A HANDBOOK OF NUCLEAR PHARMACY

Wanda M. Hibbard, M.H.E.(CNMT)

PREFACE

THE need for on-site compounding and dispensing of radiolabeled pharmaceuticals for diagnostic purposes in nuclear medicine has lead to the birth of a new science, Nuclear Pharmacy. There are two basic types of services available to the nuclear medicine department: (1) the central radiopharmacy, which is operated by a pharmacist with special training in the preparation of radiopharmaceuticals or by a nuclear scientist (physicist, chemist, or radiobiologist), and (2) the nuclear pharmacy operated by nuclear medicine technologists under direction of the physician in charge of the nuclear medicine department. It is to the second group that my comments are more specifically directed.

According to the "Nuclear Pharmacy Practice Standards," Nuclear Pharmacy is a patient-oriented service that embodies the scientific knowledge and professional judgment required to improve and promote health through assurance of the safe and efficacious use of radioactive drugs for diagnosis and therapy. This includes the following general areas: procurement, compounding, quality control, and dispensing. Each of these topics will be discussed as they pertain to the hospital nuclear pharmacy. In addition, the legal requirements and radiation protection guidelines will be presented.

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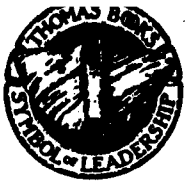

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Chapter 1

PROCUREMENT AND STORAGE

THE nuclear medicine technologist in charge of procurement has as his responsibility the ordering of both radioactive and nonradioactive drugs used by the nuclear medicine department. There are several different companies that deal in nuclear pharmaceuticals. Some carry only a few specialized products, but about a dozen companies handle the bulk of the materials produced for diagnostic purposes.

Generally, the companies that supply radioactive pharmaceuticals and isotopes also supply the kits for in-house radiolabeling with Tc-99m as well as quality control agents and related supplies. Those materials that are radioactive cannot be shipped to the user prior to the supplier's establishing that the user holds a license to possess and handle that particular isotope in the quantity ordered. The various types of licenses and the requirements for obtaining each are addressed in Chapter 7.

CHOOSING A SUPPLIER

One should choose a company that is known to be reputable, reliable, and that has a service representative who is easy to reach when problems arise. Also, most companies will be able to provide the name of a research chemist that one can contact if real problems arise and the service representative cannot supply the solution. Another factor of major concern is the delivery schedule. Packaging of the product and economics may be very important factors, but both take second place to quality, service, and ready availability. Hospital policy may require that the major items, especially the Mo-Tc generator, go out on bid. In this case, the technologist may not have final control over the companies from whom the required products are purchased. Make sure that each company presenting a bid is one whose product the technologist would be willing to use. For the short half-life pharmaceuticals that are ordered as patient studies are scheduled such as Ga-67, In-111, etc., the company one deals with may be the one that can get the needed material to the department within the best time schedule, without concern for the particular qualities of the product.

When planning procurement schedules, another factor to consider is the quantity of the product that must be ordered and the half-life or shelf life of the product. The patient cost of a radiopharmaceutical is often determined by the cost of the total quantity of a product ordered by the department rather than by the cost of the amount actually used for patient diagnosis. For example, a multidose vial of Ga-67 containing 20 mCi of Ga-67 citrate may be more cost efficient than four unit dose vials of 5 mCi each. However, if the department does only two studies from the multidose vial, the cost per patient will be more

than it would have been if unit-dose vials had been purchased.

As orders are received in the nuclear medicine department, all radiolabeled materials must be logged in with the date, quantity, manufacturer, lot number, and expiration date recorded. The same information is not required for materials that are not radiolabeled, but it can serve as a convenient guide to the utilization of those items and can readily provide reorder information. As radiolabeled compounds are administered to patients, records of their utilization must be kept, including patient identification, amount administered, and date of administration. To note the amount of radiopharmaceutical remaining is a handy reference for future use. The form shown in Figure 1 is a handy mechanism for keeping all the necessary data.

RADIOPHARMACEUTICAL UTILIZATION LOG

Affix Label Here

Name of RP_____ Mfgr._____

Date of Receipt_____ Lot #_____

Assay Date_____ Vol._____ Amount_____

_____mCi/ml Date of Expiration_____

Utilization

Patient I.D.		Date	Amount Administered		Amount Remaining	
Name	Hosp. #		Vol.	m(μ)ci	Vol.	m(μ)ci

Figure 1. Radiopharmaceutical Utilization Log. This form can be used for logging in each radiopharmaceutical received by the department and also shows the use and/or dispensation of the product.

DEPARTMENTAL REQUIREMENTS FOR RADIOPHARMACEUTICALS

There are no standard formulas that can be used to determine the quantities of radiopharmaceuticals and nonlabeled compounds that should be kept on hand. The key in determining how frequently an item should be ordered and what quantities are needed is the shelf life of the product. Some items are needed only rarely and can be purchased as patient studies are scheduled. An example of this is NP-59 (6B-iodomethyl-19-norcholesterol), used as an adrenal imaging agent. Other items that are used routinely at a fairly standard rate of usage may be placed on standing order with a review or revision of the order at six months intervals. For example, Hippuran I-131 has a shelf life of approxi-

mately two weeks. A standing order will allow for weekly fluctuations such that one will probably be able to always have it on hand for an emergency study, yet never have an over-sufficient quantity leading to loss of profits. A rule of thumb estimation of the size of Mo-Tc generator one needs to use follows.

Generator sizes are available from various manufacturers in the range of 50 mCi to 16 curies. It is important to obtain a generator that will produce sufficient quantities of pertechnetate for the acceptable performance of patient studies at the end of the week, yet, if the generator is larger than necessary, it becomes a source of unnecessary irradiation to the technologists.

The nonradioactive compounds needed by the nuclear medicine department generally are dated and should not be used beyond the expiration date. In estimating the quantities to purchase, these thoughts should be considered:

DETERMINING GENERATOR SIZE

1. Estimate the total number of mCi of Tc-pertechnetate the department will need to use on Friday.
2. Divide that value by 0.3 and round upward to the nearest hundred.
3. The result is the size of generator that will need to be ordered, i.e. if 200 mCi will be needed on Friday, 200 ÷ 0.3 = 666, or 700 mCi, when rounded up to the nearest hundred.
   For this example, a 700 mCi generator should be adequate; that is, a generator that yields 700 mCi of $NaTcO_4$ on Monday will, under normal conditions, yield 200 mCi on Friday.

Tc-SC multidose vials can usually be compounded so that all patients scheduled for a given day can be injected from one vial; one phosphate vial may be used for up to four or five bone images; however, the phosphates used for blood pool imaging will probably be used on the ratio of one or two patients per vial. Here are some guidelines to follow:

1. Make a study of your patient load over the past three months.
2. Project any factors that might alter the patient load during the next three months. (Vacation periods usually bring a decrease in work load, especially Christmas, whereas, opening a new wing of the hospital might increase the patient load. If your hospital is associated with an intern program, there is likely to be an increase in patient scheduling during the first week of a new rotation.)
3. Check the shelf life of the product.
4. Order what you project can be used during one shelf life.
5. Keep written records of utilization of each pharmaceutical, radioactive and nonradioactive. Be sure to record any vials discarded due to compounding errors, contamination, etc.
6. Discard all expired vials, etc., upon the date of expiration. **Do not use for**

patient studies.

7. Review and revise your purchasing plan at least every six months.

STORAGE REQUIREMENTS

Most radiopharmaceuticals and nonlabeled drugs can be stored at room temperature. There are, however, certain compounds that should be refrigerated or frozen. They include the organic compounds such as I-125 fibrinogen, which should be kept frozen (-20°C), and NP-59, which should be kept at 4°C to prevent deiodination. TcHSA also needs to be refrigerated after compounding and then used within a few hours, depending upon the method of compounding. Light may also cause a breakdown, particularly of iodinated compounds such as Rose Bengal, which should be stored in the dark or in a light tight container.

To prevent radiation exposure, all storage areas must be lead lined. Since the required refrigeration area is small, an under-the-counter refrigerator with a small freezer space is usually adequate, and a small amount of lead shielding (about two half value layers) is generally adequate as vial holders or as complete shielding around the refrigerator freezer.

The greatest shielding problem, by far, is that of shielding the Mo-Tc generator. The walls of the generator are sufficient shielding to meet transportation requirements, but once the generator is installed in the radiopharmacy where technologists and other personnel may spend extended periods of time, the generator must be shielded with additional thicknesses of lead. The usual shielding material is a special shield provided by the manufacturer, and one may use lead bricks to construct suitable additional shielding. It is very important that the shield be constructed to provide maximum protection to the person eluting the generator. If the generator is a self-contained unit, the shield needs to be designed so that only the withdrawal port will be exposed during elution; therefore, the technologist needs only to place the eluant vial in position each day, then replace the shield covering that area as soon as elution is completed. A generator requiring the use of a daily saline charge rather than a self-contained supply for the life of the generator will result in greater technologist exposure, so adequate shielding is even more important. The eluant should be stored in a lead vial shield, and all kit compounds should be stored in the same manner as soon as they are compounded with pertechnetate.

Iodine compounds, particularly I-131 in therapeutic quantities, should be stored behind a shield in addition to the shipping vial in which they arrive at the department. A fume hood with absorptive filters should be accessible for opening and dispensing iodinated compounds and gaseous compounds such as Xenon-133.

Chapter 2

SETTING UP THE RADIOPHARMACY

GENERAL CONSIDERATIONS

THE first requirement in the design of a radiopharmacy is personnel safety. The pharmacy needs to be located in an area away from the patient imaging areas, assay lab, waiting areas, lounges, and secretarial areas. Shielding must be adequate to protect both radiation workers and the nonradiation workers who frequent the department. Air flow patterns must be such that there is no air contamination from the hot lab to the rest of the department. Accessibility to the area with minimum of unnecessary traffic is important.

When space is not a problem, there should be separate rooms for the hot lab and compounding areas with a separate area also for record keeping. Storage of waste products should be in a well shielded area or should be outside the working area. When separate rooms are not possible, extra shielding will be needed to reduce exposure in the radiopharmacy.

The composition of the workbench top and floors should be a material that can be easily decontaminated or removed. Stainless steel sinks in work areas are recommended with laminated plastics being a second choice. A tiled floor with removable tiles facilitates cleanup when large spills occur. A laminar flow hood installed in the dispensing area is particularly desirable for storage and dispensing of radioactive compounds.

There must be sufficient storage space for nonradioactive pharmaceuticals used in compounding, for quality control materials, and for dispensing materials. Under counter and wall cabinets are excellent, but be careful to place materials not sensitive to radiation and materials seldom used in storage areas near the hot storage (generator) areas. All cabinets should have doors that can be closed to prevent contamination of shelf products in the event of a spill. **Do not store film in or near the hot lab since radiation emissions may cause film fog.**

Floor Plan

Few technologists have the privilege of being involved with drawing floor plans for the ideal design of a radiopharmacy in a new department. More often, the radiopharmacy is built into an out-of-the-way closet, alcove, or small room adjacent to the nuclear medicine department. Renovations or structural alterations are, however, frequently required, and the technologist may be consulted in regard to the appropriate floor plans.

The corner of the room farthest from the door, and preferably along an outside or corridor wall, should be used for the generator and the hot storage. An area opposite the generator area, and as far away from it as possible, should be

used as the work area. The compounding area will not be used as much or as frequently as the dispensing and record keeping area. A basic design for a small hospital radiopharmacy, using one room for all phases of pharmacy activity, is given in Figure 2.

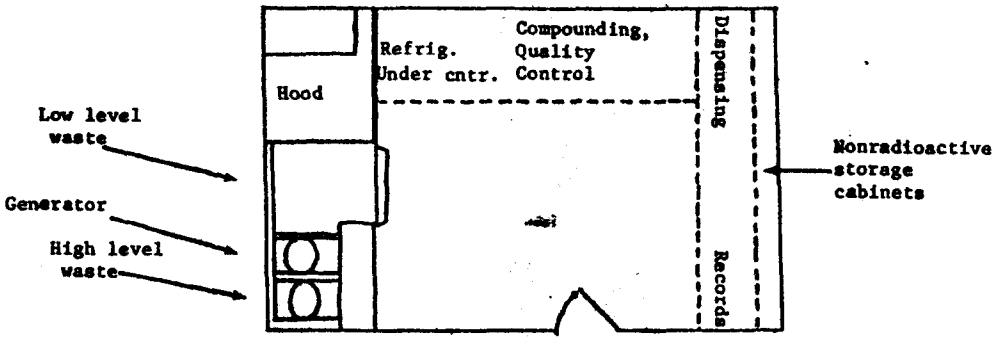

Figure 2. A simple design for a radiopharmacy, utilizing a minimum of space and maximum personnel safety.

Room Shielding

The radiopharmacy should be located in a well shielded room to reduce radiation exposure to patients and workers in the department. Although it is not necessary to lead-line the entire pharmacy, particularly when good radiation handling technique is employed, many hospitals do so, using a one-sixteenth inch lead plate up to a wall height of four feet.

It is highly recommended that at least the area housing the generator and high level waste be isolated, preferably in a separate room or closet with lead-lined walls. There must be adequate lead cabinets and shields to completely contain the high level activity except for brief time periods when the area must be accessed if there is not a separate well shielded area. If a shielded room is not available, the use of lead bricks and sheet lead can be effective in shielding small areas, but care must be taken to reduce cracks between the bricks or sheets to a minimum.

All compounding and dispensing areas should be arranged so that the technologists will be able to work behind body shields while handling radioactive materials. These should be designed with leaded glass ports providing clear visibility as well as protection and must be the appropriate height and width to allow the technologist to work with ease.

If the radiopharmacy is appropriately shielded, an area survey should show readings at or near background level outside the room, except in areas forming an outside wall where likelihood of personnel exposure is very limited.

MAJOR EQUIPMENT AND ACCESSORIES

The standard pieces of equipment that every radiopharmacy should contain

include a dose calibrator and an area survey meter as well as various other items used in radiopharmaceutical preparation and quality control. In the absence of a dose calibrator, or as a back-up mechanism when the calibrator may be inoperable, patient doses and generator eluates may be assayed with an uptake probe or well counter, and materials are available commercially for that procedure; however, there is less accuracy and the procedure is not recommended.

Dose Calibrator — Use and Quality Control

In choosing a dose calibrator, select a reliable manufacturer who gives good service and who will periodically standardize the dose calibrator with approved standards. It should be capable of measuring, with acceptable accuracy, a wide range of energies and levels of activity. Certain routine quality control procedures should be done to assure dose calibrator function is within acceptable limits. These include daily as well as periodic procedures. These are outlined here, and a chart for daily and weekly data recording is included in Figure 3.

TEST OF INSTRUMENT LINEARITY (ANNUALLY). The linearity of the dose calibrator should be measured over the entire range of activities employed. This test will utilize a vial of Tc-99m whose activity is equivalent to the maximum anticipated activity to be assayed (perhaps up to several hundred millicuries).

PROCEDURE FOR CHECKING LINEARITY OF DOSE CALIBRATOR

1. Assay the Tc-99m vial in the dose calibrator and subtract background to obtain net activity in millicuries.
2. Repeat step 1 at time intervals of 6, 24, 30, and 48 hours after the initial assay.
3. Using the 30 hour activity measurement as a starting point, calculate the decay predicted activities at 0, 6, 24, and 48 hours, using the following correction factors:

Assay Time (hrs.)	*Correction Factor*
0	32
6	16
24	2
30	1
48	0.125

Example: If the net activity measured at 30 hrs. was 18.4 millicuries, then the predicted activity for 6 to 48 hrs. would be 18.4mCi × 16 = 294.4mCi and 18.4mCi × 0.125 = 2.3mC respectively.

4. Plot the measured net activity for each time interval versus the decay predicted activity on semilog graph paper. The activities plotted should be within ± 5 percent of the decay predicted curve if the instrument is linear and functioning properly. Errors greater than ± 5 percent indicate the need for repair or adjustment of the instrument.

Month (Date)________________

DOSE CALIBRATOR QUALITY CONTROL RECORD
FOR INSTRUMENT ACCURACY AND CONSTANCY

Date Cs-137 mCi Tc-99m mCi

Daily

Week of ________ to ________

Weekly

Mo-99 mCi
Tl-201 mCi
I-131 mCi
Ga-67 mCi
Xe-133 mCi

Week of ________ to ________

Weekly

Mo-99 mCi
Tl-201 mCi
I-131 mCi
Ga-67 mCi
Xe-133 mCi

Week of ________ to ________

Weekly

Mo-99 mCi
Tl-201 mCi
I-131 mCi
Ga-67 mCi
Xe-133 mCi

Week of ________ to ________

Weekly

Mo-99 mCi
Tl-201 mCi
I-131 mCi
Ga-67 mCi
Xe-133 mCi

Figure 3. Dose Calibrator Control Record for Instrument Accuracy and Constancy.

TEST FOR GEOMETRICAL VARIATION (AT INSTALLATION). There may be significant geometrical variation in activity measured as a function of sample volume or configuration, depending on the volume and size of the ionization chamber used in the dose calibrator. The extent of geometrical variation should be determined for commonly used radionuclides and appropriate correction factors computed if variations are significant, i.e. greater ± 2 percent.

To measure variation with liquid volume, a 30cc vial containing 2 mCi of Tc-99m or Co-57, or other appropriate radionuclide, in a volume of 1 ml can be used.

DOSE CALIBRATOR GEOMETRICAL VARIATION TEST

1. Assay the vial at the appropriate instrument setting and subtract background to obtain net activity.
2. Increase the volume of liquid in the vial incrementally to 2, 4, 8, 10, 20, and 25 ml by adding the appropriate amount of water or saline. After each addition, gently shake the vial to mix contents and assay as in step 1.
3. Select the volume closest to the volume of Tc-99m eluate volume as a standard and calculate the ratio of measured activities for each volume to the reference volume activity. This represents the volume correction factor.
   Example: If activities of 10.4, 10.38, and 10.34 mCi are measured for 4, 8, and 10 ml volumes and 4 ml is the reference volume selected, then
   $$\text{10 ml Volume CF} = \frac{10.23}{10.40} = .944$$
4. Plot the correction factors against the volume on linear graph paper. Use your graph to select the proper volume correction factors for routine assay of that radionuclide.
5. The true activity of a sample is calculated as follows:
   True Activity = Measured Activity × CF
   where the CF used is for the same volume and geometrical configuration as the sample measured.
6. Similarly *the same activity* of Tc-99m in a syringe may be compared with that of 4 ml in a 30 cc vial and a correction factor calculated.

TEST FOR INSTRUMENT ACCURACY (WEEKLY). The accuracy of the dose calibrator should be checked for several radionuclides such as Cs-137, Co-57, and I-131 using appropriate reference standards whose activity is traceable to the National Bureau of Standards (NBS). The activity levels of the reference sources used should approximate those levels normally measured in the department. The lower energy reference standards (Tc-99m, Xe-133, I-125) must be in vials with the same thickness of glass as the actual samples to be measured for best accuracy.

Assay the reference standard in the dose calibrator at the appropriate setting