambers tested at the NIST and NIH.



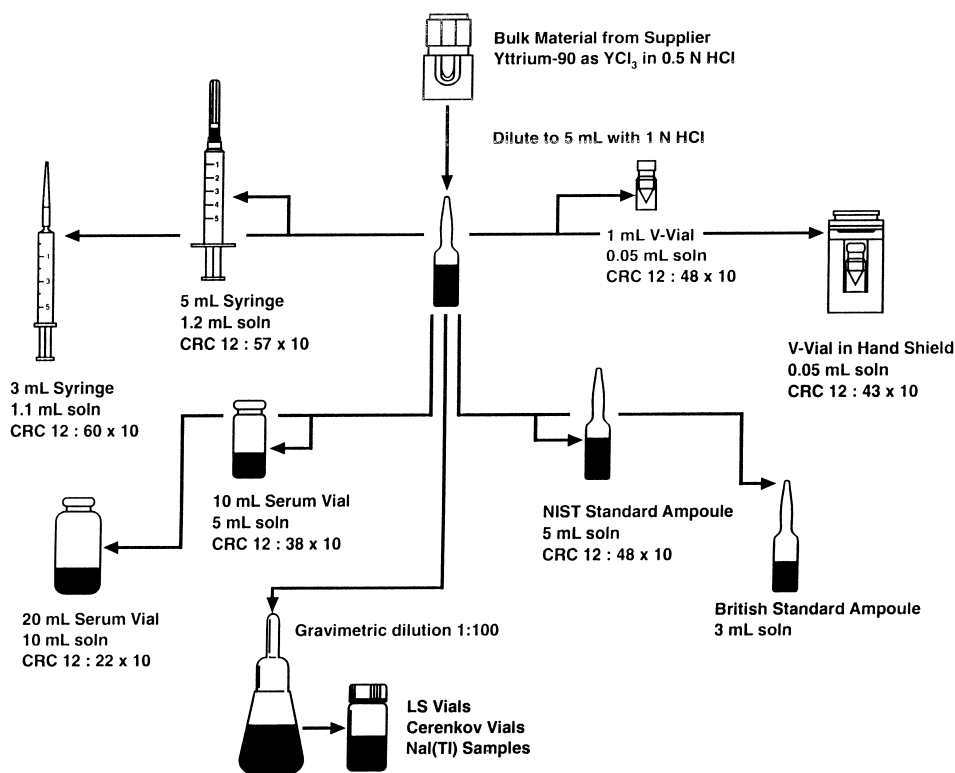


Fig. 3. Typical dilution scheme for preparing counting sources and standards of  $^{90}\text{Y}$ . The relevant Capintec dose calibrator settings for the different source geometries are given after the “CRC 12” symbol.

A typical dilution and counting source preparation schema is shown in Fig. 3. Material received from the suppliers as no-carrier-added  $^{90}\text{Y}$  in dilute hydrochloric acid is checked for photon-emitting impurities with germanium spectrometers and is then used to quantitatively prepare GBq-level samples for radionuclide calibrators and  $\text{kBq} \cdot \text{g}^{-1}$  activity concentration solutions for scintillation measurements. The working, diluted solution for the lower-level measurements is standardized by the CIEMAT/NIST method of liquid-scintillation efficiency tracing with  $^3\text{H}$ . To do this, two series of LS vials are prepared (one for tritium and one for  $^{90}\text{Y}$ ) containing 10 mL of a commercially prepared scintillator such as PCS (Amersham), UltimaGold (Packard), or ReadySafe (Beckman). Samples are gravimetrically deposited in the scintillation vials, and each series is serially quenched by the addition of 0–250  $\mu\text{L}$  chloroform. LS spectra obtained for  $^{90}\text{Y}$  using the two NIST LS spectrometers are shown in Fig. 4a and 4b.

We have observed that the  $^{90}\text{Y}$  LS counting efficiency is not strongly dependent on either quenching or sample volume. The quenching effect is negligible even for 250  $\mu\text{L}$  of chloroform. For example, using 10 mL PCS scintillator, the unquenched efficiency for  $^{90}\text{Y}$  in a Beckman LS 7800 was 0.9975, while for a sample quenched with 1.5 mL of chloroform, the efficiency was 0.977. Likewise, there is a nearly negligible volume dependence for scintillator volumes between 1 and 20 mL. These high counting efficiencies stem from the fact that approximately  $10^4$  photons are produced

in each  $^{90}\text{Y}$   $\beta$ -particle decay. Even allowing for substantial inefficiencies in light transmission through scintillators and interfaces, one still has a large enough signal to result in detection of the event.

The certificate for the  $^{90}\text{Y}$  SRM 4427H-B is shown in Fig. 5. A detailed listing of the uncertainties is shown on the reverse (Fig. 5b).

The National Institute of Standards and Technology has also been working with several of the pharmaceutical suppliers to calibrate different geometries for their radionuclide calibrators. These include: the standard 5-mL ampoule; 1 mL in plastic syringes; 50  $\mu\text{L}$  slurry of glass microspheres in “v-vials”; and two different-sized serum vials of capacity 10 and 20 mL, respectively. The dilution scheme in Fig. 3 shows the Capintec dose calibrator settings obtained for a Model CRC12 for several of these counting geometries. At various times, we have used both 1N HCl and normal saline for these measurements. For the most careful measurements, HCl with added yttrium carrier (20 ppm) was used. These data illustrate the importance of calibrating the radionuclide calibrator for the sample geometry actually used in practice. This may be accomplished by obtaining a standardized solution of the nuclide from a commercial or government standards laboratory. Alternatively, solutions may be standardized by liquid-scintillation counting using the methods described here, and those working solutions may be used to calibrate the radionuclide calibrators.

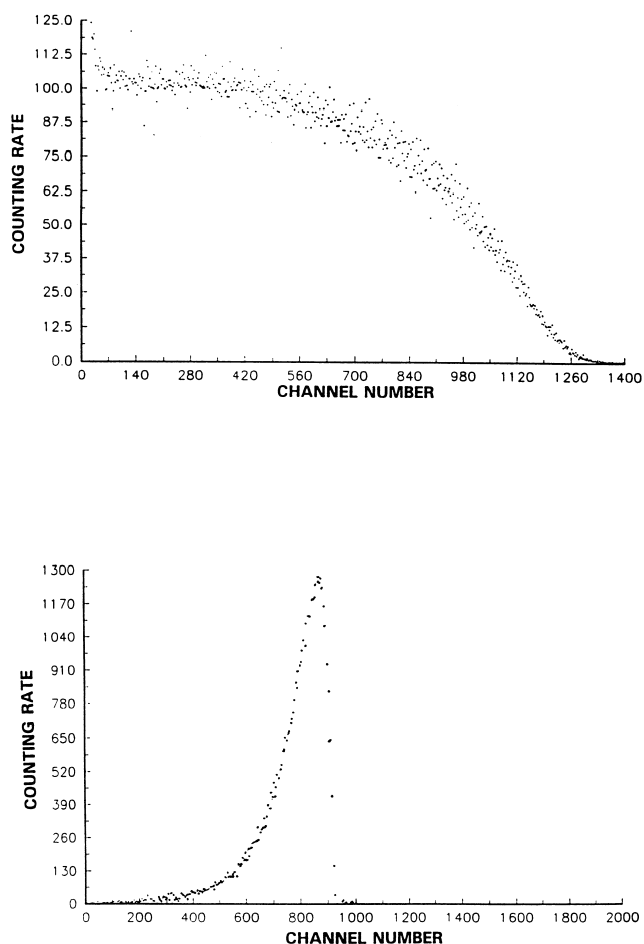


Fig. 4. Experimental LS spectra for  $^{90}\text{Y}$  obtained with the NIST Spectrometer Systems P (a) and B (b). The ordinate axis in both spectra are given, relatively, in terms of the number of counts (per unit time) per channel. In the first spectrum (a), the channel number of approximately 1400 roughly corresponds to the  $E_{\beta}(\text{max})$  given in Fig. 2b. The spectrum in (b) was obtained with logarithmic amplification such that the energy difference ( $c_1 - c_2$ ) between any two channels  $c_1$  and  $c_2$  is given by the proportionality:  $(c_1 - c_2) \propto \log_{10}(E_1/E_2)$ .

### Phosphorus-32

The National Institute of Standards and Technology has supplied SRMs of  $^{32}\text{P}$  for many years to North American radiopharmaceutical manufacturers. Many of these have been measured as “blinds” by the manufacturers as a part of their quality assurance programs. The results from the manufacturers over 2 decades are shown in Fig. 6. At present, the manufacturers can assay  $^{32}\text{P}$  within  $\pm 5\%$  with little difficulty. In the early years of the program, there were some discrepant results (of the order of 10% lower than the NIST value). These resulted from losses of the material in making dilutions. Methods developed at NIST for diluting standard solutions and LS counting have been transferred to the manufacturers.

The National Institute of Standards and Technology has also recently developed a chemical digestion and radionuclidic assay method for TiNi-encapsulated  $^{32}\text{P}$  intravascular brachytherapy sources. The  $^{32}\text{P}$  activity determination for a

NeoCardia source was obtained from a cut-off 35-mm-long section at the end of the source which contained the active 27-mm seed portion. The assay was based on a chemical digestion of the TiNi-encapsulated seed, followed by LS standardization (with the CIEMAT/NIST method) of a resulting solution that had a well-known, gravimetrically determined dilution.

For the digestion, the seed was initially immersed in a small-volume (nominal 10-mL) bath of a dilute nitric acid solution ( $1.5 \text{ mol} \cdot \text{L}^{-1} \text{ HNO}_3$ ) having a large excess of inactive phosphate carrier ions ( $240 \mu\text{g PO}_4^{-3}/\text{g}$  of solution). The solution and seed were contained within a conventional 22-mL, high-density polyethylene LS vial (which could be used for later direct LS evaluations of any residual activity). The TiNi jacket was subsequently dissolved by adding a few tenths of a milliliter of concentrated hydrofluoric acid (nominal  $30 \text{ mol} \cdot \text{L}^{-1} \text{ HF}$ ) to the bath. The dissolution of the relatively chemically impervious jacket required use of a strong nonoxidizing acid such as HF, but it could not be directly used because of the possibility of losing  $^{32}\text{P}$  by the formation and release of phosphine ( $\text{PH}_3$ ). Hence, the  $\text{HNO}_3/\text{PO}_4^{-}$  bath was used to ensure retention of the  $^{32}\text{P}$  in solution. Following removal of excess HF, the  $^{32}\text{P}$  was brought into solution by exchange with the  $\text{HNO}_3/\text{PO}_4^{-}$  bath by a sequence of carefully controlled quantitative solution transfers and rinses that were performed over about 8 days with periodic ultrasonic agitation. All of the transfers and rinses were added to a large-volume (nominal 500-mL), very dilute phosphoric acid ( $0.01 \text{ mol} \cdot \text{L}^{-1} \text{ H}_3\text{PO}_4$ ) master solution whose total dilution mass was gravimetrically determined. Each of the individual steps of the chemical procedure was independently evaluated for possible  $^{32}\text{P}$  losses by performing tracing experiments with known  $^{32}\text{P}$  solutions. Residual activities in the dissolution vial and transfer pycnometer were evaluated by LS spectrometry. A 7-mm length of the originally submitted source, adjacent to the active seed portion, was also assayed by LS spectrometry for any contained  $^{32}\text{P}$  activity.

The total  $^{32}\text{P}$  (and  $^{33}\text{P}$  impurity) activity content of the seed was obtained from LS measurements with two sets of counting-source cocktails that were prepared with gravimetrically determined aliquants of the master solution. The respective  $^{32}\text{P}$  and  $^{33}\text{P}$  LS detection efficiencies were determined by efficiency tracing with composition-matched  $^3\text{H}$ -standard cocktails using the CIEMAT/NIST methodology described above. The two components were resolved by following the counting rates of the LS sources as a function of time and fitting the background-corrected net rate to a function of the sum of the two  $^{32}\text{P}$  and  $^{33}\text{P}$  exponentially decaying terms to extract (as fitted parameters) the  $^{32}\text{P}$  and  $^{33}\text{P}$  activities. The LS measurements were performed over an approximate 18-day period, which was more than adequate to precisely resolve the two components (24). Impurity analyses for possible  $\gamma$ -ray-emitting impurities (e.g., the



# National Institute of Standards & Technology

## Certificate

### Standard Reference Material 4427H-B Radioactivity Standard

Radionuclide	Yttrium-90
Source identification	4427H-B
Source description	Liquid in NIST borosilicate-glass ampoule [1]*
Solution composition	Approximately 305 $\mu\text{g}$ yttrium, as chloride, per gram of approximately 1 $\text{mol}\cdot\text{L}^{-1}$ hydrochloric acid [2]
Mass	grams
Radioactivity concentration	$5.592 \times 10^7 \text{ Bq}\cdot\text{g}^{-1}$
Reference time	1200 EST October 22, 1996
Relative expanded uncertainty	0.79 percent [3]
Photon-emitting impurities	None observed [4]
Half life	$64.10 \pm 0.08$ hours [5]
Measuring instrument	NIST $4\pi\beta$ liquid-scintillation counting systems using NIST/CIEMAT efficiency tracing technique

This Standard Reference Material was prepared in the Physics Laboratory, Ionizing Radiation Division, Radioactivity Group, J. M. Robin Hutchinson, Group Leader.

Gaithersburg, MD 20899  
January 1997

Thomas E. Gills, Chief  
Standard Reference Materials Program

\*Notes on back

Fig. 5. Certificate for  $^{90}\text{Y}$  SRM 4427H-B: (a) front; (b) back.

**NOTES**

- [1] Approximately five milliliters of solution. Ampoule specifications:

body diameter	$16.5 \pm 0.5$ mm
wall thickness	$0.60 \pm 0.04$ mm
barium content	less than 2.5 percent
lead oxide content	less than 0.02 percent
other heavy elements	trace quantities

- [2] Solution density  $1.015 \pm 0.002$  g•mL<sup>-1</sup> at 24.5 °C.

- [3] The uncertainty analysis methodology and nomenclature used for the reported uncertainties are based on uniform NIST guidelines and are compatible with those adopted by the principal international metrology standardization bodies [cf., B.N. Taylor and C.E. Kuyatt, *NIST Technical Note 1297* (1994)].

The relative **combined standard uncertainty**,  $u_c = 0.39$  percent, is the quadratic combination of the standard deviations (or standard deviations of the mean where appropriate), or approximations thereof, for the following component uncertainties:

a) liquid-scintillation (LS) measurement precision for ten replicate measurements on six samples with a single LS counter	0.05 percent
b) <sup>3</sup> H efficiency tracing calculations including extrapolations	0.02 percent
c) gravimetric measurements	0.05 percent
d) LS efficiency due to uncertainty in <sup>3</sup> H efficiency	0.002 percent
e) dilutions	0.10 percent
f) LS cocktail instability	0.10 percent
g) timer	0.10 percent
h) dead time	0.34 percent
i) between counter LS measurement precision	0.04 percent
j) half life	0.04 percent
k) <sup>90</sup> Sr impurity	0.01 percent

The **relative expanded uncertainty**,  $U = 0.79$  percent, is obtained by multiplying  $u_c$  by a coverage factor of  $k = 2$  and is assumed to provide an uncertainty interval of approximately 95 percent confidence.

- [4] Limits of detection, in terms of impurity gamma rays per Bq of <sup>90</sup>Y, are

0.0005 γ/s between 12 and 88 keV
0.0003 γ/s between 96 and 507 keV
0.0001 γ/s between 515 and 1456.8 keV
0.00005 γ/s between 1464.8 and 3200 keV .

At the time of certification the ratio of the emission rate of β-emitting impurity radionuclides, including <sup>90</sup>Sr, to that of <sup>90</sup>Y was  $(4 \pm 1) \times 10^{-6}$ .

- [5] Evaluated Nuclear Structure Data File (ENSDF), October 1996.

Fig. 5. (Cont'd)



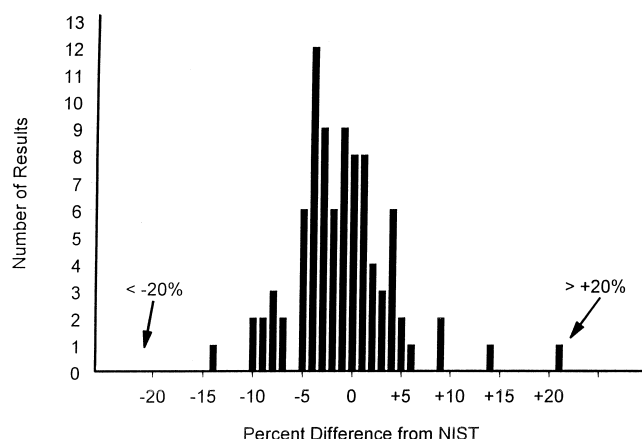


Fig. 6. Results for  $^{32}\text{P}$  blind measurements made by North American radiopharmaceutical manufacturers as part of the NEI/NIST Radiopharmaceutical Measurement Assurance Program from the period June 1975 to December 1996.

detected  $^{124}\text{Sb}$ ) were also performed on the original undigested seed by high-resolution HPGe  $\gamma$ -ray spectrometry.

#### Rhenium-188

A third nuclide that is a candidate for use in intravascular brachytherapy is  $^{188}\text{Re}$ , a 17.01-h-half-life  $\beta$ -particle emitter that has an end-point energy close to that of  $^{90}\text{Y}$ . The  $^{188}\text{Re}$  solution can be obtained by milking a generator loaded with the 69.4-day parent nuclide  $^{188}\text{W}$ . The nuclear decay scheme for the parent–daughter pair is shown in Fig. 7. NIST has developed a calibration method for  $^{188}\text{Re}$  in collaboration with F. F. Knapp, Jr., and S. Mirzadeh, at ORNL. ORNL produces a generator which can be eluted with normal saline (0.9% NaCl). The chemical form of the Re is sodium perrhenate. Solutions from ORNL were standardized for activity by the CIEMAT/NIST method as described previously. The LS spectra are given elsewhere (25). They look much like those for  $^{90}\text{Y}$  given in Fig. 5. The calculated counting efficiency for  $^{188}\text{Re}$  for NIST Spectrometry System B was 99.6%. Impurities detected in the  $^{188}\text{Re}$

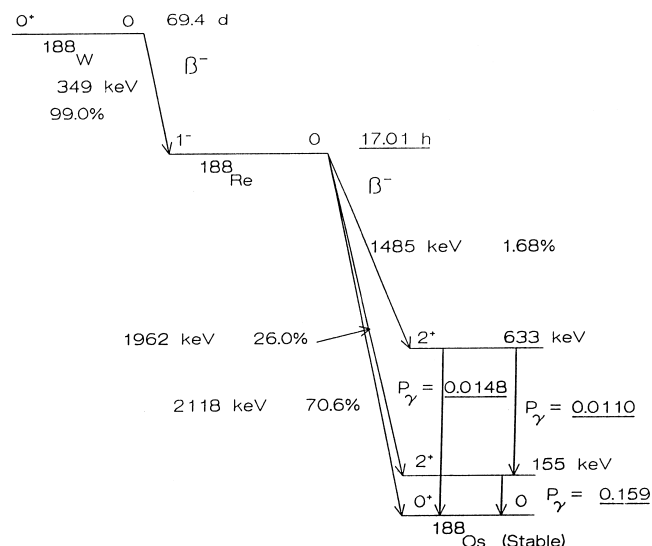


Fig. 7. Decay scheme for  $^{188}\text{W}/^{188}\text{Re}$  from Coursey *et al.* (1990). The data underlined were measured at NIST.

eluant included  $^{188}\text{W}$  (10–30 ppm) and lesser amounts of  $^{134}\text{Cs}$ ,  $^{192}\text{Ir}$ ,  $^{110}\text{mAg}$ , and  $^{191}\text{Os}$ . The NIST-measured half life for  $^{188}\text{Re}$  was  $17.01 \pm 0.01$  h (1 relative standard deviation).

## CONCLUSIONS

High-energy  $\beta$ -particle emitters, which are being widely used in therapeutic nuclear medicine and are being evaluated for use in intravascular brachytherapy, may be accurately standardized by high-efficiency liquid-scintillation counting. Solutions standardized by this technique may then be used to establish the counting efficiencies for various practical sample geometries for dose calibrators and NaI(Tl)  $\gamma$  counters. These very practical instruments are exceedingly useful for relative measurements, but standards are needed to first calibrate the instrument. Unacceptably large errors (>50%) may be encountered if one compares sources of different geometries in simple dose calibrator-type well detectors.

## REFERENCES

- Adelstein, S. J.; Kassis, A. Radiobiologic Implications of the microscopic distribution of energy from radionuclides. *Nucl. Med. Biol.* 14:165; 1987.
- Volkert, W. A.; Goeckeler, W. F.; Ehrhardt, G. J.; Ketring, A. R. Therapeutic radionuclides: Production and decay property considerations. *J. Nucl. Med.* 32:174; 1991.
- USNRC. Information Notice 94-70: Issues associated with the use of strontium-89 and other beta emitting radiopharmaceuticals. Washington, DC, 29 September 1994.
- USNRC. Code of Federal Regulations 10 CFR 35.53: Measurement of dosages of unsealed by-product material, 1997.
- Capintec Instruments. Operator's manual for dose calibrators. Ramsey, NJ: Capintec Instruments, 1997.
- Soares, C. G.; Halpern, D. G.; Wang, C.-K. *Med. Phys.* (to appear).
- Coursey, B. M.; Goodman, L.; Hoppes, D. D.; Loevinger, R.; McLaughlin, W. L.; Soares, C. G.; Weaver, J. T. Needs for brachytherapy source calibrations in the United States. *Nucl. Instrum. Meth. A* A312:246; 1992.
- Woods, M. J.; Munster, A. S.; Sephton, J. P.; Lucas, S. E. M.; Paton Walsh, C. Calibration of the NPL secondary standard radionuclide calibrator for  $^{32}\text{P}$ ,  $^{89}\text{Sr}$ , and  $^{90}\text{Y}$ . *Nucl. Instrum. Meth. A* 369:698; 1996.
- Golas, D. B. USCEA/NIST measurement assurance programs for the radiopharmaceutical and nuclear power industries. In: *Proceedings of the Workshop on Measurement Quality Assurance for Ionizing Radiation*, 16–18 March 1993.
- Golas, D. B. NEI Radiopharmaceutical Standard Reference Materials and the NEI/NIST Radiopharmaceutical Measurement Assurance Program. *Appl. Radiat. Isot.* (to appear).
- Grau Malonda, A.; Garcia-Torano, E. Evaluation of counting

- efficiency in liquid scintillation counting of pure beta-ray emitters. *Int. J. Appl. Radiat. Isot.* 33:249; 1982.
12. Coursey, B. M.; Mann, W. B.; Grau Malonda, A.; Garcia-Torano, E.; Los Arcos, J. M.; Gibson, J. A. B.; Reher, D. Standardization of carbon-14 by  $4\pi\beta$  liquid-scintillation efficiency tracing with hydrogen-3. *Int. J. Appl. Radiat. Isotopes* 37:403; 1986.
  13. Garcia-Torano, E.; Grau Malonda, A. EFFY: A new program to calculate the counting efficiency of beta particles in liquid scintillation. *Comput. Phys. Commun.* 36:307; 1985.
  14. Grau Malonda, A.; Garcia-Torano, E.; Los Arcos, J. M. Liquid scintillation counting efficiency as a function of the figure of merit for pure beta-particle emitters. *Int. J. Appl. Radiat. Isot.* 36:157; 1985.
  15. Collé, R. Cocktail mismatch effects in  $4\pi\beta$  liquid scintillation spectrometry: Implications based on the systematics of  $^3\text{H}$  detection efficiency and quench indicating parameter variations with total cocktail mass (volume) and  $\text{H}_2\text{O}$  fraction. *Appl. Radiat. Isot.* (to appear).
  16. Collé, R.; Zimmerman, B. E. A compendium on the NIST radionuclide assays of the massic activity of  $^{63}\text{Ni}$  and  $^{55}\text{Fe}$  solutions used for an international intercomparison of liquid scintillation spectrometry techniques. *NIST J. Res.* 102:523; 1997.
  17. Schima, F. J. Gamma-ray emission probability of the 909.12 keV transition for  $^{89}\text{Sr}$ . *Appl. Radiat. Isot.* (to appear).
  18. Unterweger, M. P.; Hoppes, D. D.; Schima, F. J. New and revised half-life measurement results. *Nucl. Instrum. Meth.* A312:349; 1992.
  19. Coursey, B. M.; Hoppes, D. D.; Schima, F. J. Determination of the photon emission rates of the NBS Long-Lived Mixed-Radionuclide Standard. *Nucl. Instrum. Meth.* 193:1; 1982.
  20. Carrasquillo, J. A.; Kramer, B.; Fleisher, T.; Perentesis, P.; Boland, C. J.; Foss, F.; Rotman, M.; Reynolds, J. C.; Mulshine, J. L.; Camera, L.; Frincke, J.; Lollo, C.; Neuman, R. D.; Larson, S. M.; Raubitschek, A.  $^{111}\text{In}$  versus  $^{90}\text{Y}$ , T101 biodistribution in patients with hematopoietic malignancies. *J. Nucl. Med.* 32:970; 1991.
  21. Houle, S.; Tsui-Chun, K. Y.; Shepherd, F. A.; Rotstein, L. E.; Sniderman, K. W.; Theis, E.; Cawthorn, R. W.; Richmond-Cox, K. Hepatocellular carcinoma: Pilot trial of treatment with  $^{90}\text{Y}$  microspheres. *Radiology* 172:857; 1989.
  22. Wike, J. S.; Guyer, C. E.; Ramey, D. W.; Phillips, B. P. Chemistry for commercial scale production of yttrium-90 for medical research. *Appl. Radiat. Isot.* 41:861; 1990.
  23. Coursey, B. M.; Calhoun, J. M.; Cessna, J. T. Radioassays of yttrium-90 for use in nuclear medicine. *Nucl. Med. Biol.* 20:693; 1993.
  24. Collé, R. A simple transform to linearize and resolve two-component decay data: Illustration of its use and efficiency for assaying  $^{32}\text{P}/^{33}\text{P}$  mixtures. *Radioact. Radiochem.* (to appear).
  25. Coursey, B. M.; Calhoun, J. M.; Cessna, J.; Hoppes, D. D.; Golas, D. B.; Callahan, A. P.; Mirzadeh, S.; Knapp, F. F., Jr. Assay of the eluent from the alumina-based tungsten-188-rhenium-188 generator. *Radioact. Radiochem.* 4:38; 1990.