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AIF-NBS RADIOACTIVITY MEASUREMENTS ASSURANCE PROGRAM FOR THE RADIOPHARMACEUTICAL INDUSTRY

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The National Bureau of Standards supervises and administers on behalf of the Atomic Industrial Forum (AIF) a radioactivity measurements technology quality assurance program for the radiopharmaceutical industry. The program provides for a monthly distribution of both millicurie- and microcurie-level Standard Reference Materials to each of eight participating commercial radiopharmaceutical manufacturers. A number of the standards are distributed as "blind" samples to establish traceability to the national radioactivity measurements system. In addition to identifying measurement discrepancies, assistance is provided to the participants in eliminating the sources of difficulties, and in correcting errors in their measurement techniques. In this report, results for the "blind"-sample traceability exercises are given, and a discussion of identified sources of measurement errors and recommendations are also presented.

(Assurance; measurement; radioactivity; radiopharmaceutical; standards; traceability)

In August of 1973 at a symposium quite similar to the present one, Seidel and Brantley[1] reviewed a number of serious questions and problems which faced commercial radionuclide manufacturers as related to the needs for radioactivity standards. Some of the basic difficulties they cited were: 1) the lack of direct standards for approximately 75% of the more than 100 radionuclides produced by the industry at that time; 2) the sometimes inconvenient physical form or activity levels of the available standards; and 3) the failure to have industry-wide adopted decay-scheme data upon which to base derived standard instrument calibrations in the absence of direct calibrations based on national standards. Although the American National Standards Institute (ANSI) Quality Assurance Program which was described at that time[1] (the current status of which will be the subject of the next paper[2]) addresses a number of these difficulties, it is concerned, however, only with microcurie-level measurements and its participants include hospitals, nuclear-power plants and industry. The Atomic Industrial Forum (AIF) and the National Bureau of Standards (NBS) therefore entered into an agreement on a research associate program 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. Eight radiopharmaceutical suppliers are participating in this program. Concurrently, on the authority of an interagency agreement, NBS is providing the Food and Drug Administration (FDA) with services similar to those being given the AIF participants. These participants are listed in Table 1. The purpose of the program is to insure 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.

The major effort of the program consists of a monthly distribution of both millicurie- and microcurie-level Standard Reference Materials (SRM) to each of the participants. With the exception of a future ^{133}Xe gaseous standard, all of the SRMs are solution standards contained in "5-ml" flame-sealed borosilicate glass ampoules. Those which have been already issued under the program are listed in Table 2. The choice of radionuclides, their activity levels as well as an order of priority for them are selected by a steering committee representing each of the AIF participants. Obviously these selections must be made in cooperation with NBS, taking into consideration the compatibility

Table 1

Participants[a]

Standards Program for the Radiopharmaceutical Industry

Food and Drug Administration
Bureau of Drugs
Division of Drug Chemistry
Washington, D.C.

Atomic Industrial Forum Participants

Atomic Energy of Canada, Ltd.
Ottawa, Canada

General Electric Co.
Pleasanton, California

Mallinckrodt Nuclear
St. Louis, Missouri

Medi-Physics, Inc.
Emeryville, California

New England Nuclear
North Billerica, Massachusetts

E.R. Squibb & Sons, Inc.
New Brunswick, New Jersey

Union Carbide Corp.
Tuxedo, New York

Amersham/Searle Corp.[b]
Arlington Heights, Illinois

[a]The order in which participants are listed in this table does not correspond to the order in which the results are listed in Table 3.

[b]Participation terminated November, 1975.

with their scheduling capabilities and existing standard developments. This does however provide a viable mechanism in which the radiopharmaceutical industry can direct requests to NBS to establish standards for those radionuclides which are of prime interest and major concern to them. As seen in Table 2, the trend is certainly toward shorter-lived radionuclides, reflecting the needs of the nuclear-medicine community which is served by the radiopharmaceutical industry. Although the trend is "healthy," particularly for patients, it does in itself present difficulties in the preparation and distribution of the standards. The millicurie-level standards made available by this program, compared with the typically microcurie-level standards normally handled at NBS, are of greater convenience and direct value for instrument calibrations at activity levels more closely matching those found in the manufacturing process.

A second major aspect of the program attempts to satisfy the increasing demands of both consumers and regulatory agencies to demonstrate "traceability" to the national radioactivity measurements system, embodied in the NBS. Satisfaction of this requirement also simultaneously fulfills the manufacturers' goal of achieving an industry-wide uniformity in measurements. Although the monthly distribution of standards serves to insure a regular supply of radioactivity standards to calibrate measuring equipment, the mere use of them does not constitute traceability. Despite the term's increased usage lately, a clear

Table 2

Standard Reference Materials[a]

Issued Under the Standards Program for the Radiopharmaceutical Industry

Radio-Nuclide	Half-Life (Days)	SRM NO.	Issued	Approx. Activity (mCi)
^{51}Cr	27.7	4400H 4400L	April,1975	50. 0.4
^{131}I	8.04	4401H 4401L	May, 1975	20. 0.1
^{113}Sn	115.	4402H 4402L	June, 1975	20. 0.1
^{125}I	60.1	4407H 4407L	July, 1975	20. 0.1
^{57}Co	271.	4408H 4408L	Aug., 1975	10. 0.2
^{85}Sr	64.9	4403H 4403L	Sept.,1975	30. 0.1
^{75}Se	120.	4409H 4409L	Oct., 1975	10. 0.1
^{32}P	14.3	4406H 4406L	Nov., 1975	40. 0.2
^{198}Au	2.70	4405H 4405L	Dec., 1975	80. 0.8
^{59}Fe	44.5	4411H 4411L	Jan., 1976	30. 0.2
^{99m}Tc	0.25	4410	Feb., 1976	20.
^{99}Mo	2.75	4412H 4412L	March,1976	25. 0.1

Future SRM's to be issued are: ^{133}Xe(5.3d); ^{197}Hg(2.7d); ^{123}I(0.55d); ^{201}Tl(3.0d); ^{67}Ga(3.3d) and ^{111}In(2.8d).

[a]Contained in 5-ml flame-sealed borosilicate glass ampoules.

understanding of exactly what constitutes such traceability does not appear to be universal. A working definition has been given as "competence that can be periodically demonstrated."[3] This can be accomplished by participation in a round robin distribution of calibrated, but "blind" samples of unknown (to the participant) quantity for assay by the participant. At the present time, approximately one-third of the monthly distributed SRMs for this program are issued as "blinds." These are selected by the steering committee with the understanding that participants may take substitutes and exempt themselves from the traceability exercises involving those radionuclides which they do not market. Upon receipt of their result for the "blind," the participant receives a Certificate for the SRM. A detailed reporting form and questionnaire issued with the "blind" aids NBS in helping to identify errors or measurement discrepancies. To satisfy a request by the participants of this program for proof of demonstrated traceability, each participant in the "blind" round robin will receive a Certificate of Traceability to the National Measurements System. Participation in the "blind" round robins, although voluntary for the most part, is really of great advantage to the manufacturers in not only continually monitoring their measurements performance (i.e. assurance) but also documenting this performance (i.e. traceability). The NBS encourages a greater participation in this aspect of the program and would like to see the program gradually proceed from a distribution of standards to a distribution of "blinds."

The results for the "blind" round robin distributions for 1975 are summarized in Table 3. They include measurements on both the H-level (multi-millicurie) and L-level (multi-microcurie) standards for ^{113}Sn, ^{125}I, ^{85}Sr and ^{32}P as well as a few additional

Table 3

Standards Program for the Radiopharmaceutical Industry

Results for the Standard Reference Material "Blinds"

Values Reported are X/NBS

^{113}Sn		^{125}I		^{85}Sr		^{32}P		Others*	
4402H	4402L	4407H	4407L	4403H	4403L	4406H	4406L	H	L
0.8978[a]	0.9822[a] 0.9980[a]	0.9416	0.8832 0.9102	0.8717	0.8846	0.9015 0.9371 0.9609	0.9292 1.0185	0.8517[e]	0.8633[e]
0.9340	0.9628	0.9380 1.0124	0.9581 1.0481	0.9520	0.9451	0.9514 0.9549 0.9786	0.9612 0.9987	0.9998	1.0768 1.0626
0.9678	0.9638	0.9881	1.0245	0.9813 1.0018	0.9706 0.9905	0.9727	0.8985[d]	1.0006	1.0056
0.9826	0.9669	0.9886	0.9873	1.0052	1.0226	0.9905	0.9686	1.0261	0.9224[f]
0.9844	0.9728	1.0105	1.0037	1.0182	1.0579	1.0024	0.9877		
0.9882[b]	1.0030	1.0805	1.0599	1.0182	1.0080 1.0280	1.0064	0.3410		
		1.1805	c	1.0053 1.0562	0.9774 1.0733	1.1363	1.0482		

*One each for ^{57}Co(4408H and 4408L) and ^{75}Se(4409H and 4409L) and two each for ^{198}Au(4405H and 4405L).

[a]Revised values after increasing by 54.%

[b]Revised value after increasing by 0.8%.

[c]Not measured.

[d]Revised value after decreasing by 491.%.

[e]On retest with M-level activity SRM, X/NBS=1.0282

[f]Revised value after decreasing by 279.%.

The results in each column of this table are listed in order of increasing values of X/NBS (for the H-level SRM) and does not correspond to the order in which the participants are listed in Table 1.

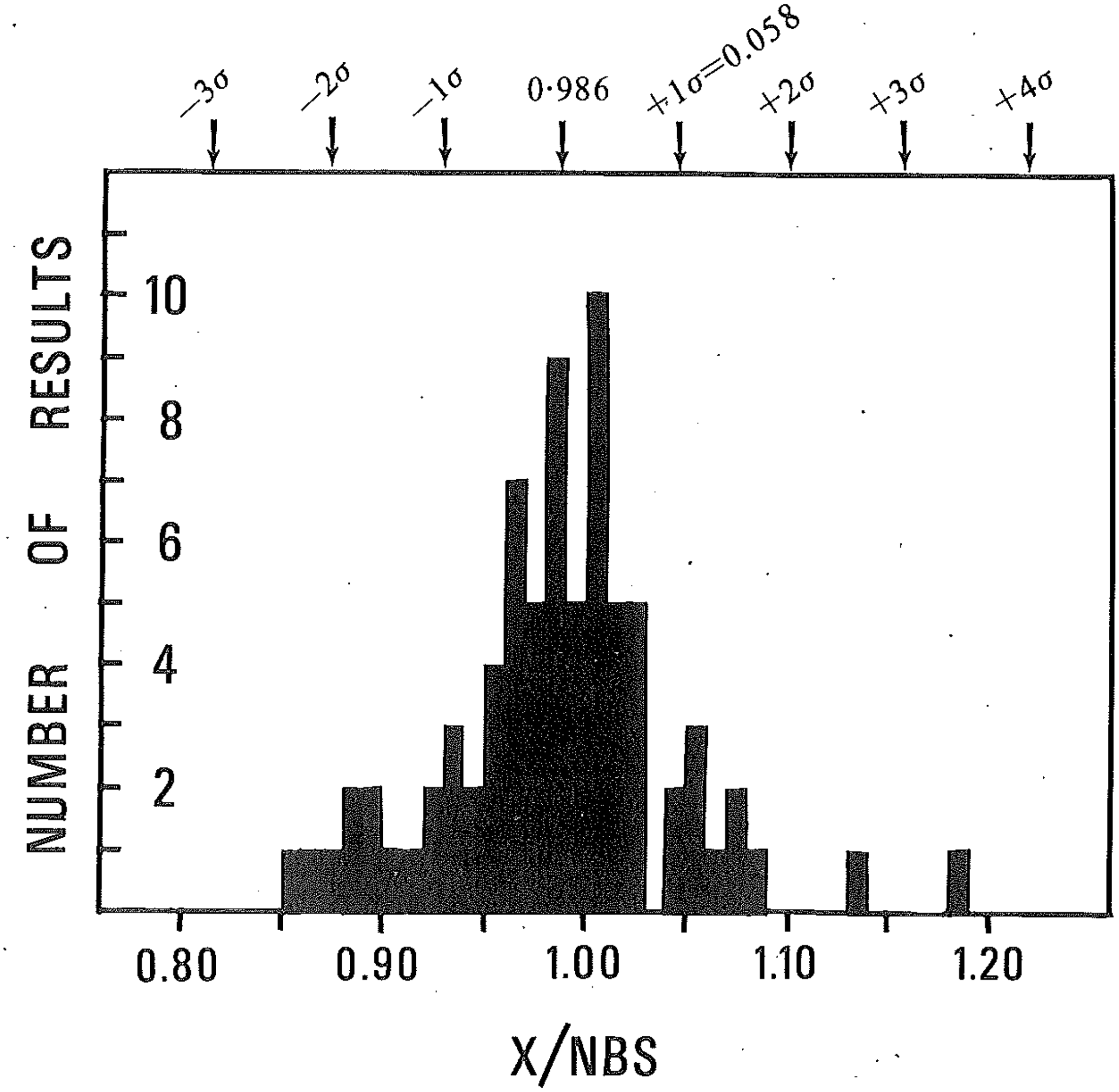

FIGURE 1 Distribution of reported results (data of Table 3 using revised values when applicable) for the 1975 SRM "blinds."

One outlier not plotted: ^{32}P, 4406L (X/NBS = 0.3410).

results on ^{57}Co, ^{75}Se and ^{198}Au. In most cases, the reported values were activity per unit weight, and after correcting for decay were divided by the NBS values to obtain X/NBS. There is a total of 78 reported values on 61 blind samples. Several participants reported the results of measurements by different methods on the same sample. Close inspection of Table 3 indicates that there are no major systematic trends. With the possible exception of ^{113}Sn, where the reported values tend to be slightly low, all the radionuclides appear to have been measured about equally well. Similarly, there are no major differences between the measurements of the H-level and L-level samples. Although not provided in the table, there was also no apparent evidence that one assay method or instrument was superior to another. In general, the results indicate a fairly satisfactory agreement with NBS values. There are, however, a number of mistakes in data handling which should be distinguished from systematic or random errors in the measurements. These mistakes included a 54% error because of the incorrect use of a branching ratio (gamma-ray abundance), a 279% error due to a miscalculated decay correction, and a 491% reporting error resulting from the failure to distinguish between total activity and activity per unit weight. Oftentimes these can be detected directly from the questionnaire responses, when sufficient information is provided, and can be revised (as has been done in Table 3) to reflect the true measurement capability. Unfortunately these cases are not that rare, occurring nearly 10% of the time. A distribution of the results (data of Table 3 using the revised values when applicable) is provided in Figure 1. As can be seen, the reported values are distributed about the mean value of X/NBS = 0.986 with a standard deviation of 0.058. The values on the wings of the histogram, which are of the order of 10 - 20% deviation from the NBS values, are usually attributable to either unaccountable systematic errors such as in dilution or dispensing, or systematic errors such as in decay corrections, detection efficiency and instrument calibration factors which can be adjusted after receiving the NBS value and Certificate. A number of participants have been aided in identifying sources of discrepancies in their measurements and have been provided with suggestions for eliminating them and/or with information for improving their procedures. A good example of this is shown in the first values listed in the last column of Table 3 where measurements on both the H-level and L-level samples showed an approximately 15% discrepancy. On pursuing it with the participant, a long-existing systematic error in an instrument calibration factor (arising from an incorrect decay correction in a reference source) was discovered. On adjusting the calibration after receiving the NBS value, the participant was "retested" with an intermediate-level activity (M-level) sample of the same radionuclide. The reported value on this retest was within 3% of the NBS value.

I have tried to give an overview of the entire AIF-NBS Radioactivity Measurements Assurance Program for the Radiopharmaceutical Industry and hope you now have a better understanding of its objectives and progress. After spending considerable time discussing errors and discrepancies, I would, in conclusion, like to emphasize that the radioactivity measurements made by the radiopharmaceutical industry are now, after eliminating data-handling mistakes, generally within ±20% of the NBS values. The program has been successful in meeting many of the needs of the radiopharmaceutical industry and I believe we all look forward to its continued success.

Acknowledgement

It is a pleasure to acknowledge the extensive efforts of Dr. W. B. Mann, Miss L. M. Cavallo, Mr. R. W. Medlock and the many other personnel of the Radioactivity Section at NBS who have contributed to the success of this program.

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