NUREG/CR-5877
BNL-NUREG-52328

# Aspects of Monitoring and Quality Assurance for Radiolabeled Antibodies

Prepared by
D. E. Barber

School of Public Health
University of Minnesota

Brookhaven National Laboratory

Prepared for
U.S. Nuclear Regulatory Commission

9207140062 920630
PDR NUREG
CR-5877 R PDR

## AVAILABILITY NOTICE

Availability of Reference Materials Cited in NRC Publications

Most documents cited in NRC publications will be available from one of the following sources:

1. The NRC Public Document Room, 2120 L Street, NW., Lower Level, Washington, DC 20555
2. The Superintendent of Documents, U.S. Government Printing Office, P.O. Box 37082, Washington, DC 20013-7082
3. The National Technical Information Service, Springfield, VA 22161

Although the listing that follows represents the majority of documents cited in NRC publications, it is not intended to be exhaustive.

Referenced documents available for inspection and copying for a fee from the NRC Public Document Room include NRC correspondence and internal NRC memoranda; NRC bulletins, circulars, information notices, inspection and investigation notices; licensee event reports; vendor reports and correspondence; Commission papers; and applicant and licensee documents and correspondence.

The following documents in the NUREG series are available for purchase from the GPO Sales Program: formal NRC staff and contractor reports, NRC-sponsored conference proceedings, international agreement reports, grant publications, and NRC booklets and brochures. Also available are regulatory guides, NRC regulations in the *Code of Federal Regulations*, and *Nuclear Regulatory Commission Issuances*.

Documents available from the National Technical Information Service include NUREG-series reports and technical reports prepared by other Federal agencies and reports prepared by the Atomic Energy Commission, forerunner agency to the Nuclear Regulatory Commission.

Documents available from public and special technical libraries include all open literature items, such as books, journal articles, and transactions. *Federal Register* notices, Federal and State legislation, and congressional reports can usually be obtained from these libraries.

Documents such as theses, dissertations, foreign reports and translations, and non-NRC conference proceedings are available for purchase from the organization sponsoring the publication cited.

Single copies of NRC draft reports are available free, to the extent of supply, upon written request to the Office of Administration, Distribution and Mail Services Section, U.S. Nuclear Regulatory Commission, Washington, DC 20555.

Copies of industry codes and standards used in a substantive manner in the NRC regulatory process are maintained at the NRC Library, 7920 Norfolk Avenue, Bethesda, Maryland, for use by the public. Codes and standards are usually copyrighted and may be purchased from the originating organization or, if they are American National Standards, from the American National Standards Institute, 1430 Broadway, New York, NY 10018.


## DISCLAIMER NOTICE

This report was prepared as an account of work sponsored by an agency of the United States Government. Neither the United States Government nor any agency thereof, or any of their employees, makes any warranty, expressed or implied, or assumes any legal liability of responsibility for any third party's use, or the results of such use, of any information, apparatus, product or process disclosed in this report, or represents that its use by such third party would not infringe privately owned rights.

NUREG/CR-5877
BNL-NUREG-52328

# Aspects of Monitoring and Quality Assurance for Radiolabeled Antibodies

Prepared by
D. E. Barber

School of Public Health
University of Minnesota

Brookhaven National Laboratory

Prepared for
U.S. Nuclear Regulatory Commission

9207140262 920630
PDR NUREG
CR-5877 R PDR

## AVAILABILITY NOTICE

Availability of Reference Materials Cited in NRC Publications

Most documents cited in NRC publications will be available from one of the following sources:

1. The NRC Public Document Room, 2120 L Street, NW., Lower Level, Washington, DC 20555

2. The Superintendent of Documents, U.S. Government Printing Office, P.O. Box 37082, Washington, DC 20013-7082

3. The National Technical Information Service, Springfield, VA 22161

Although the listing that follows represents the majority of documents cited in NRC publications, it is not intended to be exhaustive.

Referenced documents available for inspection and copying for a fee from the NRC Public Document Room include NRC correspondence and internal NRC memoranda; NRC bulletins, circulars, information notices, inspection and investigation notices; licensee event reports; vendor reports and correspondence; Commission papers; and applicant and licensee documents and correspondence.

The following documents in the NUREG series are available for purchase from the GPO Sales Program: formal NRC staff and contractor reports, NRC-sponsored conference proceedings, international agreement reports, grant publications, and NRC booklets and brochures. Also available are regulatory guides, NRC regulations in the *Code of Federal Regulations*, and *Nuclear Regulatory Commission Issuances*.

Documents available from the National Technical Information Service include NUREG-series reports and technical reports prepared by other Federal agencies and reports prepared by the Atomic Energy Commission, forerunner agency to the Nuclear Regulatory Commission.

Documents available from public and special technical libraries include all open literature items, such as books, journal articles, and transactions. *Federal Register* notices, Federal and State legislation, and congressional reports can usually be obtained from these libraries.

Documents such as theses, dissertations, foreign reports and translations, and non-NRC conference proceedings are available for purchase from the organization sponsoring the publication cited.

Single copies of NRC draft reports are available free, to the extent of supply, upon written request to the Office of Administration, Distribution and Mail Services Section, U.S. Nuclear Regulatory Commission, Washington, DC 20555.

Copies of industry codes and standards used in a substantive manner in the NRC regulatory process are maintained at the NRC Library, 7920 Norfolk Avenue, Bethesda, Maryland, for use by the public. Codes and standards are usually copyrighted and may be purchased from the originating organization or, if they are American National Standards, from the American National Standards Institute, 1430 Broadway, New York, NY 10018.


## DISCLAIMER NOTICE

This report was prepared as an account of work sponsored by an agency of the United States Government. Neither the United States Government nor any agency thereof, or any of their employees, makes any warranty, expressed or implied, or assumes any legal liability of responsibility for any third party's use, or the results of such use, of any information, apparatus, product or process disclosed in this report, or represents that its use by such third party would not infringe privately owned rights.

NUREG/CR-5877
BNL-NUREG-52328
CF,CY,RO,XM,9H,9L

# Aspects of Monitoring and Quality Assurance for Radiolabeled Antibodies

Manuscript Completed: March 1992
Date Published: June 1992

Prepared by
D. E. Barber

School of Public Health
University of Minnesota
Minneapolis, MN 55455

Under Contract to:
Brookhaven National Laboratory
Upton, NY 11973

D. B. Rowe, NRC Technical Monitor

**Prepared for**
**Division of Regulatory Applications**
**Office of Nuclear Regulatory Research**
**U.S. Nuclear Regulatory Commission**
**Washington, DC 20555**
**NRC FIN L1284**

## ABSTRACT

This report is intended as an informational resource and guide for the U.S. Nuclear Regulatory Commission (NRC) and NRC licensees who produce or use radiolabeled antibodies (RABs). Components of quality assurance programs related to the production and use of RABs are reviewed and evaluated, and recommendations are made on dosage calibrations, exposure control, monitoring, and personnel requirements. Special emphasis is placed on dose calibrators because these instruments are used extensively to measure the dosages of radiopharmaceuticals to be administered to patients. The difficulties of using dose calibrators to quantify dosages of beta- and alpha-emitters are discussed. The advantages and disadvantages of using other instruments are examined, and recommendations are made on the types of instruments to be used for different applications.

TABLE OF CONTENTS


| | | Page |
|---|---|---|
| ABSTRACT | | iii |
| TABLE OF CONTENTS | | v |
| LIST OF TABLES | | vii |
| EXECUTIVE SUMMARY | | ix |
| ACKNOWLEDGEMENTS | | xi |
| 1. INTRODUCTION | | 1 |
| 1.1 | Peculiarities of Radiolabeled Antibodies (RABs) | 1 |
| 1.2 | Objectives of this Work | 3 |
| 1.3 | Points of Control | 3 |
| 1.4 | Radionuclides of Special Concern | 4 |
| 1.5 | Biological Considerations | 4 |
| 2. INSTRUMENTS | | 5 |
| 2.1 | General Comments | 5 |
| 2.2 | Practical Considerations | 6 |
| 2.3 | Alpha-detectors | 6 |
| 2.4 | Beta-detectors | 7 |
| 2.5 | Beta-gamma-detectors | 8 |
| 2.6 | The Dose Calibrator | 8 |
| 2.6.1 | Principles and Characteristics | 9 |
| 2.6.2 | Accuracy | 9 |
| 2.6.3 | Beta-radiation and Bremsstrahlung | 9 |
| 2.6.4 | Range of Activity Measured | 10 |
| 2.6.5 | Linearity | 13 |
| 2.6.6 | Energy Dependence | 14 |
| 2.6.7 | Geometry Dependence | 14 |
| 2.6.8 | Constancy | 15 |
| 2.7 | Survey Instruments | 15 |
| 2.8 | Recommended Instruments | 15 |
| 3. CALIBRATION AND CHECK SOURCES | | 17 |
| 3.1 | Dose Calibrators | 17 |
| 3.2 | GeLi or HPGe Spectrometers | 17 |
| 3.3 | Alpha-survey Meters | 18 |
| 3.4 | Beta-survey Meters | 19 |
| 3.5 | Exposure Rate Meters | 19 |
| 3.6 | NaI Detectors | 19 |

TABLE OF CONTENTS (continued)


Page

4. DOSAGE CALIBRATIONS ..... 19

4.1 Producers ..... 19
4.2 Radiopharmacies ..... 21
4.3 Users ..... 21
4.4 Unit vs. Multidosage Vials ..... 21

5. EXPOSURE CONTROL AND MONITORING ..... 22

5.1 Occupational ..... 22

5.1.1 External Dose ..... 22
5.1.2 Internal Dose ..... 22
5.1.3 Exposure from Inpatients ..... 23

5.2 Release of Patients from the Hospital ..... 24
5.3 Outpatients and the Public ..... 27
5.4 Waste Control ..... 27

6. PERSONNEL AND KNOWLEDGE REQUIREMENTS ..... 28

6.1 The Team ..... 28
6.2 Radiation Safety Officers ..... 29
6.3 Radiation Safety Committee ..... 29
6.4 Individual Users ..... 30

7. SUMMARY AND RECOMMENDATIONS ..... 30

7.1 General ..... 30
7.2 Instruments ..... 30
7.3 Calibration and Check Sources ..... 31
7.4 Dosage Calibrations ..... 31
7.5 Exposure Control and Monitoring ..... 31
7.6 Personnel and Knowledge Requirements ..... 32

8. REFERENCES ..... 35

APPENDIX I, UNPUBLISHED REFERENCES ..... 38

## LIST OF TABLES


Page

Table 1.1 Characteristics of some radionuclides used for labeling antibodies. . . . . 1

Table 1.2 Examples of the radionuclides and dosages used in RABs in clinical trials. . . 2

Table 2.1 Approximate activity required to saturate a dose calibrator for common standard sources . . . . . 11

Table 2.2 Approximate activity required to saturate a dose calibrator for some radionuclides used in RABs . . . . . 12

Table 2.3 Radiation detection and measurement instruments recommended for users and producers for dosage determinations and radiation safety purposes related to RABs by type of radiation to be measured . . . . . 16

Table 3.1 Sources suggested by DOE (1990) for calibrating GeLi or HPGe spectrometers . . . . . 18

Table 5.1 Most restrictive derived air concentrations (DACs), and environmental release concentrations from 10 CFR 20 (NRC, 1991) for radionuclides used in RABs . . . . . 26

Table 5.2 Ratios of concentration of a given radionuclide to the comparable concentration for I-131 based on the most restrictive derived air concentrations (DACs), and environmental release concentrations given in 10 CFR 20 (NRC, 1991) . . . . . 27

## EXECUTIVE SUMMARY

This report is intended as an informational resource and guide for the U. S. Nuclear Regulatory Commission (NRC) and NRC licensees on quality assurance related to the use of radiolabeled antibodies (RABs) in patients. Instrumentation components of quality assurance programs are addressed, and related to the peculiarities of RABs. The implications of using dose calibrators to quantify RAB dosages are emphasized because these instruments are often the only instruments used in clinics to quantify the dosages administered to patients.

The levels of activity used for imaging or therapy are sufficiently high that even when the relative abundance of photons per disintegration of a radionuclide is low, there are still sufficient photons to enable them to be detected and measured in a dose calibrator. Also, bremsstrahlung from pure beta-emitters is detected easily from clinical dosages. However, for these radiations, careful attention must be given to goemetry and calibration of the dose calibrator.

Producers and users of RABs must have the equipment necessary to detect and measure the radiations emitted by the radioactive material at all levels of concern. Measurements are required that discriminate between the types and energies of radiation, and quantify the dosage before it is administered to a patient. Alpha-, beta-, or gamma-radiation spectrometry is necessary to identify and quantify the radioactivity in RABs because contaminants can be present, depending on the method by which the radionuclide was produced. Producers of RABs should use spectormetry equipment in their quality assurance programs. However, such equipment is impractical in a clinical setting. In many situations, the user must rely on specifications and calibrations provided by the producer. Producers include organizations and individuals who prepare and/or label RABs. It is essential that they have in place the quality control and quality assurance procedures to assure that the specified RAB, in the specified form and quantity, is delivered to the user.

Quality control measurements made just before a RAB is administered to a patient must be fast and accurate so they do not delay attention to the patient, and unnecessarily increase the cost of healthcare. In some instances, it is impossible to be fast and accurate because of the complexity of quantifying the dosage. In such instances, the user must rely on the producer's calibration. Consequently, producers bear a special responsibility to supply reliable calibrations with their products.

Quality control procedures also must be expeditious when radionuclides with short half-lives are used. In many cases, it may be necessary to administer a RAB to a patient before final quality control measurements are performed. Under such circumstances, RAB quality depends on good manufacturing practices (as defined by the U.S. Food and Drug Administration), process control, rapid quality control procedures, and, in some cases, retrospective testing (e.g., for sterility and apyrogenicity) for RABs that have a history of satisfactory use. Administrations of new RABs require confirmation of the radiological, biological, chemical, and pharmaceutical quality before the RAB is administered to a patient. Such practices rely on a well-qualified and trained staff.

Those responsible for the preparation and administration of the prescribed dosage to the patient must be trained and skilled in quality assurance procedures. One person (no matter how competent) cannot do all that must be done. A team approach is required. The medical director, medical physicist, and radiopharmacist (or radiochemist) have quality control and quality assurance responsibilities. The medical director is responsible for the overall quality of care provided to patients. The medical physicist is responsible for radiation safety and

quality control, as well as data handling and computations for nuclear medicine tests. The radiopharmacist (or radiochemist) is responsible for the development, production, quality assurance, and quality control of RABs.

The instruments required for quality assurance programs depend on the particular environment— the clinic, pharmacy, or manufacturing facility. The appropriate instrument to be used depends on the level and type of radiation to be measured, and the intended purpose of the results. From the standpoint and therapy, the objective is to administer the prescribed activity of a specific radionuclide. From the standpoint of radiation safety, the objective is to minimize the dose to patients and staff (without jeopardizing the effectiveness of the procedure), and to control contamination of the environment.

The requirements for measuring and monitoring of radiation for RABs labeled with photon-emitting radionuclides are similar to those for common radiopharmaceuticals because the detection and measurement of x-rays, bremsstrahlung, or gamma rays has little to do with whether a radiopharmaceutical is a RAB or not. However, RABs that emit predominantly beta particles require careful attention to the calibration of the instruments used to quantify them. If alpha-emitters are used, alpha-detectors are a necessary addition to the instrument inventories of producers and users.

RABs labeled with Y-90 present the potential for extraordinarily high beta-doses to the skin of the fingers and hands if intervening materials (gloves, vials, syringes, shields) are not thick enough to absorb the beta particles. Bremsstrahlung can produce measurable exposure, but it is only a small fraction of the exposure produced by gamma- or x-radiation.

The extent of control required for RAB outpatients who receive dosages less than 30 mCi (1110 MBq) and therapy patients who are released from the hospital cannot be determined until the whole-body effective half-lives of RABs are known. The risk related to internal exposure of the public, family members, and the patient's attendants appears to be little different from the risk associated with patients with comparable levels of I-131 activity. However, the actual levels of environmental contamination associated with patients containing alpha- and beta-emitting RABs have not been determined. This could be especially important in cases where a patient cares for a family.

The potential for external exposure could be higher with RABs than with common radiopharmaceuticals because of longer whole-body half-lives. However, assessment of the exposure potential for people in the occupational and public domains requires the evaluation of information on the whole-body half-lives of RABs that is not yet available. Comparative risks between RABs and common radiopharmaceuticals cannot be made until more is known about the clearance of RABs from patients. However, control is necessary for inpatients and outpatients.

## ACKNOWLEDGEMENTS

The author gratefully acknowledges the help of the following reviewers who took time from their busy schedules to read and comment on the draft of this report:

Dr. William R. Hendee, Medical College of Wisconsin
Mr. Thomas J. Herold, Mayo Clinic
Dr. Joseph C. Hung, Mayo Clinic
Dr. Edward Kaplan, Brookhaven National Laboratory
Dr. Michael K. O'Connor, Mayo Clinic
Dr. Suresh C. Srivastava, Brookhaven National Laboratory
Dr. J-L Vanderheyden, Mallinckrodt Medical, Inc.
Dr. Richard J. Vetter, Mayo Clinic
Dr. Avril Woodhead, Brookhaven National Laboratory

# 1. INTRODUCTION

## 1.1 Peculiarities of Radiolabeled Antibodies (RABs)

The use of radiolabeled antibodies (RABs) poses new issues in radiation safety. These issues and the people most affected by them have been discussed in detail elsewhere (Barber, et al., 1991). In the current report, instrumentation, measurement, and monitoring requirements for producers, pharmacists, and users of RABs are emphasized. Also, emphasis is placed more on what action should be considered than why that action is necessary. The intent is to optimize the usefulness of this report for NRC personnel and licensees.

A summary of some of the characteristics of radionuclides being used to label RABs is given in Table 1.1. Example diseases being detected by imaging procedures and treated with RABs, and the dosages that have been used are given in Table 1.2.

**Table 1.1 Characteristics of some radionuclides used for labeling antibodies. (Adapted from Barber, et al., 1991)**

| Radionuclide | Exposure rate constant[1] R cm$^2$ mCi$^{-1}$ h$^{-1}$ | Physical half-life, h |
|---|---|---|
| Y-90 | 0.042[3] | 64.0 |
| Tc-99m | 0.63 | 6.01 |
| In-111[2] | 3.21 | 67.3 |
| I-131 | 2.20 | 192 |
| Re-186 | 0.22[4] | 89.3[5] |
| Re-188 | 0.39[4] | 17.0 |
| At-211[2] | ~0.03[6] | 7.21 |
| Pb-212 | 0.76 | 10.9 |

1. Excluding photons < 20 keV. Multiply by 6.97 x 10$^{-6}$ to obtain $\mu$C kg$^{-1}$ cm$^2$ MBq$^{-1}$ h$^{-1}$.
2. Not a byproduct material.
3. Based on the exposure rate from bremsstrahlung (Williams, et al., 1989).
4. Stabin, 1991.
5. Coursey, et al., 1991.
6. The approximation includes photons from the daughter of At-211 (Po-211, 0.52 s half-life).

**Table 1.2 Examples of the radionuclides and dosages used in RABs in clinical trials. (Adapted from Barber, et al., 1991)**

| Disease or Condition | Radionuclide | | Dosage, mCi[a] | |
|---|---|---|---|---|
| | Imaging | Therapy | Imaging | Therapy |
| Blood clot | Tc-99m | | 20 | |
| Breast cancer | I-131 | I-131 | 10 | 50 x 3[b] |
| Colon cancer | I-125 | I-131 | 2 | 253 |
| | I-131 | Re-186 | 10 | 350 |
| | In-111 | Y-90 | 5 | 20 |
| | Tc-99m | | 15 - 30 | |
| Hematologic B-cell lymphomas | I-131 | I-131 | 10 | 30 x 10[c] |
| | In-111 | | 5 | 10 + 10 + 15[d] |
| Hepatoma | | Y-90 | | 30 |
| | | I-131 | | 50 |
| Hodgkins | In-111 | Y-90 | 3 - 5 | 30 |
| | | I-131 | | 50 |
| Leukemia | I-131 | I-131 | 10 | 30 x 10[c] |
| Lung cancer | Tc-99m | I-131 | 15 - 30 | 20 |
| | | Re-186 | | 350 |
| Myocardial infarction | In-111 | | 2 | |
| Ovarian cancer | In-111 | Re-186 | 5 | 220 |
| | | I-131 | | 205 |
| | | Y-90 | | 15 |

a. Multiply by 37 to obtain MBq.
b. Three administrations of 50 mCi (1850 MBq) each.
c. Ten administrations of 30 mCi (1110 MBq) each. Dosages up to 633 mCi (23.4 GBq) have been administered.
d. Sequential dosages.

Although some RABs are labeled with common radionuclides (e.g., Tc-99m and I-131), there are several issues of radiological quality assurance that are attributable to differences between RABs and more common gamma-emitting radiopharmaceuticals. The issues are related to the following points:

1. Some RABs are labeled with radionuclides that are not commonly used in nuclear medicine, especially beta-emitters such as Y-90. The use of beta-emitters to label RABs may increase.

2. Dose calibrators are designed to detect gamma rays, and are not usually calibrated for different types of radiation nor for broad spectrum radiation. Their suitability for quantifying dosages of alpha- and beta-emitting RABs requires examination.

3. High energy beta-emitters, such as Y-90, require special attention to personnel dosimetry, especially monitoring of the skin of the hands.

4. The prospect of using alpha-emitters in RABs for radiation therapy is new.

5. Some therapeutic protocols with RABs involve significantly higher levels of activity than those commonly used.

6. Different methods of administering RABs can require different radiation safety procedures. The methods of administering RABs to patients introduce new opportunities for the occupational exposure of staff.

7. Different types and energies of radiations require different types of instruments and calibration procedures to accurately quantify the activity.

8. The different pharmacokinetic behavior of RABs raises questions concerning the appropriateness of existing confinement limits used to determine when a patient may be released from hospitalization.

## 1.2 Objectives of this Work

The differences between RABs and common radiopharmaceuticals has raised questions about the applicability of radiation safety procedures used with the latter. The objective of this report is to examine the implications of these differences from a regulatory viewpoint to determine if additional regulatory action (related especially to measurement and monitoring), and new quality assurance procedures should be considered in the interests of health and safety. This report is intended to answer the question, "What radiation safety and quality assurance procedures, unique to RABs, require consideration before a licensee should be permitted to use RABs for diagnosis and/or therapy?"

## 1.3 Points of Control

Several points in the history of an antibody and a radionuclide provide opportunities for quality assurance and control:

1. production, purification, and reconstitution of the antibody or radionuclide,

2. radiolabeling the antibody,

3. shipping and receiving the radionuclide, antibody, or RAB,

4. preparation of the RAB dosage for administration to a patient,

5. administering the RAB to the patient, and

6. control after administration to a patient, either as an inpatient or an outpatient.

The equipment and the complexity of procedures required to assure that a quality product, in the proper dosage, in a quality environment is administered to a patient varies depending on the points in the process at which quality assurance procedures are applied.

## 1.4 Radionuclides of Special Concern

The radionuclides that are attractive for labeling RABs are produced by nuclear reactions in nuclear reactors, extracting radioactive materials from fission products, inducing activity in target materials with accelerators, or eluting the daughter products from generators. Different methods of producing radionuclides for labeling RABs result in different products and contaminating radionuclides. Some radionuclides used to label RABs have a history of use in other radiopharmaceuticals. However, there is interest in labeling RABs for radiation therapy with radionuclides that emit primarily beta- or alpha-radiation (Barber et al., 1991).

The emphasis in the current report is on byproduct material as defined by 10 CFR 30 (NRC, 1989) because the U.S. Nuclear Regulatory Commission (NRC) has statutory and regulatory responsibilities for these materials. Byproduct materials of particular interest are Y-90, I-131, Re-186, and Re-188. Although I-131 is commonly used in radiopharmaceuticals, it is used in higher dosages in RABs.

## 1.5 Biological Considerations

The commonest radiopharmaceutical parameters that require monitoring are sterility, apyrogenicity, purity, and safety (Paras, 1977). The FDA Good Manufacturing practices and procedures for producing and testing antibodies (FDA, 1987) should be followed by all producers of RABs. The production of sterile dosages relies on starting with sterile materials and maintaining sterility throughout production by using aseptic facilities and techniques because autoclaving the final product would destroy it (Horton and Bell, 1986). A RAB is typically administered through a sterile filter with a pore size of 0.22 μm or less. Testing of sterility can be completed retrospectively if the methods and materials are kept under surveillance, and if testing has demonstrated that the procedures result in a safe product.

Institutionally prepared (i.e., non-commercial manufacturer or supplier) pharmaceuticals require careful quality control (Vera-Ruiz et al., 1990). When an antibody is prepared institutionally only small amounts of antibody are available for preliminary studies. Therefore, rigorous protein purification and labeling methods must be developed that result in high recovery of the antibody. The first step (before labeling) is to establish the purity of the antibody by chromatography (Zoghbi et al., 1987). Chromatographic analysis of an antibody preparation can be used as a quality assurance step before it is conjugated with a chelating agent. Characterizing of modified antibodies is critical to the reproducibility of results.

Quality control testing for radiochemical purity of compounds that are complexes of metallic radionuclides can be carried out with simple and rapid methods such as electrophoresis, paper chromatography, and thin layer chromatography (Vera-Ruiz et al., 1990). Covalently bound radionuclides (e.g., iodine) demand more time consuming methods.

Simple mistakes, such as the inadvertent drying out of specimens intended for paper chromatographic analysis, significantly affect the results obtained (Mallol, 1990). Long-term changes in resolution, compound retention, and peak artifacts can occur with deteriorated chromatographic columns (Vera-Ruiz et al., 1990). If the needles used to depressurize vials are left in place for an entire day, they may cause microbiological contamination of the

radiopharmaceutical (Pfeiffer, 1984). Careful technique, attention to detail, and regular calibration of the analytical procedures with appropriate standards helps to avoid such pitfalls.

In clinical situations, quality assurance measurements must be made on the final product because of the small quantity of RAB available. Few aliquots can be taken and discarded after testing because of the low availability and high cost of the RABs. Further, quality assurance based on aliquots introduces a greater opportunity for error in the final dosage administered to the patient. Optimally, the identity and activity of the radionuclide should be determined without taking separate aliquots for testing. This requires the dosage to be measured in the vial or syringe from which it will be administered.

Quality assurance tests on a dosage must be completed in a short time in the clinical setting. This is especially important when radionuclides with short half-lives are used. In many cases, it may be necessary to administer the RAB to the patient before making final quality control measurements (Vera-Ruiz et al., 1990). Otherwise, it may be necessary to begin work with high levels of activity to allow for decay during the evaluation, and patients may have to wait for an unnecessarily long time. RAB quality depends on good production practices, process control, rapid quality control procedures, and, in some cases, retrospective testing (e.g., for sterility and apyrogenicity). Retrospective testing also may be necessary when RABs are labeled just before being administered to the patient.

Visual inspection of the physical appearance of the RAB and its expiration date is important because some RABs have short shelf-lives. When the material is not as clear as it should be or if clumps occur, the dosage should not be administered.

## 2. INSTRUMENTS

### 2.1 General Comments

Quality control begins with the selection and performance testing of instrumentation. Acceptance tests ensure that instrument specifications are met, and the results serve as references for comparisons with the future performance of the instrument (Shields, 1986). Reference tests fall into two categories: operational tests to be undertaken each time the instrument is used, and periodic measurements of performance depending upon the anticipated reliability of the instrument.

Quality control procedures in the clinic must be accomplished in a reasonable time so they do not unduly delay attention being given to the patient, cause repetition of dosages, and unnecessarily increase the cost of healthcare. Instruments should be calibrated and tested before diagnosis or treatment of the patient. Calibration checks should be performed at the beginning of each 24 hours in which patients are to be diagnosed or treated (see 10 CFR 35.5).

Instruments should be examined visually to see that everything is in order. The performance of each instrument then should be checked against its initial performance. If the response of dose calibrators and spectrometers is not within ± 5% (see Regulatory Guide 10.8, Appendix C, 1987) of the initial response, the reason for the inconsistency should be determined and the instrument should be re-checked, re-calibrated, or repaired until the instrument is operating properly and its calibration is confirmed.

The requirements for measuring and monitoring radiation for RABs labeled with photon-emitters are similar to the current requirements for common radiopharmaceuticals

because the detection and measurement of x rays, bremsstrahlung, or gamma rays has little to do with whether or not a radiopharmaceutical is a RAB. However, if alpha-emitters are used (those currently being considered are not byproduct materials), alpha-detectors must be added to the instrument inventories for producers and users of RABs. Producers and users also should be aware of additional concerns and difficulties with the use of radionuclides that emit predominantly alpha or beta particles. The newest concerns are related to the use of the byproduct materials Y-90, Re-186, Re-188, and high levels of I-131.

The minimum requirements for instruments in quality assurance programs related to RABs depend on whether they will be used in a clinic, pharmacy, or manufacturing facility. The appropriateness of the instrument also depends on the amount of activity and the type of radiation to be measured, and the intended purpose of the results. Further, the appropriate instrumentation and procedures depend on the particular concerns about quality assurance. For example, alpha- and beta-emitters at activity levels commonly used for radiopharmaceutical dosages can be detected and measured with gamma-ray detecting instruments because of the bremsstrahlung associated with beta-particle emitters, and the characteristic x or gamma rays emitted by some alpha-emitters. Exceptional care must be taken in calibrating dose calibrators if the dosages are to be based on bremsstrahlung measurements or the measurement of low energy photons. If surface contamination is to be controlled, and air contamination monitored, the alpha particles and beta particles must be detected directly because the relative abundance of gamma rays, x rays, and bremsstrahlung is too low to detect them at low levels of activity.

Radiation spectrometry should be used to identify and quantify the radioactivity in a radiopharmaceutical because contaminants can be present depending on the method used to produce the radioactive label. Analyses can be performed by the producer, the pharmacy, the radiation safety officer, radiological physicist, or the nuclear medicine technologist in the clinic. Regardless of where the analyses are performed, a measurement of the product after it is finally packaged is required to assure that the proper dosage is administered to the patient.

## 2.2 Practical Considerations

It is unrealistic to expect individual clinics or individuals to have spectrometric equipment available for the routine identification and calibration of RABs. In many situations users must rely on specifications and calibrations provided by producers. Therefore, it is essential that producers of RABs use quality control and quality assurance procedures that assure that the RAB, in the specified form and quantity, is delivered to the user. Producers of RABs have more quality assurance options available than are possible in the clinical setting. The instruments available for calibrating dosages in clinics are likely to be dose calibrators and well-type NaI scintillation counters.

## 2.3 Alpha-detectors

Alpha-emitters being investigated for labeling RABs also emit gamma- or x rays in low abundance. However, dose calibrators can detect such radionuclides, as shown by the incorporation of points for Am-241 in calibration data (Suzuki et al., 1976). A dose calibrator can be used to measure dosages of alpha-emitters just before administration to patients, provided it is properly calibrated and sufficient gamma-rays are emitted.

One producer of alpha-emitters uses a gamma-ray spectrometer to quantify the activity of alpha-emitters based on known decay schemes and the measurement of associated gamma rays

(Atcher, 1991). Liquid scintillation spectrometers also could be used to measure alpha-activity in RABs, but there are problems with this method (see section 4.1).

Alpha particle spectrometry is possible with detectors composed of silicon drifted with lithium (SiLi) detectors. However, the sample must be meticulously prepared. An aliquot of the pharmaceutical would have to be prepared in the form of an infinitely thin layer (probably electroplated) that would tolerate the vacuum required for alpha-spectrometry. Further, SiLi detectors require stable temperatures if reproducible results are to be obtained (DOE, 1990). Although alpha-spectrometry is impractical in the clinical setting, it could be used by producers.

The low relative abundance of photon emissions from alpha- emitters makes it unlikely that the photons will be detectable at levels of activity of concern in occupational exposure control (e.g., for monitoring air or surface contamination). Therefore, the instrument of choice is a portable, large area, alpha-scintillator (e.g., a 4-inch diameter ZnS scintillation probe attached to a portable rate meter or scaler). Such an instrument can detect surface contamination on laboratory surfaces, on filters used to collect air samples, and on wipe samples from surfaces.

ZnS scintillation detectors are efficient detectors of alpha emitters and they have low backgrounds without shielding. Portable, commercial detectors are available at modest cost. Users and producers of RABs labeled with alpha-emitters should have at least one of these detectors for environmental monitoring. The efficiency of ZnS detectors is a function of alpha particle energy because of self-absorption in sources of different thicknesses and attenuation by air between the source and detector. Therefore, the energy of the alpha particles must be known to accurately quantify the activity present. The magnitude of error associated with failure to correct for this energy dependence of the detector is acceptable for detecting and controlling surface contamination, but it is too large for determining RAB dosages for patients. Typical efficiencies range from 20 to 30 percent for 4.2 to 5.5 MeV alpha particles.

### 2.4 Beta-detectors

Although the use of Y-90 in radiotherapy is not new (Ehrhardt and Day, 1987; Williams et al., 1989), its use in RAB therapy has renewed interest in the calibration of dosages of beta-emitters with dose calibrators and in bremsstrahlung dosimetry.

The nuclear medicine community has had some experience with another pure beta-emitter, P-32. A comparison with Y-90 is appropriate for the benefit of those who have used P-32. Dosages of up to 5 mCi (185 MBq) per treatment were used for many years (and continue to be used) to treat polycythemia vera (St. Germain, 1986; Weber, 1990). However, when Y-90 is used in RABs as much as 30 mCi (1110 MBq) may be administered. Also, the maximum energy of beta particles emitted by Y-90 (2.28 MeV) is much higher than that of P-32 (1.71 MeV). So, Y-90 presents a significantly greater potential hazard than P-32, and users and producers of RABs labeled with Y-90 should be well acquainted with, and equipped to detect and quantify high-energy beta-emitters.

G-M detectors with thin windows can be used to control contamination. They are efficient detectors of energetic beta particles such as those emitted by Y-90. G-M counters also are used to detect gamma- and x-radiations. However, they are subject to high dead-time losses, and their response per unit of activity is a function of both the type and energy of radiation being detected. The energy dependence of this type of detector is usually acceptable for contamina-

tion control. Producers and users of RABs labeled with radionuclides that emit primarily beta particles should have at least one G-M counter for contamination surveys.

Liquid scintillation counters can be used to measure beta-activity in RABs (see section 4.1), and also to measure the contamination on wipe samples for both alpha- and beta-emitters. However, liquid scintillation counters rarely are found in clinics.

### 2.5 Beta-gamma-detectors

Sodium iodide crystals (usually with wells in them) are often available in nuclear medicine clinics. They are highly energy dependent for photons and are sensitive to other types of radiation if the radiation deposits energy in the crystal. Their encapsulation attenuates radiations, such as alpha- and beta-radiations, that might otherwise be detected. They are excellent gamma-ray detectors, and can be calibrated for specific energies of gamma-rays, but their resolution is poor. Their high sensitivity to x- and gamma-radiations necessitates the use of heavy shields to reduce and stabilize the background count. They are also subject to significant dead-time losses for activity levels of about a microcurie (about 37 kBq). However, when they are properly shielded, they can be used to make comparative measurements on samples of low activity (e.g., activity on liquid chromatography strips).

Detectors made of high purity germanium (HPGe) or germanium drifted with lithum (GeLi) can measure gamma rays with excellent energy resolution. These detectors are preferred for identifying and quantifying radionuclides by gamma-ray spectrometry before an antibody is labeled. Dead-time losses and overload problems would occur in these types of detectors for RAB dosages. They are designed to quantify the activity in samples containing much less activity, and are, therefore, of limited usefulness in a clinical setting. Also, a cryostat must be used with these detectors. This precludes the detection of alpha- or beta-emitters that do not also emit or produce photons because of absorption in the material covering the detector.

### 2.6 The Dose Calibrator

Dose calibrators are used in clinics (almost to the exclusion of all other dosage measurements) to measure activity levels in radiopharmaceuticals prepared for human use (ACNP, 1984). Much of what is discussed in this section applies to any radiopharmaceutical, not just RABs. However, knowledge of dose calibrator operation and quality assurance is important to understand the extraordinary attention required when working with RABs. Dose calibrators are designed to quantify the dosage to be administered to a patient by measuring the gamma radiation emitted. Bremsstrahlung and x rays can also be detected if they are produced in sufficient quantity. However, special care is essential if RAB dosages are to be based on bremsstrahlung measurements.

The radionuclides currently used in RABs all emit (or produce) some bremsstrahlung, x- or gamma-radiation. A dose calibrator can be used to calibrate dosages in the clinic just before administration. If the dose calibrator is calibrated for the specific radionuclide, in a standardized container, and has a standardized geometry, it can be used to determine the activity in a dosage for human administration for all the alpha-, beta-, and beta-gamma emitters currently used in RABs. However, the relative abundance of the photons being measured must be well known, radionuclide contaminants must be negligible, and appropriate calibration standards must be used.

When measurements with a dose calibrator differ from those of the manufacturer of either the instrument or the RAB, the reason for the inconsistency should be determined to assure that the correct dosage is administered to the patient.

### 2.6.1 Principles and Characteristics

The dose calibrator consists of an ionization chamber known as a reentrant (well-type) ionization chamber coupled to an electrometer to measure the activity in gamma-ray emitting radiopharmaceuticals (Leach, 1986). The chamber is pressurized and sealed. This increases its sensitivity to gamma radiation and eliminates the need to correct the ionization current for changes in temperature and atmospheric pressure. The well in the center of the chamber accommodates samples of different sizes and shapes.

Dose calibrators are available with different well dimensions and wall thicknesses, and containing different gases at different pressures. Although the well is large (typically about 6 cm diameter by 25 cm or more deep) sample self-absorption and geometry-dependent effects can occur, especially for low energy gamma-ray emitters, even when the sample is carefully centered. The response of a dose calibrator is affected by the gas used and its pressure in the ionization chamber, the composition of the electrodes and walls, the geometry of the chamber, and the external configuration of the external shield (Suzuki et al., 1976).

Every dose calibrator must be calibrated because of these variables (see section 3.1).

### 2.6.2 Accuracy

Numerous factors affect the accuracy of measurements made with a dose calibrator. These factors are related to the radionuclide, detector, electronic system, geometry, attenuation, scattering, and contamination. It would be unrealistic to believe that all these factors could be checked regularly. Most of these factors are taken into consideration in the design and manufacture of dose calibrators. Comprehensive tests should be made when the dose calibrator is installed (see 10 CFR 35.50) to determine that it meets specifications when it is first delivered, followed by periodic tests with sources with calibrations traceable to the U.S. National Institute of Science and Technology (NIST). These tests should suffice to assure that dosage errors attributable to dosage calibration errors are minimized. Initial and annual calibrations are especially important if low energy photons are to be used as the basis for dosage calibrations.

The accuracy must be determined over the range of energies to be used to determine dosages.

### 2.6.3 Beta-radiation and Bremsstrahlung

Sufficient bremsstrahlung is produced by the absorption of energetic beta particles to enable the bremsstrahlung to be used to calibrate dosages of beta-emitters in commercial dose calibrators. For example, Williams et al.(1989) estimated the exposure rate at 3 cm from 1 mCi (37 MBq) of Y-90 to be 4.7 ± 0.8 mR $h^{-1}$ (1.2 ± 0.2 $\mu C\ kg^{-1}\ h^{-1}$). The uncertainty in this exposure rate is ± 17%. If bremsstrahlung measurements are used to calibrate RAB dosage, the measurements must be made in a highly reproducible manner. The authors also noted that the effective half-value-layer for the bremsstrahlung from Y-90 was approximately 15 cm in soft-tissue at source-to-detector distances of >5 cm. This finding indicates that the average energy of the bremsstrahlung radiation is sufficiently high to easily penetrate the wall of the ionization chambers of commercial dose calibrators. However, because the bremsstrahlung

spectrum includes many low energy photons, a calibration based on bremsstrahlung requires careful and consistent attention to type and geometry of the container in the well of the dose calibrator.

The ionization chambers in some dose calibrators have aluminum walls that are 0.16 cm (429 mg $cm^{-2}$) thick and contain argon pressurized to 10 atmospheres (Suzuki, 1990). The wall of a plastic syringe is typically 1 mm thick (100 mg $cm^{-2}$). Therefore, the combined thickness of the chamber wall and plastic syringe (529 mg $cm^{-2}$) will absorb completely beta particles having energies less than 1.25 MeV. If a glass syringe with a wall thickness of 1 mm were used, the total thickness would be 664 mg $cm^{-2}$, which will stop beta-particles having energies less than 1.50 MeV. For Y-90 beta particles (2.28 MeV max.), a thickness of 1100 mg $cm^{-2}$ is required to stop the beta-particles. Well liners can be used to increase the thickness between the chamber and the sample. Beta particle absorbers should be made of a material of low atomic number to minimize the production of characteristic x-rays that might interfere with the measurement of the bremsstrahlung.

### 2.6.4 Range of Activity Measured

Specifications for dose calibrators vary by manufacturer and model. It is especially important to consider the specifications on the range of activity that is measurable. One manufacturer specifies an activity range of 0.1 mCi (3.7 kBq) to 5 Ci (185 GBq) for Tc-99m. If the radius from the center of the well to the center of the chamber were 6 cm (a common dimension for dose calibrators), then 0.1 mCi (3.7 kBq) of Tc-99m in the center of the well would produce an average exposure rate of 1.8 mR $h^{-1}$ (0.5 $\mu$C $kg^{-1}$ $h^{-1}$) at the center of the chamber and 5 Ci (185 GBq) would produce an exposure rate of 88 R h-1 (23 mC $kg^{-1}$ $h^{-1}$). This maximum is higher than the saturation exposure rate for the dose calibrator and would be in the non-linear portion of a graph of meter reading vs. activity.

Depending on the type of gas and its pressurization in the chamber, about 1.3 to 8.1 pA are produced in the chamber if a 27 $\mu$Ci (1 MBq) source is placed in the well (Santry and Bowes, 1989). If the electrometer in the dose calibrator saturates at a current of 0.1 mA, then the maximum activity measurable would be about 2 Ci (74 GBq). Higher levels of activity can be measured by using attenuators in the chamber well or by correcting for non-linearity in the graph of dosage vs. meter reading. Tables 2.1 and 2.2 list the saturation activities to be expected for a dose calibrator (based on typical manufacturers' specifications for Tc-99m) for several common standards and different radionuclides used in RABs. Except for I-131 and In-111, the saturation activities are larger than the saturation activity for Tc-99m.

**Table 2.1 Approximate activity required to saturate a dose calibrator for common standard sources.**

| Nuclide | Half-life, y | Exposure[1] rate constant | Saturation activity, Ci[2,3] | Exposure[4] rate at 6 cm |
|---|---|---|---|---|
| Co-57 | 0.745 | 0.57 | 2.2 | 35 |
| Co-60 | 5.27 | 13.0 | 0.097 | 35 |
| Ba-133 | 10.5 | 2.95 | 0.43 | 35 |
| Cs-137 | 30.0 | 3.27 | 0.39 | 35 |

1. Excluding photons < 20 keV (Stabin, 1990). Numerals are in units of R $cm^2$ $mCi^{-1}$ $h^{-1}$. Multiply by $6.97 \times 10^{-6}$ to obtain $\mu C\ kg^{-1}\ cm^2\ MBq^{-1}\ h^{-1}$.

2. Multiply by 37 to obtain GBq. Based on manufacturers' indication of saturation at 2 Ci (74 GBq) of Tc-99m.

3. The saturation activity is the activity below which recombination losses in the ionization chamber are negligible. The response of the instrument is expected to be a linear function of activity for an activity less than the saturation activity of a given radionuclide.

4. Source-to-chamber-center-distance taken to be 6 cm; numerals are in units of R $h^{-1}$. Multiply by 258 to obtain $\mu C\ kg^{-1}\ h^{-1}$.

**Table 2.2 Approximate activity required to saturate a dose calibrator for some radionuclides used in RABs.**

| Nuclide | Half-life, h | Exposure[1] rate constant | Saturation activity, Ci[2,3] | Exposure[4] rate at 6 cm |
|---|---|---|---|---|
| Tc-99m | 6.01 | 0.63 | 2.0[5] | 35 |
| Y-90 | 64.0 | 0.042[6] | 30 | 35 |
| In-111[7] | 67.3 | 3.21 | 0.39 | 35 |
| I-131 | 192 | 2.20 | 0.57 | 35 |
| Re-186 | 89.3 | ~0.20[8] | ~6.3 | ~35 |
| Re-188 | 17.0 | 0.26 | 4.8 | 35 |
| At-211[7] | 7.21 | ~0.03[9] | ~42 | ~35 |

1. Excluding photons < 20 keV (Stabin, 1990). Numerals are in units of R $cm^2$ $mCi^{-1}$ $h^{-1}$. Multiply by $6.97 \times 10^{-6}$ to obtain $\mu C$ $kg^{-1}$ $cm^2$ $MBq^{-1}$ $h^{-1}$.
2. Multiply by 37 to obtain GBq.
3. The saturation activity is the activity below which recombination losses in the ionization chamber are negligible. The response of the instrument is expected to be a linear function of activity for an activity less than the saturation activity of a given radionuclide.
4. Source-to-chamber-center distance taken to be 6 cm; numerals are in units of R $h^{-1}$. Multiply by 258 to obtain $\mu C$ $kg^{-1}$ $h^{-1}$.
5. Based on manufacturers' specifications.
6. Based on the exposure rate from bremsstrahlung (Williams, et al., 1989).
7. Not a byproduct material.
8. Shleien and Terpilak, 1984.
9. The approximation includes the photons from the daughter of At-211 (Po-211, 0.52 s half-life).

### 2.6.5 Linearity

Non-linearity in meter readings are caused by electronic irregularities, electrometer saturation, or recombination of ions in the ionization chamber. Tests for linearity with Tc-99m are adequate to determine linearity for alpha- and beta-emitters with complex decay schemes. Except for I-131 and In-111, Tc-99m produces saturation currents at lower levels of activity than other radionuclides used to label RABs. Therefore, if a non-linearity is observed in a graph of activity vs. meter reading for Tc-99m, it will also be observed in a graph for an equal amount of activity of the other radionuclides, except for I-131 and In-111. Conversely, if linearity is observed with Tc-99m, linearity will be observed with equal amounts of activity for the radionuclides listed in Table 2.2, except for I-131 and In-111. If the dosage to be used is in the nonlinear portion of the dose calibrator response graph, the dosage must be corrected by the percentage of deviation from linearity.

If dosages are expected to approach saturation levels for the electrometer or the chamber (see Table 2.2), multiple sources of Cs-137 could be used in lieu of the maximum dosage for a specific radionuclide. Measurements could be made with four sealed sources, each containing about 0.1 mCi (3.7 MBq) taken one, two, three, and four at a time in the center of the dose calibrator well. If a graph of dose calibrator reading vs. activity is linear, then linearity is assured for the radionuclides and the activities indicated in Table 2.2 If higher levels of I-131 are to be measured, proportionately higher activity standards must be used to obtain a correction factor for the non-linearity that will occur unless attenuators are used in the well.

Using sealed Cs-137 sources to test linearity is cost- and dose-effective. The half-life of Cs-137 is 30 y, so it does not decay rapidly. Further, the use of sealed sources minimizes occupational doses because the handling of radioactive standards for linearity testing can be completed quickly. There is also minimal potential for contamination. If Tc-99m is used and the decay method for testing linearity is used, it may be necessary to start with as much as 2 Ci (74 MBq).

RABs are administered at activity levels lower than those listed in Table 2.2, except for I-131 (Barber et al., 1991). Special care must be taken with I-131 to be certain that linearity errors either do not occur or are corrected for in measuring activity levels above 0.57 Ci (21 GBq) with a dose calibrator. If linearity is tested with Tc-99m, levels of activity that produce comparable effects on saturation should be used.

Linearity testing by the decay method, (NRC, 1987) with short half-lived radionuclides (e.g., Tc-99m) involves errors attributable to uncertainties in recorded time and the half-life used for the radionuclide (Chu, 1988). A difference of 1% in the half-life used to correct for decay will result in a difference of more than 4% in the calculated activity after 12 half-lives. Santry and Bowes (1989) suggested the standardization of half-lives to improve consistency in checking the linearity of dose calibrators. They recommend that a half-life of 6.007 ± 0.002 hours be used for Tc-99m.

If Tc-99m is used to test for linearity, two or three days may be required to cover the activity range of interest using a single source (Ahluwalia, 1985). When the decay method is used, sources must be inserted and removed from the dose calibrator several times over a few days, unless the dose calibrator is dedicated exclusively to the procedure. Using aliquots from a stock solution of a short-lived radionuclide such as Tc-99m, requires very careful micro-pipetting, and much handling of radioactive material. Therefore, such an approach would increase the risk of contaminating personnel, instruments, and the laboratory.

The linearity of a dose calibrator may also be tested using attenuators (the shield method) rather than measuring activity as a function of time (NRC, 1987).

### 2.6.6 Energy Dependence

Dose calibrators are designed to measure ionization current produced by photons ranging from about 25 keV to 3 Mev. RABs emit or produce photon energies from less than 20 keV to 900 keV.

Photoelectric and Compton interactions, attenuation in the wall of the ionization chamber, and different abundances of photons for different radionuclides result in the production of different ionization currents per unit of activity for different radionuclides. These differences are compensated for by changing the gain of the amplifier used with the ionization chamber or with microprocessor modules.

The extent to which the composition and thickness of the specimen container in a dose calibrator affects the response of the instrument depends on the type and energy of radiation emitted. If low energy gamma rays (about 25 keV or lower) are the cause of differences in response with different source containers, the differences can be reduced by attenuating the low energy photons with an absorber until they are an insignificant fraction of the photon fluence rate reaching the inside of the ionization chamber (Wiarda, 1984). However, the sensitivity of the instrument per unit of activity in the container is reduced, and characteristic x rays complicate the calibration of the dose calibrator (Harris et al., 1984).

The x rays emitted following electron capture are characteristic x rays. The different transitions result in x rays being emitted with different energies. This presents a problem in calibrating dose calibrators for radionuclides based on their x ray emissions.

### 2.6.7 Geometry Dependence

Different geometries and containers are used to calibrate dose calibrators and dosages to be administered to patients. Manufacturers of dose calibrators in the United States use radionuclides in 5-mL sealed, glass ampoules (the geometry used at the NIST), or radioactivity distributed in 20 mL of epoxy in a sealed 30-mL vial (ACNP, 1984). Radiopharmaceuticals are often measured in elution vials or injection syringes in clinics (Calhoun et al., 1987). The composition of the container also varies from one user to another(e.g., glass vs. plastic). Harris et al. (1988) demonstrated the importance of the container's composition and source geometry on dose calibrator calibration for low energy photons, such as those emitted by RABs. Standardization of geometries and containers should be considered for calibrating dose calibrators and dosages to be administered to patients.

Regardless of the brand of dose calibrator used, a calibration factor for each source geometry should be determined to ensure the highest accuracy. For Co-57 and Tc-99m, as much as a 9% difference in indicated activity has been attributed to differences in volumetric distribution and the container's composition, even when the operator reads the correct activity for an ampoule reference source (Calhoun et al., 1987). Because of the low photon energies for Co-57 (122 keV and 139 keV) and Tc-99m (141 keV), differences in the response of the dose calibrator attributable to volume differences were larger than differences attributable to the container's composition. Re-186 emits 137 keV photons 9.2% of the time and Re-188 emits 155 keV photons 15% of the time (Erdtman and Soyka, 1979).

Many radionuclides can be assayed independently of the sample's size if the ionization chamber well is much larger than the sample, and the sample is placed in the center of the well (Suzuki et al., 1976). However, low energy photon emitters require careful attention to the configuration and the type of container.

2.6.8 Constancy

Current methods for checking the constancy of a dose calibrator are adequate for RABs.

2.7 Survey Instruments

The radiation safety requirements for instrumentation for beta- or gamma-emitting RABs are similar to those associated with common radiopharmaceuticals, except that Y-90 requires special attention to skin dosimetry, and air samples should be taken and assayed for halogens (see section 5.1.2). Instrumentation requirements for exposure and exposure rate measurements are no different from those required for common radiopharmaceuticals.

Facilities that use alpha-emitters must have an alpha-detecting instrument for radiation-safety surveys. A ZnS scintillation detector connected to a portable rate meter or scaler will suffice for contamination surveys. A scaler should be used if air samples are to be evaluated for alpha-activity (see Section 4.1.2).

Detection efficiencies for ZnS detectors and thin-windowed G-M counters are sufficiently high under field conditions to detect levels of surface contamination specified by NRC regulations (see 10 CFR 35.70; 10 CFR 35.315; 10 CFR 71.87).

2.8 Recommended Instruments

A summary of recommended instruments for clinics, pharmacies, and manufacturers is given in Table 2.3. The preferred instrumentation for the purposes indicated and the minimum required instrumentation for the manufacture and use of RABs in humans are indicated. Additionally, in situations where activity may be released to air, air samples should be evaluated (see Section 5.1.2; Regulatory Guide 8.25; Hickey et al., 1991).

Survey instruments should not be used to calibrate dosages for administration to patients, and dose calibrators are of no use for environmental monitoring. A dose calibrator is of no use in detecting and measuring concentrations of activity at or below the limits specified in 10 CFR 20 (NRC, 1991).

**Table 2.3 Radiation detection and measurement instruments recommended for users and producers for dosage determinations and radiation safety purposes related to RABs by type of radiation to be measured.**

| Situation | Radiation | For dosage measurements | For contamination measurements Surface | For contamination measurements Air |
|---|---|---|---|---|
| User | $\alpha$ | Dose calibrator[1] | ZnS | ZnS |
| | $\beta$ | Dose calibrator | G-M | G-M |
| | $\beta$-$\gamma$ | Dose calibrator | G-M | HPGe or GeLi |
| | $\gamma$ | Dose calibrator | NaI | HPGe or GeLi |
| Producer[2] | $\alpha$ | SiLi or liquid scintillation | ZnS | ZnS |
| | $\beta$ | Liquid scintillation | G-M | G-M |
| | $\beta$-$\gamma$ | HPGe, GeLi, or dose calibrator | G-M | HPGe or GeLi |
| | $\gamma$ | HPGe, GeLi, or dose calibrator | NaI | HPGe or GeLi |

1. If the radionuclide emits or produces no x rays, bremsstrahlung, or gamma-radiation, the dosage should be calculated based on the calibration by the manufacturer or the pharmacy provided the calibration is based on measurements with instruments calibrated with sources traceable to the NIST.

2. A producer is an organization or individual who prepares and/or labels RABs for users.

## 3. CALIBRATION AND CHECK SOURCES

### 3.1 Dose Calibrators

Standards of the specific radionuclides to be used (or sources which emit equivalent energies of radiation) must be used to calibrate dose calibrators. Calibration is usually done by the manufacturer, and checked with a few sources by the user. At least one manufacturer provides calibration factors for Re-188 and some alpha emitters (e.g., Bi-212 and Am-241) in addition to many other radionuclides.

The use of long-lived check sources that are cross-referenced to other dose calibrators is highly recommended to detect instrument problems (Kearfott, 1989). Commonly available radionuclides, such as Co-57 (122 and 139 keV), Cs-137 (662 keV), and Ba-133 (80 and 356 keV) are used for daily checks on the constancy of the dose calibrator (Ahluwalia, 1985).

Calibration sources are available commercially and from the National Institute of Standards and Technology (NIST). Each standard from NIST consists of 5 mL of solution in a flame-sealed borosilicate glass ampoule. The numerous radionuclides available from NIST include Tc-99m, In-111, and P-32, but not Y-90, Re-186, or Re-188 (NIST, 1990). However, only a few sources are readily available, and commonly used to cover the photon energy range from about 80 keV to 1.3 MeV. These are Co-57 (used as an alternative for Tc-99m because of its longer half-life), Ba-133, Cs-137, and Co-60 (ACNP,1984). Cs-137 is a good reference source for calibrating and checking the constancy of the response of a dose calibrator. Standards for Y-90, and Re-186 are available, but they are expensive, short-lived, and special arrangements must be made with the supplier.

Calibration factors for radionuclides for which standards are not available can be estimated, provided that the photon probability per decay for each photon energy is known, and the number of photons with energies below about 200 keV is small (NCRP, 1978; Suzuki et al., 1976; ANSI, 1986; ACNP, 1984). However, most radionuclides used in RABs emit photons with energies well below 200 keV. Therefore, special attention must be given to the calibration of the dose calibrator using activities that have been determined with methods that assure that the activity is known within ± 5%. The calibration of the dose calibrator should be confirmed at least annually, for the specific radionuclides to be measured.

The operation of a dose calibrator, or G-M or exposure rate survey meter can be checked with Cs-137 if the instrument is used regularly and was calibrated for accuracy and linearity in the past year. Gamma-ray check-sources should be sealed and have long radioactive half-lives (e.g., Cs-137) to minimize errors that might occur in corrections for the decay of a short-lived radioactive material.

The amount of activity used to determine the accuracy for radionuclides that emit photons for which the exposure rate constant is < 0.03 R $cm^2$ $mCi^{-1}$ $h^{-1}$ (2 x $10^{-7}$ $\mu C$ $kg^{-1}$ $cm^2$ $MBq^{-1}$ $h^{-1}$) should be greater than 50 uCi (1.9 MBq). The approximate minimum activity required for such radionuclides would be 50 times the quotient of the exposure rate constant for Tc-99m divided by the exposure rate constant for the radionuclide in question.

### 3.2 GeLi or HPGe Spectrometers

Sources that have been suggested for calibrating spectrometers are listed in Table 3.1 (DOE, 1990). Good choices for calibrating spectrometers for RABs would be Pb-210 or Am-241, and Cs-137 or Co-60. Other sources that emit comparable energies can be used. However, Ra-226

is not recommended because of its potential for contamination. The radionuclides used in RABs have half-lives that are much shorter than the radionuclides in Table 3.1. Consequently, they are not practical for routine checks of instrument performance. However, an initial, and annual calibration is recommended with the specific radionuclides intended to be measured.

For the initial calibration, sources should be used that cover the full range of response of the spectrometer. Thereafter, if the slope and intercept of a count rate vs. energy graph remains unchanged when checked with two different gamma ray energies, the calibration remains valid (DOE, 1990). Confirmation of this response should be made each day the spectrometer is used to calibrate RABs.

## 3.3 Alpha-survey Meters

Alpha-survey meters should be calibrated with sources that emit alpha particles in the range of 3 to 6 MeV. The response of ZnS detectors is independent of energy over the range of interest if the source is in contact with the phosphor (DOE, 1990). The response of a large area ZnS detector is nearly independent of energy for sources within about 1 cm from the detector. Periodic checks for constancy of response of the instrument can be made with any dedicated source that emits alpha particles.

A single radionuclide that emits alpha particles between 3 and 6 MeV will suffice if the source can be fractionated (as with partial covers) to create apparent activities that produce at least two different readings on each of the ranges to be used on the instrument.

**Table 3.1 Sources suggested by DOE (1990) for calibrating GeLi or HPGe spectrometers.**

| Nuclide | Calibration energy, keV | Half-life |
|---|---|---|
| Pb-210 | 46.5 | 22.3 y |
| Am-241 | 59.5 | 433.0 y |
| Cd-109 | 88 | 462.0 d |
| Ce-141 | 145 | 32.5 d |
| Cr-51 | 320 | 27.7 d |
| Cs-137 | 662 | 30.2 y |
| Mn-54 | 835 | 312.0 d |
| Na-22 | 511, 1275 | 2.31 y |
| Y-88 | 898, 1836 | 107.0 d |
| Co-60 | 1173, 1332 | 5.27 y |
| Ra-226* | 186, 352, 609, 1120, 1765 | 1600.0 y |

* In equilibrium with its decay products.

Alpha-emitting calibration and check sources should be either in fixed form (electroplated or flamed) or have a thin covering to preclude loss of activity with improper handling and contamination of people or facilities.

### 3.4 Beta-survey Meters

There are no exceptional attributes of sources used to calibrate beta-survey instruments (e.g., G-M rate meters) for RABs.

### 3.5 Exposure Rate Meters

There are no exceptional attributes of sources used to calibrate exposure rate meters for RABs.

### 3.6 NaI Detectors

NaI detectors should be calibrated with the standards of the specific radionuclides to be measured.

## 4. DOSAGE CALIBRATIONS

### 4.1 Producers

Quality control measurements made just before administering a RAB to a patient must be fast and accurate. In some instances these requirements cannot be met because of the complexity of quantifying the activity. In such instances the user must rely on the calibration provided by the producer. Users often rely on calibrations by producers (Paras, 1981) because primary standards for many radionuclides used in nuclear medicine are not readily available. For example, hospitals rely on the activity value provided by the producer of radiopharmaceuticals labeled with P-32 and Sr-89 (Santry, 1991). Therefore, producers of RABs bear a special responsibility to supply reliable calibrations.

More than 90% of all radiopharmaceuticals used in imaging are labeled with Tc-99m prepared from commercial kits and Mo-99/Tc-99m generator eluate. Defective or incomplete labeling can occur, even with such common materials, if the purity of the reagents is not controlled (Mallol, 1990). The labeling of antibodies presents an even greater challenge. Consequently, the RAB dosages to be administered to patients must be calibrated carefully. Generally, the higher the dosage, the more accurate the dosage measurement should be.

Alpha- and/or gamma-spectrometry should be used to identify and quantify the primary and any contaminating radionuclides in a RAB. Checking for the anticipated radionuclides does not rule out the possibility of contaminants being present. The contaminants will depend on the method of production for the parent radionuclide, and the chemical protocols used to label the compound to be administered. On the other hand, contaminants that do not affect the process or the patient should be ignored.

To calibrate dosages of alpha-emitters that also emit gamma- or x-radiation, gamma-ray spectrometry with a high-purity germanium (HPGe) or a lithium-drifted germanium (GeLi) detector is recommended as the primary reference for quantifying the activity. Such spectrometers are rarely available in clinics and small pharmacies. Hence, the primary calibration of a dosage of RABs labeled with alpha- or beta-emitters is likely to be the

responsibility of the producer. Producers should have the necessary spectrometry equipment to provide primary calibrations for the users.

If the producer does not use spectrometry to calibrate RAB dosages, a dose calibrator that has been carefully calibrated may be used if attention is given to the special problems of alpha-, beta-, and low energy photon-emitters (see sections 2.3 and 2.6). Comparisons of calibrations by the user and the producer would assure that the proper dosage is administered to the patient. Standardization of sources, containers, and dosage geometries between supplier and user would facilitate such comparisons. Producers should indicate to users the type of calibration they used to determine the dosage.

Measurements of Y-90 dosage can be based on bremsstrahlung calibration of a dose calibrator if careful attention is given to geometry and container standardization. Beta particles from Y-90 can reach the sensitive volume of a dose calibrator and interfere with the measurement unless a well-insert thick enough to stop the most energetic beta particles emitted is used (see section 2.6.3). If a dose calibrator is used to measure the dosage of a beta-emitter based on bremsstrahlung production, a well-liner (absorber) should be used to make the total thickness between the sensitive volume of the chamber and the radioactive material equal to or greater than the thickness that will completely absorb the most energetic beta particle emitted. Otherwise, ionization produced by beta particles will interfere with the measurement of activity based on photons (see section 2.6.3). The calibration should be based on photon detection only.

Producers may use liquid scintillation counters for alpha- or beta-emitters. Complicated decay schemes involving different types and energies of radiation make this method a difficult option for quantifying the activity of some radionuclides. However, there are some advantages to liquid scintillation counting. For example, commercial pulse-shape analyzers can be used in liquid scintillation counters to produce separate alpha- and beta-spectra simultaneously. Less than 27 fCi (1 mBq) of alpha activity per sample can be detected in 100 minutes using this method (Oikari et al., 1987). Clinical dosages involve levels of activity that would require only a few minutes to produce simultaneous alpha- and beta-spectra.

The background for alpha-counting with a liquid scintillation counter can be as low as that of a solid-state detector, yet sample volumes can be considerably larger. There is $4\pi$ geometry, good precision and accuracy, nearly 100% counting efficiency, no self-absorption problems, and no vacuum or electroplating is involved.

The following difficulties make liquid scintillation counting impractical in a clinical setting, but manageable for producers:

1. Reference sources traceable to NIST must be used to calibrate the instrument for specific RABs because chemical and color quenching is likely to differ for different RABs.
2. Aliquots of the RAB dosage to be administered must be available.
3. For high-energy beta-emitters, such as Y-90, Cerenkov radiation is also detected (Parker, 1986).

If the producer does not provide pre-labeled RABs, instructions must be provided on the procedures to be followed for labeling. The user is expected to follow the procedures prescribed by the producer, regardless of whether the radionuclide is obtained directly from the producer of the antibody or from another source because the producer is likely to know more about the antibody and its labeling than the user.

## 4.2 Radiopharmacies

A pharmacy that is included as a part of a Notice of Claimed Investigational Exemption (IND) should be permitted to prepare RABs in accordance with the IND protocol if adequate radiological calibration equipment and trained staff are available. Radiopharmacies should be as well equipped as any producer if they compound or reconstitute RABs and calibrate dosages. After a RAB has been approved as a new drug, a radiopharmacy that only dispenses dosages requires only needs survey equipment to assure the safety of personnel.

## 4.3 Users

The identity and amount of the radionuclide in a RAB should be checked soon after it is received from the supplier by either clinical personnel or staff of the radiation safety officer, using instruments appropriate for the radiations emitted from the radionuclide.

The instructions of the producer on temperature and timely use should be followed. This is especially important with biologicals such as RABs, and short-lived radioactive materials.

A dose calibrator (see section 2.6) should be used in the clinic to determine the activity in a dosage just before it is administered to a patient. This requirement applies to alpha- and beta-emitters that also produce photons, and gamma-emitters.

Dosages less than 10 μCi (370 kBq) of gamma-emitters cannot be calibrated with a dose calibrator. A more sensitive instrument must be used, such as a well-type NaI(Tl) detector. However, this is not a problem for RABs because dosages for imaging or therapy are greater than 1 mCi (37 MBq) (Barber et al., 1991) (see Table 1.2).

If a NaI well-type counter is used to assay the smaller dosages it is advisable to keep the volume of the sample small compared to the volume of the well. Errors attributable to volume differences will be a few percent at most if the sample occupies no more than half the volume of the well. For example, the counting efficiency for 0.511 MeV photons when the well is full is 85% of the efficiency when the well is one-third full (Kearfott, 1989). However, the magnitude of this error will depend on the source geometry, and the energy of the photons. Plastic inserts designed to facilitate reproducible geometries in well counters reduce errors attributable to positioning of the sample.

## 4.4 Unit vs. Multidosage Vials

If the dosage to be administered is to be based on the producer's calibration, only single-dose vials should be used, and any differences observed between the clinical measurements and those of the producer should be reconciled before a dosage is administered to a patient.

Multi-dosage vials may be used if dosage calibrations by the producer or radiopharmacy, and user (for individual dosages) agree, and if the user is a member of a medical facility which has a license of broad scope. Guidance from a radiation safety committee that includes at least one member who has experience with quantifying alpha- and beta-emitters is essential.

# 5. EXPOSURE CONTROL AND MONITORING

## 5.1 Occupational

### 5.1.1 External Dose

Monitoring of areas and personnel requires ionization chamber rate meters and personnel dosimeters that can measure the dose rates and doses to which personnel are exposed. The alpha particles emitted by radionuclides likely to be used to label RABs do not present external problems of exposure. However, photon emissions from the decay products of some alpha-emitters may contribute to external exposure.

Personnel dosimeters that use film, thermoluminescent materials, or pocket ionization chambers are commonly used to measure the doses from beta- gamma-, and x-radiations. These dosimeters can be used to monitor personnel who work with RABs. A whole-body dosimeter will provide an adequate measure of the occupational dose received from radiation emanating from a patient or from containers in a pharmacy or manufacturing facility.

High energy beta-emitters present the potential for extraordinarily high beta-doses to the skin of the fingers and hands if intervening materials (gloves, vials, syringes, shields) are not thick enough to absorb the beta particles. Bremsstrahlung can produce measurable exposure, but it is not of the same order as exposure produced by gamma- or x-radiation.

There are two cautions related to the use of personnel dosimeters for monitoring doses from RABs. The first involves notifying the processor of the dosimeter of the specific radionuclides used. Interpretation of energy deposition in personnel dosimeters is especially difficult for beta particles and low energy x rays such as those emitted by RABs. Second, finger dosimeters must be used because of the potential for high doses to the skin of the fingers and hands. When contractors provide personnel monitoring services for a facility, the contractor should be notified of the specific radionuclides to which the dosimeters are exposed. This is especially important for RABs that emit photons with energies less than 35 keV. Special attention should be given to skin dosimetry when Y-90 is used.

When RABs containing gamma-emitters are administered by infusions that take more than a minute, personnel should remain in sight of, (but as remote as possible from), the patient. In close quarters, portable transparent shields could be used to keep doses to personnel ALARA. Beta-emitters are not an external exposure problem if the infusion lines and reservoirs are thick enough to completely absorb the beta particles. However, Y-90 beta particles are capable of penetrating thicknesses up to 1100 mg $cm^{-2}$. Therefore, infusion reservoirs and lines must be handled carefully to avoid unnecessary exposure and contamination.

### 5.1.2 Internal Dose

Y-90 in environmental samples can be measured with thin, plastic scintillators. Detection efficiencies of 40-50% have been observed for Y-90 beta-particles when the source is in contact with the scintillator (DOE, 1990). However, measurements with thin-windowed G-M counters are preferable for controlling contamination for beta- and beta-gamma emitters.

The primary concern for alpha-emitters and properly shielded beta-emitters is contamination of the environment by excretions from patients and procedures that can result in the ingestion, absorption through the skin, or inhalation of the radioactive material. To control contamination from alpha-emitters, a ZnS scintillation detector should be used.

Air sampling equipment that can measure air concentrations of alpha- or beta-emitters at or below release limits should be available for use in situations where activity may be released to the air (in a patient's room, a RAB preparation area, a manufacturing facility, or a pharmacy where RABs may be reconstituted). This is especially important with patients who receive therapy dosages of RABs labeled with halogens such as iodine or astatine.

Samples of halogens taken through activated charcoal or particulates collected on a filter having a pore size <0.45 μm can be measured with HPGe or GeLi spectrometers (for gamma- or x-ray-emitters, ZnS scintillation counters (for alpha-emitters), and G-M counters (for beta-emitters). The alpha-emitters likely to be used to label RABs either decay into gamma-emitting radionuclides or have associated gamma-radiation emissions. The collection and evaluation of environmental samples may be done by the licensee or a contractor.

If only a few liters of air are collected, concentrations of alpha-emitting particulates below the public release limits specified in 10 CFR 20 (NRC, 1991) can be detected with a ZnS detector in less than 10 minutes counting time. Such a small sample can also be used to detect concentrations of Y-90 in air less than the public release limit with a thin-windowed G-M counter. However, radon decay products will interfere with the assay of air samples unless the counts are corrected for the presence of these decay products, or the sample is kept for 4 or more hours before it is evaluated.

Large volumes of air and long counting periods are required to detect the release concentrations specified in 10 CFR 20 based on gamma-ray spectrometry because of the low efficiency of HPGe or GeLi detectors.

A dose calibrator is of no use in detecting and measuring concentrations of activity at or below the limits specified in 10 CFR 20 (NRC, 1991).

For facilities in which I-131 is used and adequately controlled, there is likely to be no problem in controlling contamination and exposures from other radionuclides used to label RABs (see section 5.3). However, producers and users of RABs labeled with radionuclides that emit predominantly alpha- or beta-radiation must have instruments capable of confirming that levels of surface or air contamination are compatible with NRC regulations.

### 5.1.3 Exposure from Inpatients

High levels of activity are sometimes administered to RAB-patients. Hence, the potential for both external exposure of others, and contamination of facilities is greater than with patients containing common radiopharmaceuticals. Spills are especially of concern, and there should be a protocol for managing them.

All lines connected to the patient should be surveyed and disposed of as radioactive waste. The syringe(s), shields, gloves, and other material that is potentially contaminated should be returned to the laboratory (pharmacy) to be surveyed and stored for re-used or disposal.

The thyroid burden of each individual attending a patient who has received a therapeutic dosage of a RAB labeled with I-131 should be measured after about half of the patient's hospital confinement has elapsed. With RABs labeled with I-131 a smaller fraction of the dosage (depending on the labeling procedure) goes to the thyroid gland than with common radiopharmaceuticals. As the RAB is catabolized, free iodine becomes available for uptake. Hence, the potential for thyroid uptake by the attendants increases with time after-administration. However, the amount of radioactive material in the patient decreases

with time due to natural decay and elimination, so less is available for uptake by attendants. The pharmokinetic behavior and radioactive decay of the RAB are somewhat self-compensating with respect to radiation safety. However, sufficient data are not available to determine the optimum time to measure the thyroid burdens of individuals who attend RAB patients.

External exposure rates from patients undergoing therapy with RABs are likely to be higher for longer periods compared to the rates from patients containing common radiopharmaceuticals. Staff should be made aware of this, so that they can modify the time spent in close proximity to RAB patients. The external exposure of staff and visitors to RABs labeled with I-131 is of great concern.

The exposure rate at 1 m from the patient should be measured with an ionization chamber rate meter at intervals of about 8 hours, beginning as soon as possible after administration. These measurements enable the determination of occupancy times for staff attending the patient and visitors, when the patient can be released from confinement, and the whole-body effective half-life for the RAB. The latter measurement is required to estimate external doses to family members and the public. It is also useful to determine if environmental contamination in the patient's home is likely to be a problem. This is especially important if the patient provides care for a family.

If RABs labeled with halogens are used, the air in the patient's rooms should be monitored to show that it does not exceed either occupational or public limits if the patient receives visitors.

Otherwise, care for patients containing RABs should be no different from that of patients containing common radiopharmaceuticals.

## 5.2 Release of Patients from the Hospital

The data that would enable release limits for patients to be determined on the basis of potential contamination of their environments or potential external dose equivalents to the public remain to be assembled. Information on the whole-body clearance rates of various types of RABs for various diseases is required before release limits for RABs can be determined (Barber et al., 1991).

Patients should not be released until it has been determined that the intake by a member of the public will not exceed the Annual Limit of Intake prescribed by 10 CFR 20 (NRC, 1991). Again, information on whole-body clearance rates must be examined before specific recommendations can be made.

The most restrictive Derived Air Concentrations (DACs), and environmental release concentrations given in 10 CFR 20 (NRC, 1991) for radionuclides used in RABs are listed in Table 5.1. The DACs for the alpha-emitters in Table 5.1 are of the same order as the DACs for I-131.

The ratios for (radionuclide concentration) / (I-131 concentration) for the radionuclides in Table 5.1 are listed in Table 5.2. Radionuclides for which the ratio is less than one involve greater internal dose risks than I-131. From Table 5.2 it is clear that At-211 in air, represents a greater risk to the public than I-131. In the occupational domain, At-211 is no more threatening than I-131. Pb-212 in air presents a greater risk than I-131 in the occupational and public domains. However, in the worst case (Pb-212 in public air), the risk is only four times that associated with I-131. If release limits for RAB patients were based on equivalence to I-131, then, for most of the radionuclides used in RABs, the risk of internal exposure or

contamination of the environment in either the occupational or public domains would be no greater than that for I-131 patients.

**Table 5.1 Most restrictive derived air concentrations (DACs), and environmental release concentrations from 10 CFR 20 (NRC, 1991) for radionuclides used in RABs.**

| Nuclide | DAC, pCi $ml^{-1}$ | Release concentration Air, fCi $ml^{-1}$ | Release concentration Sewer, nCi $ml^{-1}$ |
|---|---|---|---|
| I-131 | 0.02 | 0.2 | 0.01 |
| Y-90 | 0.2 | 0.9 | 0.07 |
| Tc-99m | 60 | 200 | 10 |
| In-111 | 3 | 9 | 0.6 |
| Re-186 | 0.7 | 2 | 0.3 |
| Re-188 | 1 | 4 | 0.2 |
| At-211 | 0.02 | 0.08 | 0.02 |
| Pb-212 | 0.01 | 0.05 | 0.02 |

Notes:

Multiply nCi $ml^{-1}$ by 37 to obtain Bq $ml^{-1}$.
Multiply pCi $ml^{-1}$ by 0.037 to obtain Bq $ml^{-1}$.
Multiply fCi $ml^{-1}$ by 37 to obtain $\mu$Bq $ml^{-1}$.

Table 5.2 Ratios[1] of concentration of a given radionuclide to the comparable concentration for I-131 based on the most restrictive derived air concentrations (DACs), and environmental release concentrations giv n in 10 CFR 20 (NRC, 1991).

| Nuclide | DAC ratio | Release concentration ratio Air | Release concentration ratio Sewer |
|---|---|---|---|
| I-131 | 1 | 1 | 1 |
| Y-90 | 10 | 4.5 | 7 |
| Tc-99m | 3000 | 1000 | 1000 |
| In-111 | 150 | 45 | 60 |
| Re-186 | 35 | 10 | 30 |
| Re-188 | 50 | 20 | 20 |
| At-211 | 1 | 0.4 | 2 |
| Pb-212 | 0.5 | 0.25 | 2 |

1. Ratio = (radionuclide concentration) / (I-131 concentrat n)

## 5.3 Outpatients and the Public

The extent of control required for RAB outpatients who receive dosages less than 30 mCi (1110 MBq) and therapy patients who are released from the hospital cannot be determined until the whole-body effective half-lives of RABs are known. However, the risk of internal exposure to members of the public appears to be comparable to the risk associated with patients containing comparable amounts of I-131 activity. For I-131, persons who are cuddled by the patient are at greatest risk. Children nurtured by patients at home may be at greatest risk.

The potential for external exposure could be higher with RABs than with common radiopharmaceuticals because of longer whole-body half-lives. However, the differences between RABs and common radiopharmaceuticals that would contribute to differences in population risks cannot be evaluated without additional data on the clearance of various types of RABs from the body.

## 5.4 Waste Control

The waste-control issues related to RABs labeled with byproduct material are not significantly different from those of handling common radiopharmaceuticals. Consideration of physical half-life, types of radiation emitted, and compliance with regulations are the same for RABs as for any radioactive waste.

## 6. PERSONNEL AND KNOWLEDGE REQUIREMENTS

### 6.1 The Team

Those responsible for the preparation and administration of a prescribed dosage must be trained and skilled in quality assurance procedures. One person (no matter how competent) cannot do all that must be done. A team approach is required.

The medical director, medical physicist, and radiopharmacist (or radiochemist) have responsibilities for quality control and quality assurance (ICRP, 1987; JCAHO, 1990). The medical director is responsible for the overall quality of care provided to patients. The medical physicist is responsible for radiation safety and quality control, as well as for data handling and computations associated with nuclear medicine tests. The radiopharmacist (or radiochemist) is responsible for development, production, quality assurance, and control of radiopharmaceuticals, including RABs.

Nuclear medicine technologists certified by the Nuclear Medicine Technologist Certification Board should be competent to calibrate dose calibrators for RABs because the Board includes the following in its critical list of tasks for technologists (Blossr et al., 1988). These tasks apply to both RABs and other types of radiopharmaceuticals.

1. Ascertain the linearity of a dose calibrator over the range of radionuclide activity to be measured.

2. Test for significant geometrical variation in activity measured as a function of the sample's volume or configuration, and determine correction factors.

3. Test the accuracy for radionuclides that have adequate reference standards.

4. Check the constancy of the reading with a standard, long-lived radionuclide.

5. Maintain records of the procedures.

6. Verify the dosage or radioactivity with a dose calibrator.

7. Confirm the calculated activity with a dose calibrator.

The technologist is usually the person who prepares or confirms dosages just before they are administered to patients. Technologists should understand the use and limitations of dose calibrators, know how to calibrate the dose calibrator when reference standards for the particular radionuclides are not available, and should be able to determine correction factors for deviations from linearity. Dose calibrators vary in their complexity, and the calibration required depends upon the needs of the user. Hence, detailed instructions on how to calibrate a calibrator are not included here. The principles and procedures are given in NCRP (1978), Suzuki et al. (1976), ANSI (1986), or ACNP (1984).

When technologists are involved in confirming and administering RAB dosages to patients, they must know how to cope with the special problems of measuring and surveying radionuclides that emit predominantly alpha- or beta-radiations. Even in major facilities staffed with qualified radiation safety officers, radiation safety (including environmental contamination surveys) is often the responsibility of the user.

## 6.2 Radiation Safety Officers

Radiation Safety Officers (RSOs) occupy a critical point in the chain of supply and waste disposal of all radioactive materials. They should have access to instrumentation that can identify and determine the activity of many different types of radioactive materials.

RSOs who are responsible for controlling RABs should be familiar with the principles and operation of HPGe and GeLi spectrometers and dose calibrators. They should also understand the pharmacokinetic differences between RABs and common radiopharmaceuticals that can affect the level and duration of occupational exposure. They should also be responsible for measuring exposure rates, as a function of time, to determine when it is radiologically safe to release patients from the hospital. This may require more time for RAB patients than is customarily required. RSOs must also understand the differences in radiation safety problems presented by alpha-, beta-, and gamma-emitters, to assure that appropriate calibrations and surveys are incorporated into the radiation safety program.

Shipments of RABs should be measured by the RSO for conformance with the shipping specifications and labeling. RSOs are not responsible for calibrating dosages administered to patients, but they can check the activity and specific radionuclides present in a shipment by using a GeLi or HPGe spectrometer. Also, with a dose calibrator, they can determine that the amount of activity ordered was supplied. If a HPGe or GeLi spectrometer is used, the detector must be heavily shielded to attenuate the radiation emitted by packages or the packages must be measured at a distance of three feet or more through a collimator because count rates should be kept less than 120,000 cpm (DOE, 1990; Vetter, 1991). GeLi spectrometry and dose calibrators are used to confirm the radionuclides and activity in inbound shipments of radiopharmaceuticals.

## 6.3 Radiation Safety Committee

The Radiation Safety Committee (RSC) should be aware of the differences between RABs and common radiopharmaceuticals that could contribute to unusually high occupational, patient or public radiation exposure. They must also be aware of, and be prepared to exercise judgement on, biological issues related to RABs.

One or more members of the committee should have extensive training and experience in nuclear medicine. An immunologist should be included on the committee, or be consulted by the committee about biological aspects of using RABs, such as the need to test the antibody status of the patient before administering a RAB to avoid (or be prepared for) complications that can arise in patients to whom RABs have been administered previously.

Procedures equivalent to those required by the U.S. Food and Drug Administration (FDA, 1987) should be required of producers of RABs. Procedures for which the FDA has accepted a Notice of Claimed Investigational Exemption (IND) or approved a New Drug Application (NDA) should be approved by the RSC. The RSC should assure that users follow procedures described in the IND or NDA, and the instructions of the producer of the RAB. Exceptions to careful review by the RSC is required for studies if FDA approval is not required.

### 6.4 Individual Users

Individual users are responsible for the way in which radioactive materials ultimately are used. If a user does not have an RSO or an RSC, the user is wholly responsible. Such a situation requires such an immense amount of knowledge and time that it would be virtually impossible for a single individual to meet all the technical requirements essential to the safe use of RABs in humans until the results of INDs have been obtained, the indications and contraindications for a given RAB are well known, and a product is licensed by the FDA for general use.

At this time individual, independent users should not be permitted to use RABs in human investigations. Every user should be associated with a medical establishment that has the benefit of a well qualified RSO and RSC so that RABs are used safely in imaging studies or for therapeutic purposes.

Users of RABs should be not only understand radiation safety matters but also should be well informed on the biological and chemical aspects of RABs. As a minimum, they should know the FDA guides for IND applications (FDA, 1987).

## 7. SUMMARY AND RECOMMENDATIONS

The differences between RABs and common radiopharmaceuticals require some additional procedures on radiation safety and quality assurance to safeguard the health and safety of patients, those occupationally exposed, and the public. These additional requirements are summarized in the following recommendations that should be considered before a licensee is permitted to use RABs for diagnosis or therapy.

### 7.1 General

Procedures equivalent to the FDA Good Manufacturing practices for producing and testing antibodies (FDA, 1987) should be followed by drug manufacturers and those who produce RABs for their own use. The RSC should assure that users follow procedures described in an IND or NDA, and the instructions of the producer of the RAB. Exceptionally careful review by the RSC is required for studies if approval of the FDA is not required.

The RAB must be approved for IND or NDA applications by the FDA or a state board of pharmacy for use in humans. Pharmacists and individual users may rely on manufacturing specifications and certifications for single dosages if the product has been manufactured in accordance with FDA regulations and guidelines, and dosage specifications are based on methods recommended in this report.

Users should not be self-sufficient. A team approach to the use of RABs should be required, especially in investigational phases involving use in humans. As a minimum, the user should have the benefit of review by a qualified radiation safety committee.

### 7.2 Instruments

Producers should be required to use HPGe or GeLi spectrometry to identify and quantify the primary radionuclides and contaminants in their RABs.

Alpha-detectors are necessary instruments for producers and users if alpha-emitters are to be used. Zinc sulfide detectors should be used to quantify environmental contamination with

alpha-emitters. The detector should be calibrated with a standard source which emits alpha particles within ± 20% of the energy of the alpha particles to be measured.

Special care must be taken with RABs labeled with I-131 to be certain that linearity errors either do not occur or are corrected for in measuring activity levels above 0.57 Ci (21 GBq) with a dose calibrator. If
linearity is tested with Tc-99m, levels of activity that produce comparable effects on saturation should be used.

Calibrations with the specific radionuclides (or radionuclides that emit equivalent types and energies of radiation) to be measured should be required. Calibrations for beta-emitters, such as Y-90, and radionuclides that emit low energy photons (e.g., Re-186, Re-188 and At-211) should also be made in standardized geometries and containers.

7.3 Calibration and Check Sources

Calibration sources should be certified by, or be traceable to, the National Institute of Standards and Technology.

Standard sources for calibration of dose calibrators should emit x- or gamma rays over the energy range of the RABs to be used. Calibration sources for alpha-detectors should emit alpha particles in the range of 3 to 6 MeV. Sources of different apparent activities are required to test the linearity of survey meters.

7.4 Dosage Calibrations

Visual inspection of the physical appearance of the RAB and its expiration date is important because some RABs have short shelf-lives. When the material is not as clear as it should be or if clumps occur, the dosage should not be administered.

Producers of RABs bear a special responsibility to provide reliable calibrations with their products because sometimes users may have to rely on these calibrations. GeLi or HPGe spectrometers should be used by producers for the final calibration of dosages of radionuclides which emit x- or gamma- radiation (including alpha- and beta-emitters). Shielding between the detector and source should be used to avoid overloading the detector.

Dosages of RABs labeled with Y-90 should be based on bremsstrahlung measurements in a dose calibrator that was calibrated using the same geometry and containers that will be used in the clinic. When dose calibrators are used to calibrate dosages from beta-emitters, a well-liner (absorber) should be used to make the total thickness between the sensitive volume of a dose calibrator and the radioactive material equal to, or greater than, the thickness required to completely absorb the most energetic beta particle emitted. The calibration should be based on photon detection only. Alternatively, liquid scintillation counting can be used.

7.5 Exposure Control and Monitoring

Although alpha-emitters may also emit x- and gamma rays, they are not an external radiation hazard to either the occupationally exposed or the public. The concern is whether significant radioactive contamination of the environment occurs either via the air or as a consequence of the activities of the patient.

Air sampling should be required in manufacturing facilities, pharmacies, clinics, and hospitals to confirm that airborne activity is within the limits specified by 10 CFR 20 (NRC, 1991). Sampling is especially important for halogens such as I-131 and At-211. For facilities in which I-131 is used and adequately controlled, there is likely to be no problem in controlling contamination and internal exposures from other radionuclides used to label RABs.

When contractors provide personnel monitoring services for a facility, the contractor should be notified of the specific radionuclides to which the dosimeters are exposed. This is especially important for RABs that emit photons with energies less than 35 keV. Special attention should be given to skin dosimetry when Y-90 is used.

Ionization chamber rate meters should be used to measure and monitor radiation levels in areas in which personnel may be exposed to x- or gamma-radiation. External exposure rates from RAB therapy patients are likely to be higher for longer than the external exposure rates from patients containing common radiopharmaceuticals. Staff should be made aware of this so that they may reduce the time spent in close proximity to RAB patients. The external exposure of staff and visitors to RABs labeled with I-131 is the greatest concern.

The exposure rate at 1 m from the patient should be measured with an ionization chamber rate meter at intervals of about 8 hours, beginning as soon as possible after administration. These measurements enable the determination of occupancy times for staff attending the patient and for visitors, when the patient can be released from confinement, and the whole-body effective half-life for the RAB. The whole-body effective half-life is required to estimate doses to family members and to the public.

There are no assembled data that can be used to determine release limits for patients based on the potential contamination of their environments, or potential external dose equivalents to the public. Information on the whole-body clearance rates of various RABs for various diseases is required before the release limits for RABs can be determined (Barber et al., 1991). However, from a comparison of derived air concentrations, it appears that if release limits for patients containing RABs were based on their equivalence to I-131, then for most radionuclides used in RABs, the risk of internal exposure or contamination of the environment in either the occupational or public domains would be no greater than that for I-131 patients. However, alpha- and beta-emitters could present new environmental contamination in the home, especially if the patient provides family care.

RABs used for imaging have whole-body half-lives that are shorter than those used for therapy. However, the differences between RABs and common radiopharmaceuticals that would contribute to differences in population risks cannot be evaluated without additional data on the clearance of various types of RABs from the body.

When RABs containing gamma-emitters are administered by infusions that require more than a minute, personnel should remain in sight of (but as remote as possible from) the patient. Portable shields should be used if the infusion lines and reservoirs are not thick enough to completely absorb the beta-particles. Care also must be exercised in handling infusion reservoirs and lines to avoid unnecessary exposure and contamination. A protocol for managing spills is important with RABs because of the levels of activity.

## 7.6 Personnel and Knowledge Requirements

Those responsible for measuring and administering a prescribed dosage must be trained and skilled in quality assurance procedures. One person (no matter how competent) cannot do everything. A team approach is required.

Nuclear medicine technologists certified by the Nuclear Medicine Technologist Certification Board should be competent to calibrate dose calibrators for RABs. However, additional training may be necessary if they are responsible for environmental contamination surveys, and to assure that the particular measurements and monitoring associated with RABs labeled with radionuclides that emit primarily alpha- or beta-radiations are fully understood.

RSOs who are responsible for controlling RABs should be familiar with the principles and operation of HPGe and/or GeLi spectrometers and dose calibrators. They also should understand the pharmacokinetic differences between RABs and common radiopharmaceuticals that can affect the level and duration of occupational exposure. They also should be responsible for measuring exposure rates from patients, as a function of time, to determine when it is radiologically safe to release patients from the hospital.

The RSC should be aware of the differences between RABs and common radiopharmaceuticals that could contribute to unusually high occupational, patient, or public radiation exposure including the peculiarities of alpha- and beta-emitters that require different instrumentation and measurements from those ordinarily associated with gamma-emitters. The RSC must also be aware of and be prepared to exercise judgement on biological issues related to RABs.

One or more members of the RSC should have extensive training and experience in nuclear medicine and should be well informed on measuring and monitoring of radionuclides that emit primarily alpha- or beta-radiations, as well as gamma-emitters. An immunologist should be a member of the committee or be consulted by the committee about the biological aspects of using RABs, such as the need to test the antibody status of the patient before administering a RAB to avoid (or be prepared for) complications that can arise in patients to whom RABs have been administered previously.

The RSC should assure that users follow procedures described in INDs or NDAs, and the instructions of the producer of the RAB. Procedures indicated on the package inserts of licensed products should be followed, unless a user justifies to the RSC that other procedures are safe and in the best interests of the patient, and those occupationally exposed.

## 8. REFERENCES


ACNP, 1984, Initial Testing and Quality Control for Radionuclide Dose Calibrators, Committee on Standardization of Nuclear Medicine Instrumentation, American College of Nuclear Physicians (ACNP, Washington).

ANSI, 1986, Calibration and Usage of Dose Calibrator Ionization Chambers for the Assay of Radionuclides, American National Standards Institute Report N42.13-1986 (The Institute of Electrical and Electronics Engineers, Inc., New York).

Ahluwalia, B., 1985, Dose calibrator linearity - a regulatory requirement, Health Physics 49(5):967-969.

Barber, D.E., Baum, J.W., and Meinhold, C.B., 1991, Radiation Safety Issues Related to Radiolabeled Antibodies, BNL-NUREG-52275 (National Technical Information Service, Springfield).

Blosser, N., Drew, H. and Steves, A., 1988, NMTCB task analysis validation update, J. Nucl. Med. Tech. 16(4):216-221.

Calhoun, J.M., Golas, D.B., and Harris, S.G., 1987, Effects of varying geometry on dose calibrator response: cobalt-57 and technetium-99m, J. Nucl. Med. 28(9):1478-1483.

Chu, R.Y.L., 1988, Accuracy of dose calibrator linearity test, Health Physics 55(1):95-96.

Coursey, B.M., Cessna, J., Garcia-Torano, E., Golas, D.F., Malonda, A.G., Gray, D.H., Hoppes, D.D., Los Arcos, J.M., Martin-Casallo, M.T., Schima, F.J., and Unterweger, M.P., 1991, The standardization and decay scheme of rhenium-186, Appl. Radiat. Isot. 42 (9) :865-869.

DOE, 1990, EML Procedures Manual, Environmental Measurements Laboratory, HASL-300, U.S. Department of Energy, New York, NY (National Technical Information Service, VA), pp. 4.5-7 to 4.5-27.

Ehrhardt, G.J. and Day, D.E., 1987, Therapeutic use of $^{90}Y$ microspheres, Nucl. Med. Biol. 14(3):253-242.

FDA, 1987, Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use (1987), Center for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, MD.

Harris, C.C., Jaszczak, R.J., Greer, K.L., Briner, W.H., and Coleman, R.E., 1984, Effects of characteristic x-rays on assay of I-123 by dose calibrator, J. Nucl. Med. 25(12):1367-1370.

Hickey, E.F., Stoetzel, G.A., Olsen, P.C., McGuire, S.A., 1991, Air Sampling in the Workplace, NUREG-1400, Draft Report For Comment.

Horton, P.W. and Bell, N.D.S., 1986, Radiopha[illegible]icals: Preparation and Quality Assurance, in Physics in Medicine and Biology [illegible]lia, Vol. 2 (T.F. McAlush, Ed.) (Pergamon Press, NY), pp 701-705.

ICRP, 1987, Protection of the Patient in Nuclear Medicine, International Commission on Radiological Protection, ICRP Publication 52, Annals of the ICRP 17(4).

JCAHO, 1990, Accreditation Manual for Hospitals (Joint Commission on Accreditation of Healthcare Organizations, Chicago).

Kearfott, K.J., 1989, Performance of a well counter and a dose calibrator for quantitative positron emission tomography, Health Physics 57(4):623-629.

Latner, N., Miller, K., Watnick, S., and Graveson, R.T., 1983, SPICER: A sensitive radiation survey instrument, Health Physics 44(4):379-386.

Leach, K.G., 1986, Gamma-Ray Detectors, in Physics in Medicine and Biology Encyclopedia, Vol. 1 (T.F. McAinsh, Ed.) (Pergamon Press, NY), pp 358-361.

Mallol, J., 1990, Analytical artifacts in quality control of $^{99m}$Tc radiopharmaceuticals, Int. J. Radiat. Appl. Instrum. Part B, Nucl. Med. Biol. 17(6):609-611.

NCRP, 1978, A Handbook of Radioactivity Measurements Procedures, National Council on Radiation Protection and Measurements Report No. 58 (NCRP Publications, Washington).

NIST, 1990, Standard Reference Materials Catalog 1990-1991, National Institute of Standards and Technology, U.S. Department of Commerce, NIST Special Publication 260 (U.S. Government Printing Office, Washington).

NRC, 1980, Calibration and Error Limits of Air Sampling Instruments for Total Volume of Air Sampled, Regulatory Guide 8.25, U.S. Nuclear Regulatory Commission (National Technical Information Service, Springfield).

NRC, 1987, Guide for the Preparation of Applications for Medical Use Programs, Regulatory Guide 10.8, U.S. Nuclear Commission Regulatory (U.S. Government Printing Office, Washington).

NRC, 1989, Rules of General Applicability to Domestic Licensing of Byproduct Material, Title 10, Code of Federal Regulations, Part 30 (Office of the Federal Register National Archives and Records Administration, Washington).

NRC, 1991, Standards for Protection Against Radiation,Title 10, Code of Federal Regulations, Part 20, Federal Register 56(98):23390-23470.

Olkari, T., Kojola, H. Nurmi, J. and Kaihola, L., 1987, Simultaneous counting of low alpha- and beta-particle activities with liquid-scintillation spectrometry and pulse shape analysis, Appl. Radiat. Isot., Int. J. Radiat. Appl. Instrum. Part A 38(10):875-878.

Paras, P., 1977, Quality Assurance in Nuclear Medicine (in Medical Radionuclide Imaging, Vol. I, International Atomic Energy Agency, IAEA-SM-210/301 (IAEA, Vienna).

Paras, P., 1981, Performance and Quality Control of Nuclear Medicine Instrumentation (in Medical Radionuclide Imaging 1980, Vol. II, International Atomic Energy Agency, IAEA-SM-247/208) (IAEA, Vienna).

Parker, R.P., 1986, Beta-Particle Detection, in Physics in Medicine and Biology Encyclopedia, Vol. 2 (T.F. McAinsh, Ed.) (Pergamon Press, NY), pp 30-33.

Pfeiffer, G., 1984, Quality control of radiopharmaceuticals, Nuklearmedizin 23:4-8.

Santry, D.C. and Bowes, G.C., 1989, Half-life of $^{99m}$Tc in linearity testing of radionuclide calibrators, Health Physics 57(4):673-675.

Shields, R.A., 1986, Quality Assurance in Nuclear Medicine, in Physics in Medicine and Biology Encyclopedia, Vol. 2 (T.F. McAinsh, Ed.) (Pergamon Press, NY), pp 604-610.

Shleien, B. and Terpilak, M.S.(Eds.), 1984, The Health Physics and Radiological Health Handbook (Nucleon Lectern Associates, Olney), p. 131.

Suzuki, A., Suzuki, M.N., and Weis, A.M., 1976, Analysis of a radioisotope calibrator, Jour. Nucl. Med. Tech. 4(4):193-198.

Vera-Ruiz, H., Marcus, C.S., Pike, V.W., Coenen, H.H., Fowler, J.S., Meyer, G.J., Cox, P.H., Vaalburg, W., Cantineau, R., Helus, F., and Lambrecht, R.M., 1990, Quality control of cyclotron-produced radiopharmaceuticals, Int. J. Radiat. Appl. Instrum. Part B, Nucl. Med. Biol. 17(5):445-456.

Wiarda, K.S., 1984, Use of a copper filter for dose-calibrator measurements of nuclides emitting k x-rays, J. Nucl. Med. 25(5):633-634.

Williams, L.E., Wong, J.Y.C., Findley, D.O., and Forell, B.W., 1989, Measurement and estimation of organ bremsstrahlung radiation dose, J. Nucl. Med. 30(8):1373-1377.

Zoghbi, S.S., Rassi, Z.E., Neumann, R.D., and Gottschalk, A., 1987, Quality control and the preparative purification of low antibody concentrations for radiolabelling using bifunctional chelates, Nucl. Med. Biol. 14(5):529-532.

## APPENDIX I
## UNPUBLISHED REFERENCES

Atcher, R.W., 1991, Argonne National Laboratory, Argonne, IL, personal communication.

Santry, D.C., 1991, Ionizing Radiation Standards Section, Institute for National Measurement Standards, National Research Council, Canada, personal communication.

Stabin, M., 1991, Radiopharmaceutical Internal Dose Information Center, Medical Sciences Division, Oak Ridge Associated Universities, Oak Ridge, TN, personal communication.

Suzuki, A., 1990, Capintec, Inc. Ramsey, NJ, 37th Annual Meeting, The Society of Nuclear Medicine, June 19-22, Washington, DC, personal communication.

Vetter, R.J., 1991, Radiation Safety Officer, Mayo Clinic, Rochester, MN, personal communication.

Weber, D., 1990, Brookhaven National Laboratory, Upton, NY, personal communication.

NRC FORM 335 (2-89) NRCM 1102, 3201, 3202

U.S. NUCLEAR REGULATORY COMMISSION

# BIBLIOGRAPHIC DATA SHEET

*(See instructions on the reverse)*

1. REPORT NUMBER (Assigned by NRC, Add Vol., Supp., Rev., and Addendum Numbers, if any.)

NUREG/CR-5877
BNL-NUREG-52328

2. TITLE AND SUBTITLE

Aspects of Monitoring and Quality Assurance for Radiolabeled Antibodies

3. DATE REPORT PUBLISHED

| MONTH | YEAR |
|---|---|
| June | 1992 |

4. FIN OR GRANT NUMBER

L1284

5. AUTHOR(S)

D. E. Barber

6. TYPE OF REPORT

Technical Report

7. PERIOD COVERED (Inclusive Dates)

06/23/89 to 03/92

8. PERFORMING ORGANIZATION – NAME AND ADDRESS (If NRC, provide Division, Office or Region, U.S. Nuclear Regulatory Commission, and mailing address; if contractor, provide name and mailing address.)

School of Public Health
University of Minnesota
Minneapolis, MN 55455

Under Contract to:
Brookhaven National Laboratory
Upton, NY 11973

9. SPONSORING ORGANIZATION – NAME AND ADDRESS (If NRC, type "Same as above"; if contractor, provide NRC Division, Office or Region, U.S. Nuclear Regulatory Commission, and mailing address.)

Division of Regulatory Applications
Office of Nuclear Regulatory Research
U.S. Nuclear Regulatory Commission
Washington, D.C. 20555

10. SUPPLEMENTARY NOTES

11. ABSTRACT (200 words or less)

This report is intended as an informational resource and guide for the U.S. Nuclear Regulatory Commission (NRC) and NRC licensees who produce or use radiolabeled antibodies (RABs). Components of quality assurance programs related to the production and use of RABs are reviewed and evaluated, and recommendations are made on dosage calibrations, exposure control, monitoring, and personnel requirements. Special emphasis is placed on dose calibrators because these instruments are used extensively to measure the dosages of radiopharmaceuticals to be administered to patients. The difficulties of using dose calibrators to quantify dosages of beta- and alpha-emitters are discussed. The advantages and disadvantages of using other instruments are examined, and recommendations are made on the types of instruments to be used for different applications.

12. KEY WORDS/DESCRIPTORS (List words or phrases that will assist researchers in locating the report.)

Antibodies- Radiolabeled, Nuclear Medicine, Radiopharmaceuticals, Quality Assurance, Radiation Safety, Dosage Calibrations

13. AVAILABILITY STATEMENT

Unlimited

14. SECURITY CLASSIFICATION

(This Page)
Unclassified

(This Report)
Unclassified

15. NUMBER OF PAGES

16. PRICE

THIS DOCUMENT WAS PRINTED USING RECYCLED PAPER

UNITED STATES
NUCLEAR REGULATORY COMMISSION
WASHINGTON, D.C. 20555-0001

OFFICIAL BUSINESS
PENALTY FOR PRIVATE USE, $300

FIRST CLASS MAIL
POSTAGE AND FEES PAID
USNRC
PERMIT NO. G-67

UNITED STATES
NUCLEAR REGULATORY COMMISSION
WASHINGTON, D.C. 20555-0001

OFFICIAL BUSINESS
PENALTY FOR PRIVATE USE, $300

FIRST CLASS MAIL
POSTAGE AND FEES PAID
USNRC
PERMIT NO. G-67