QUALITY CONTROL OF RADIOACTIVE PRODUCTS FOR PATIENT ADMINISTRATION AT THE NATIONAL INSTITUTES OF HEALTH.

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SUMMARY

This paper describes the quality control procedures for radioactive materials destined for patient use at the National Institutes of Health. The Radiopharmaceutical Section is responsible for attesting to pharmaceutical quality, while the Radiation Safety Section performs per-unit-volume assays and radionuclidic purity checks on these materials. Types and examples of product error are presented as well as statistical data on essay discrepancies. The frequency of error during the past ten years indicates the necessity of continued quality control testing of all radioactive materials, regardless of source of supply and prior administration to patients.

INTRODUCTION

This paper presents quality control data on radioactive materials used in patients for diagnostic, therapeutic and research studies at the National Institutes of Health (NIH). For the most part, these are commercially supplied radiopharmaceuticals, i.e., materials which have been certified as to their

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sterility, apyrogenicity, and to their medicinal and pharmaceutical qualities. However, some radioactive materials which are radiochemical grade upon receipt or are in-house labeled are formulated into radiopharmaceutical grade prior to use. Regardless of the source of the material, the U. S. Atomic Energy Commission's (AEC) criteria for licensure of medical programs (1) requires that the pharmaceutical quality and assay of byproduct material be established before its use in humans. At NIH, the Radiopharmaceutical Section is responsible for attesting to pharmaceutical quality, while the Radiation Safety Section is responsible for the assay and radionuclidic purity verification of these radioactive materials.

PHARMACEUTICAL QUALITY

The quality control procedures routinely performed by the Radiopharmaceutical Section include: label check; visual inspection; determination of radiochemical purity, pH, particle size, osmotic pressure; sterility and pyrogen testing. One or more of these test procedures is performed as indicated on each product.

The label check ascertains correct receipt of ordered material. The ideal label contains the following information: name of drug, name and address of manufacturer, lot number, volume, radioactivity present as of a given time and date, quantity of tagged material or specific activity, quantification of all other ingredients within the formulation, expiration date (if applicable), and proper storage information. Additional quality control test data should be included in a package insert. As an example of a labeling error, the label on a shipment of sodium iodide-^{131}I capsules read 49 uCi/capsule as of noon, June 21. Our assay showed 670 uCi/capsule for the same time and date. This thirteen-fold error resulted from an error in the month of calibration, where the supplier intended July rather than June.

Material should routinely be inspected visually to assure the correct color and clarity as well as the absence of particulate matter or a precipitate within

a solution, particularly if the material is to be injected. Care should be taken in viewing solutions of gamma or high energy beta emitters. A quick, scrutinizing visual examination can be done through shielding material, e.g., lead plate glass in the case of gamma emiters; plexiglass, for high energy beta emitters.

Radiochemical purity of a product can be determined using paper or thin layer chromatography, samples of which are analyzed on a radiochromatogram scanner. Figure 1 shows a good scan of thymidine-^{3}H. Note that the R_f of

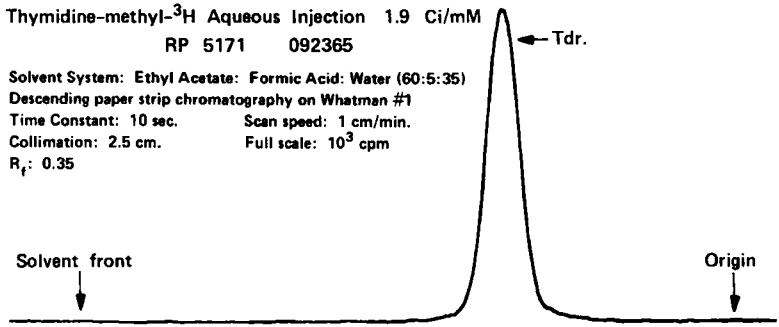

Figure 1: "Good" scan of thymidine-methyl-^{3}H.

thymidine is 0.35 and that the specific activity is 1.9 Ci/mmole. Figure 2 shows another sample of thymidine-^{3}H run in the same chromatography system. In this case the specific activity is 12.3 Ci/mmole or approximately 6.5 times that of the sample in Figure 1. The scan in Figure 2 shows evidence of radiolysis breakdown products, thymidine glycol with R_f = 0.12 and thymidine with R_f = 0.50.

Chemical purity must be determined in the use of a generator system. In the most frequently used generator system, 67 hour ^{99}Mo is adsorbed onto an alumina column. This nuclide decays by beta and gamma emission to 6 hour ^{99}Tc^{m},

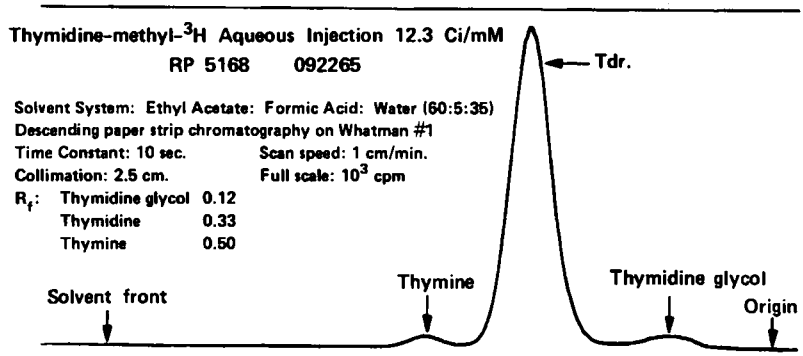

Figure 2: "Bad" scan of thymidine-methyl-^{3}H.

which can be selectively removed using normal saline. $^{99}Tc^{m}$ then decays by beta emission to $2.1x10^{5}$ year ^{99}Tc. Breakthrough of the parent, ^{99}Mo, can be determined qualitatively in a spot test using potassium ethyl xanthate in acid solution (2). If molybdenum is present, a complex compound is formed which varies in color from pink to deep red depending on concentration. The sensitivity of this test is 2 ug molybdenum/ml. The AEC limits the concentration and activity of the contaminant, ^{99}Mo, which may be administered (3). In one unacceptable product we observed 61 uCi ^{99}Mo and 29 mCi $^{99}Tc^{m}$/ml at time of calibration.

Both qualitative and quantitative determinations of aluminum (2) can be made on generator eluates. While aluminum is non-toxic, its presence may indicate generator breakdown and it causes formation of a flocculent precipitate in the preparation of sulfur colloid-$^{99}Tc^{m}$.

The pH of a product can be quite important. For example, in the case of sodium chromate-^{51}Cr, the pH must be between 7.5 and 8.5 for the chromium to be hexavalent and label red blood cells. If the pH is outside this acceptable range, the chromium may be in a trivalent or complexed state which does not bind red

blood cells and further testing is indicated. The U. S. Pharmacopeia gives a precipitation method for determination of radiochemical purity (4).

In colloidal materials and macroaggregate suspensions, particle size determines the localization and distribution of a drug. Particle size is measured by placing an aliquot on a hemocytometer under a microscope with 10-20 power objective. Particles larger than two microns can be visualized. In the case of colloids, no particles should be visible. An alternate method of particle size determination is a bioassay technique in which the material is injected into animals and the ratio of lung/liver uptake is measured.

Products such as human serum albumin labeled with ^{131}I or $^{99}Tc^{m}$ are used for cisternography and are injected intrathecally, i.e., into the spinal column. The concentration of these solutions is important and must simulate normal cerebrospinal fluid. The osmometer, which measures freezing point depression, provides a simple but accurate method for the determination of concentration or osmotic pressure.

Sterilization of radiopharmaceutical products can be accomplished in one of two ways: using saturated steam under pressure at 121°C and 18 psi in an autoclave, or passing the material through a sterilizing filter, such as a disposable, polypropylene filter with a pore size of 0.22 or 0.45 microns. The second method of sterilization is used for products unable to withstand the physical conditions of autoclaving. Procedures for sterility testing have been established by the U. S. Pharmacopeia (5).

Pyrogens are fever-producing, heat-stable substances which result from contamination by bacteria, viruses, yeasts or molds. Viable or killed organisms or even their metabolic products can cause pyrogenic reactions. Thus, sterility does not indicate apyrogenicity nor does sterilization remove pyrogens. Procedures to test for the presence of pyrogens are specified by the U. S. Pharmacopeia (6).

ASSAY

Turning our attention now to assay methods and results, it should be noted that since the opening of the Clinical Center in 1953, more than 30,000 assays have been performed on 40 different radionuclides. The equipment used for radiopharmaceutical assays consists of the following counting systems: multichannel analyzers connected to external (Figure 3) and well-type 3"X3" NaI(Tℓ) crystals, a quartz fiber electroscope (Figure 4), and two liquid scintillation counters. Full details of calibration and assay procedures will be found in the article by Cliggett and Brown (7).

Incoming shipments are "gross assayed" to determine the radionuclide and the

Figure 3: A sample of 1 ml total volume is placed at a fixed, reproducible distance from an external 3"x3" NaI(Tℓ) crystal housed in a graded lead shield.

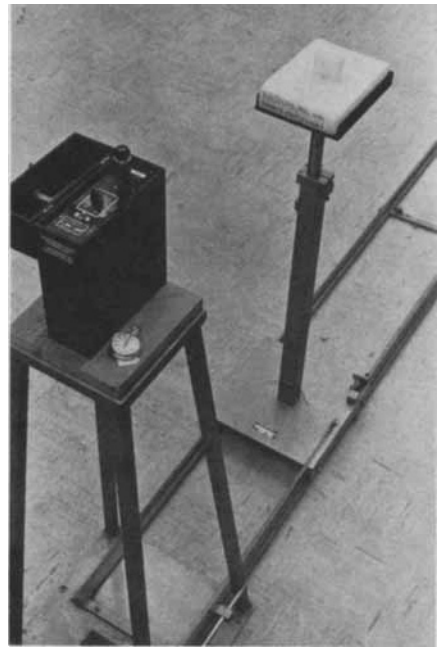

Figure 4: Electroscope on calibration range, designed to minimize extraneous scatter, is used for the assay of high activity gamma-emitting radionuclides.

total activity received. In addition, prior to any manipulation of the radioactive material, a sample is aseptically removed from the shipping vial and placed in a siliconized container. An accurately measured aliquot is transferred from this container to an appropriate counting vial. When feasible, the pipet is rinsed with carrier or water and the rinsings are added to the aliquot. The sample is assayed to identify again the major radionuclide, to calculate its activity per-unit-volume and to determine qualitatively as well as quantitatively the presence of radionuclidic impurities.

We have examined the assay data for the past ten years and have included in this study only those per-unit-volume or gross assays performed on liquid solutions

or suspensions during the period of January 1, 1962 to December 31, 1971. The NIH assay methods are considered to be accurate to ±10%. Materials are acceptable if the supplier's assay is within ±10% of the NIH value and if there is no significant contamination. If these criteria are not met, the supplier is contacted to determine the cause of the discrepancy.

The assays included in this study have been grouped according to the calendar year in which they were performed. Divergence between the supplier's assay and the NIH value was calculated by taking the difference between the two assays and arbitrarily dividing by the NIH value. The assays were then separated into various divergence intervals. The number of assays found in each interval was expressed as a percentage of the total number of assays included in the study for that year.

Table I shows our previously published (7) data for the five year period, 1962-1966. During this period, assays in the ≤0.10 divergence interval decreased from 83.5% to 70.6%. This was attributed to three factors. First, there was an increase in 1966 in the use of more recently developed and accepted radionuclides, such as ^{75}Se and ^{197}Hg. Assays of these radionuclides differed markedly from the

TABLE I
PERCENTAGE OF ASSAYS IN EACH DIVERGENCE INTERVAL DURING THE FIVE YEAR STUDY PERIOD 1962 – 1966

Divergence Interval	Calendar Year				
	1962 %	1963 %	1964 %	1965 %	1966 %
≤0.10	83.50	76.62	76.09	77.86	70.62
0.11–0.20	14.25	21.83	15.68	14.88	21.87
0.21–0.30	1.00	0.57	5.39	3.82	4.68
0.31–0.40	0.50	0.19	1.79	2.81	1.87
0.41–0.50	0.50	0.76	1.02	0.00	0.62
>0.50	0.25	0.00	0.00	0.60	0.31
Total Number of Assays Included	400	522	389	497	640

various supplier's values and standards were unavailable. Secondly, there was an increase in the number of 5 uCi human serum albumin-^{131}I syringes received in 1964. Again, these assays differed greatly from the supplier's. Thirdly, in 1964 we began performing per-unit-volume assays as well as gross assays on gamma emitters. This procedural change detected errors in per-unit-volume assays which were unnoticed previously if the supplier's volume was also erroneous.

During the more recent five year period (Table II), the assays in the ≤0.10 divergence interval hit a record low of 60.8% in 1967 and have increased to 80.8% in 1971. The year 1967 saw continual assay discrepancies in excess of ±10% with

TABLE II
PERCENTAGE OF ASSAYS IN EACH DIVERGENCE INTERVAL DURING FIVE YEAR STUDY PERIOD 1967-1971

Divergence Interval	Calendar Year				
	1967 %	1968 %	1969 %	1970 %	1971 %
≤0.10	60.81	67.45	72.44	77.16	80.84
0.11-0.20	29.02	27.07	22.32	16.71	13.08
0.21-0.30	5.36	2.35	2.28	2.78	3.97
0.31-0.40	2.40	1.56	1.37	1.11	0.47
0.41-0.50	0.74	0.62	0.91	0.56	0.70
>0.50	1.66	0.94	0.68	1.67	0.93
Total Number Of Assays Included	541	639	439	359	428

several products. Assay difficulties continued with ^{197}Hg products. Adsorption of radioactive material onto the surface of the walls of glass shipping vials was the cause of assay discrepancies with one manufacturer's strontium chloride-^{85}Sr and with commercially prepared sulfur colloid-^{99}Tc^{m}. Low assay values were observed in 88% of the shipments of the latter product. Assay discrepancies were also noted in shipments of inorganic compounds labeled with ^{24}Na and ^{82}Br.

In 1968 the difficulties with sulfur colloid-$^{99}Tc^{m}$ and sodium chloride-^{24}Na improved. With regard to the ^{85}Sr problem, two other suppliers were used. The assays of one manufacturer were consistently off by the same percentage on each shipment. When this was brought to the supplier's attention, he found that an incorrect decay factor for seven days was being used.

During the remainder of the second five year period, one other product, macroaggregated albumin-^{131}I, caused difficulties. This suspension of 10-90 micron albumin particles does not show assay discrepancies on every shipment; however, difficulties have been encountered frequently. In discussing these with the supplier, he has raised objections to our technique of sample withdrawal (e.g., length of aspiration, needle size). The use of his methodology did not change our assay values, which could be approximately 50% of the labeled value.

Some of the causes of discrepancies are: incorrect shipment, erroneous assay date, wrong volume, incorrect supplier's assay, inconsistent labels, uncertainty in decay scheme, and contamination.

Incorrect Shipment: An example of an incorrect shipment involved the receipt of a 200 mCi $^{99}Tc^{m}$ generator rather than the 300 mCi size ordered by NIH.

Erroneous Assay Date: In addition to previously reported errors, there has been one occasion in which a commercial supplier has made a one day error on the date of a $^{99}Tc^{m}$ product and three instances of two, three, and four day errors on the assay date of human serum albumin-^{131}I.

Wrong Volume: In some cases in which the concentration is high (mCi/ml) and the volume small (<1 ml), there have been discrepancies between the supplier's total assay and the NIH value. In such instances, a per-unit-volume assay may be prohibited by the small volume, ultimate use of the material (e.g., protein iodination) and/or high cost. We have compared results with the suppliers on samples of the same chemical form but of lower concentration and found agreement. One then suspects that the volume measurement is inaccurate.

A recent example of such an error occurred in a shipment of calcium chloride-^{47}Ca. The shipping documents indicated 2 mCi, while our assay showed only 1.1 mCi. After notification, the supplier forwarded the balance of the shipment.

Incorrect Supplier Assay: This type of error was observed in many different compounds labeled with various nuclides.

a) Forty-three percent of the inorganic compounds labeled with ^{82}Br or ^{24}Na were outside ±10%. In the worst case one shipment of ^{82}Br was only 43% of the labeled value.

b) A shipment of sodium iodide-^{125}I was 1.7 times the assay on the label.

c) A shipment of diisopropylfluorophosphate-^{3}H was assayed as having only 70% of the indicated activity.

d) In three recent incidents, the packing slip containing assay information on ^{47}Ca shipments has stated the per-unit-volume assay incorrectly, due to a misplaced decimal point.

Inconsistent Labels: This problem has been observed twice with respect to sodium iodide-^{131}I capsules, each from a different supplier. In the one case, the outer container's label read 59 uCi/capsule, while the label on the bottle which actually held the capsules stated 109 uCi/capsule. The latter label was correct.

Uncertainty in Decay Scheme: With the advent of newly developed and more widely accepted radionuclides, some assay problems arose from the lack of agreement of decay scheme values. This was most noticeable in the mid-1960's in the case of ^{197}Hg, later with ^{75}Se and more recently with ^{133}Xe. As standards of these nuclides become available from reputable sources such as the National Bureau of Standards, major suppliers will agree on the definition of a "millicurie" of each of these nuclides and assay difficulties will be minimized.

Contamination: Radionuclidic impurities associated with clinically used radioactive materials may be expected or unexpected. An expected contaminant of

65 hour ^{197}Hg is 47 day ^{203}Hg. Prior to the availability of enriched target materials, ^{203}Hg levels of 3-6% were routine. One unacceptable shipment of ^{197}Hg showed 16.7% ^{203}Hg. By the time the product was to be used after a weekend's delay, the contamination would have increased to almost 35%. In another case, an expected contaminant of 60 day ^{125}I is 13.1 day ^{126}I. One shipment received at NIH showed approximately 3% ^{126}I. This occurred because the manufacturer had depleted his supply of ^{125}I and had not allowed a new batch to "cool" for the normal period.

Unexpected contamination incidents include the observance of ^{169}Yb to the extent of 20% in a ^{47}Ca shipment. In a second case, ^{203}Hg was found in a sulfur colloid-$^{99}Tc^{m}$ preparation. Upon inquiry it was learned that a ^{197}Hg source had been manipulated in the same hot cell which was later used for the $^{99}Tc^{m}$ product.

While surface contamination does not affect the per-unit-volume assay and is thus not included in the above statistics, it can be troublesome. Despite repeated notification of the supplier, shipments of 110 minute ^{18}F frequently show contamination on the lead pigs and on the surface of the vials. The same is true of shipments of ^{125}I, ^{131}I and ^{32}P. In a rather peculiar case, a lead pig and a vial in a shipment of ^{67}Ga were found to be contaminated with ^{131}I. The supplier stated that he did not process any ^{131}I in his facility and it was speculated that he had purchased used lead pigs which he had failed to check for contamination.

CONCLUSION

Merrill and Lewis reported to the Metrochem 71 meeting (8) that 3.3% of the shipments they examined were clearly erroneous. If assay values outside ±20% are also considered as "definite errors" (8), then our results show that approximately 6% of all shipments in this study were defective.

In this presentation we have described the quality control procedures employed for radiopharmaceuticals at NIH. Such extensive testing may not be required for

every use of radioactive material. However, we hope that it has given you some helpful ideas and some indication of the frequency of supplier error.

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(5) Ibid., p. 851.

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(7) Cliggett, P. A. and Brown, Joseph M., Jr. J. Nucl. Med. 9: 236-40(1968).

(8) Anonymous. Chem. Eng. News 49 (No. 18): 24(1971).

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