Alternative Radiochemical Purity Testing Procedures for the Compounded Radiopharmaceuticals Approved from 1988-1997

Prepared by

Quality Control Validation Subcommittee
Section on Nuclear Pharmacy Practice
APhA-APPM

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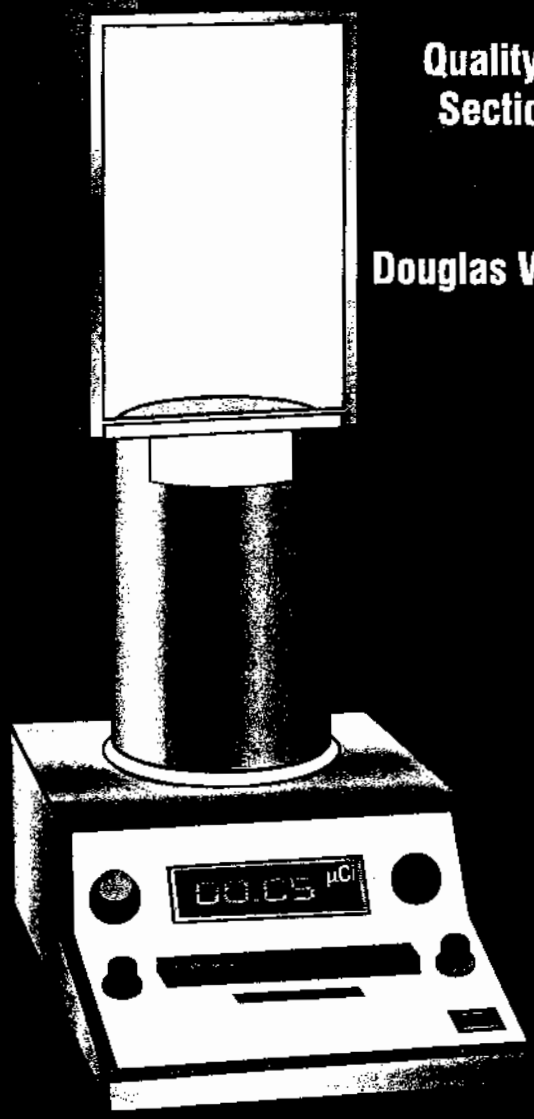

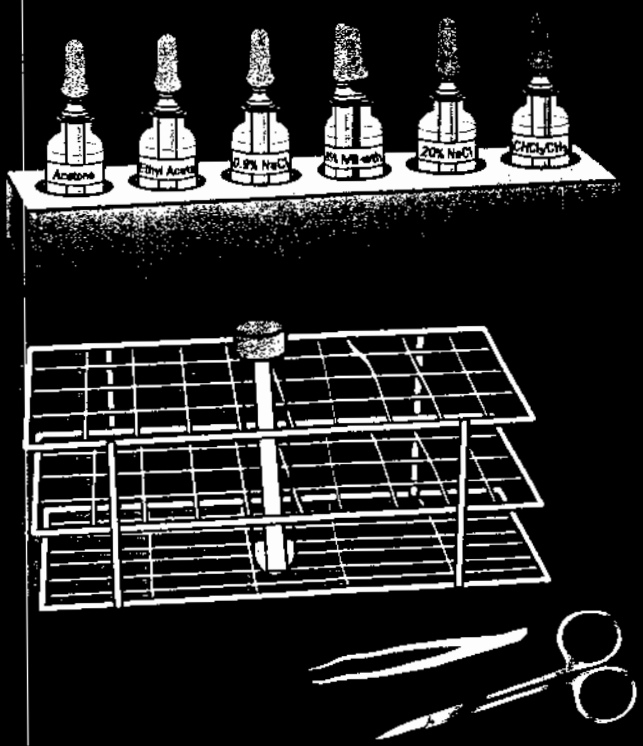

ALTERNATIVE RADIOCHEMICAL PURITY TESTING PROCEDURES FOR THE COMPOUNDED RADIOPHARMACEUTICALS APPROVED FROM 1988-1997

Prepared by

***Quality Control Validation Subcommittee*[1]**

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INTRODUCTION

The radiochemical purity (RCP) of a radiopharmaceutical is the percentage of total radioactivity that is present in the desired chemical form in a radioactive drug. The determination of RCP value of radiopharmaceuticals is an essential part of the quality control (QC) process, especially for on-site radiopharmaceutical preparations. The package insert and *The United Stated Pharmacopeia and The National Formulary* (USP/NF) are the two main sources for information on the standard methods for determination of RCP value of radiopharmaceuticals. However, due to the time-consuming processes involved and a lack of detailed information, it is usually impractical to use either source for routine RCP evaluation in a busy nuclear pharmacy laboratory.

The task of this subcommittee was to evaluate all of the published RCP testing methods (including the standard QC methods as stated in the package insert and/or USP/NF) using a rational rating system. The end user can then use the information that we present in this manual, along with their professional judgment, to select an acceptable alternative RCP testing method which will help them to simplify and expedite the routine RCP evaluation of radiopharmaceutical preparations. Since the rating system that we have used is quite subjective and the subcommittee does not possess the manpower or resources to retest and validate each proposed method using our ideal criteria, one must use his/her professional judgment to make the proper selection of an alternative QC method. Please note that none of the proposed RCP testing methods has been legally recognized and accepted by the Food and Drug Administration (FDA) or USP/NF. If one must perform RCP measurement due to legal requirements, the recommended QC methods as stated in the package insert and/or USP/NF should be used.

This manual does not favor RCP testing methods developed by a particular group of investigators, nor does this subcommittee endorse one QC method over another. Our evaluation process of the published RCP testing methods, including the

standard methods contained in the package inserts and USP/NF, are based strictly upon the unbiased and rational rating system that was developed by this subcommittee.

For our evaluation of the published RCP testing methods, we have primarily focused on (1) compounded radiopharmaceuticals which involve the use of cold kits and manufacturer-supplied radioisotopes (e.g., ^{99m}Tc or ^{111}In) and (2) cold kits that were approved by the FDA from 1988-1997.

Compounded Radiopharmaceuticals

Radiopharmaceuticals provided by the manufacturers are already monitored through a series of vigorous testing procedures; thus, it is generally not required to conduct any further quality control (QC) evaluation on the radiopharmaceuticals supplied by manufacturers. However, since the labeling reaction during the kit reconstitution process is not performed by the manufacturer but by the end user (usually nuclear pharmacists or nuclear medicine technologists), the industrial warranty will not be extended to in-house compounded radiopharmaceuticals. Consequently, it becomes the ultimate responsibility of the end user to ensure that the reconstituted product passes the required RCP testing.

1988-1997 Period

There are two main reasons that we evaluated only the RCP testing methods for compounded radiopharmaceuticals that were approved by the FDA from 1988 to 1997.

(1) Ceretec™ (kit for the preparation of ^{99m}Tc-exametazime) was initially approved by the FDA on December 30, 1988, and the package insert contains a statement that RCP determination of ^{99m}Tc-exametazime must

be performed before administration to the patient (*1*). Since then, the majority of package inserts for the newer compounded radiopharmaceuticals have a similar QC requirement (i.e., ^{99m}Tc-mertiatide, ^{111}In-pentetreotide, ^{99m}Tc-arcitumomab, ^{99m}Tc-nofetumomab merpentan, and ^{111}In-capromab pendetide) (*2-6*).

(2) With regard to alternative RCP testing methods for ^{99m}Tc-radiopharmaceuticals approved by the FDA prior to 1988, one can refer to an excellent booklet titled "*Chromatography of Technetium-99m Radiopharmaceuticals – A Practical Guide*" by Philip J. Robbins (*7*).

CRITERIA FOR SELECTING AN ALTERNATIVE RCP TESTING METHOD

Common Characteristics

To begin the process for selection of an RCP testing method to serve as an alternative to the recommended method, we first established the common characteristics for an ideal replacement for the recommended RCP testing methods. An alternative acceptable method for RCP determination should posses as many as of the following characteristics as possible: **F**ast, **A**LARA, **S**afe, **T**rue, **E**conomical, and **R**easonable (**FASTER**).

- **F**aster: This is a vital aspect of an alternative RCP testing method and is the primary reason for seeking another procedure to replace the recommended method(s).

- **A**LARA (as low as reasonably achievable): ALARA is a common principle for use whenever one handles any amount (no matter how small) of radioactive material in order to minimize radiation exposure to radiation workers. Any QC method that involves the use of a large radioactive sample (e.g., > 0.1 ml) from a high-activity kit preparation, and/or the radiochemical separation requires a long manipulation process would certainly not be in keeping with the spirit of the ALARA principle.

- **S**afe: This refers to the safety of chemical solvent(s) used in the RCP testing process. The performance of RCP evaluation usually involves the use of chemical solvent(s). To protect the safety of the end user and laboratory facility, a chemical solvent that is biologically safer and least likely to cause a fire hazard or to provoke a violent chemical reaction would be the preferred choice.

- **T**rue: The RCP value determined by the alternative method should be identical or as close as possible to the value determined by the recommended method.

- **E**conomical: The alternative RCP testing method should be cost-effective. Consideration should not only be given to the need for inexpensive materials and equipment to be used in the analytical process, but should also take into account such variables as shelf-life for less replacement costs.

- **R**easonable: The QC system used in determination of RCP value should be based upon technical simplicity. Less need for handling of the RCP testing materials and equipment either before or during the RCP testing process will undoubtedly result in better compliance with QC requirements and will minimize the possibility for error as well.

Scoring System

Based upon the relative importance of the aforementioned six common characteristics (i.e., **FASTER**), we established a rational 100-point scoring system as the basis for evaluation of the recommended and proposed RCP testing methods. The numerical scale of each of the six common characteristics and the associated selection criteria is described as follows:

- **Fast (20 points)**
  - RCP testing time $\leq$ 5 min (20 points)
  - 5 < RCP testing time $\leq$ 10 min (10 points)
  - 10 < RCP testing time < 20 min (5 points)

- **ALARA (5 points)**
  - Sample spot size ≤ 5 μl (5 points)
  - 5 < Sample spot size < 25 μl (2.5 points)

- **Safe (10 points)**
  - water, saline, 0.05 M DTPA solution (10 points)
  - 0.001 N HCl (8.1 points)
  - chloroform (6.3 points)
  - dichloromethane (5.6 points)
  - acetone, ethyl acetate, tetrahydrofuran (THF) (5.0 points)
  - methanol (4.4 points)
  - acetonitrile, ether, methyl ethyl ketone (MEK, butanone) (3.8 points)
  - ethanol (3.1 points)

NOTES:

(1) The chemical solvents listed are the mobile phases commonly used for the determination of RCP values. Please refer to Table 1 for a complete list of the safety ratings for the chemical solvents used in the QC methods that were evaluated in this manual.

(2) The assigned score for each chemical solvent takes into account the relative importance of biological, fire safety, and chemical reactivity of each chemical substance. We have adopted the rating systems of the National Fire Protection Association (NFPA) (*8*) and Baker SAF-T-DATA (*9*).

Both rating systems provide information relating to the severity of health, flammability, reactivity, and contact that may be presented by short-term, acute exposure to material during handling. Each of the four hazard categories has a numerical severity rating from 4 (extremely hazardous) to 0 (non-hazardous) (*8,9*).

Our scoring system simply takes an average rating of the four categories for each chemical solvent, and a score is assigned accordingly (i.e., full 10 point for the highest rating of 0 and 0 point for the lowest rating of 4).

According to the rating systems of the NFPA (*8*) and Baker SAF-T-DATA (*9*), ethanol has a scale rating of 3, 4, 2, and 2 for the four hazard categories; *i.e.*, health, flammability, reactivity, and contact, respectively (average rating of 2.75). Therefore, based upon our 10-

point scale for chemical safety, ethanol is assigned a score of 4.7 points (10 – [(10/4) x 2.75] = 3.1).

- **True (55 points)**

  - ***Range of Investigation* (15 points)**
    - More than 20-50% of trials performed below acceptance limit (15 points)
    - 5-20% of the trials performed below acceptance limit (7.5 points)

  - ***Validity of the Proposed Method* (10 points)**
    - Correlation coefficient > 0.9 requiring no calibration (10 points)
    - Correlation coefficient > 0.9 requiring calibration (5 points)

  - ***Accuracy of the Proposed Method* (10 points)**
    - 0% < false positive rate ≤ 5% and false negative < 20% (10 points)
    - 5% < false positive rate ≤ 10% and false negative < 20% (5 points)

  - ***Measurement of % Bound* (10 points)**

    Note:

    Only an RCP testing method that determines % activity of the radiolabeled compound (i.e., % bound) earns a full 10 points. QC methods which only provide a partial measurement of the final RCP value (i.e., % free Tc-99m or % hydrolyzed-reduced Tc-99m) do not receive any score.

  - ***Replication of Trials (5 points)***
    - Some replication (e.g., duplicate or triplicate measurements) with the variability within 50-100% of the standard method (5 points)
    - Some replication (e.g., duplicate or triplicate measurements) with the variability greater than 100% of the standard method (2.5 points)

- ***Sample Size*** **(5 points)**
  - If more than 20 trials were performed below the acceptance limit (5 points)
  - If between 15 to 20 trials were performed below the acceptance limit (2.5 points)

- **Economical (5 points)**
  - Dose calibrator as a counting device* (2 points)
  - Paper chromatography† or solvent extraction (2 points)
  - Non-HPLC grade‡ or other inexpensive chemical (1 point)

*Although other counting devices (e.g., well scintillation counter, radiochromatogram scanner, gamma camera, etc.) can be used to measure radioactivity of the QC component, a dose calibrator is the only device that is required equipment for every nuclear medicine/nuclear pharmacy laboratory. Thus, no additional expense is incurred for purchasing other counting devices to be used in the QC process.

†Paper strip used in the paper chromatography method is the least expensive material used in the RCP testing process.

‡HPLC-grade chemical solvent costs more than the non-HPLC-grade solvent.

- **Reasonable (5 points)**
  - Paper chromatography*, solvent extraction, or centrifugation process (2.5 points)
  - Simple chemical solvent (2.5 points)

*Paper strip that used in the paper chromatography does not require any pretreatment (e.g., drying process in the oven or activation with chemical solvent(s)).

Table 1. Safety Ratings of the QC Chemical Solvents

Chemical Solvent	Health	Flammability	Reactivity	Contact	Rating	Score
Acetone	1	4	2	1	2.00	5.0
Acetonitrile	2	4	2	2	2.50	3.8
Ammonium acetate	1	1	1	1	1.00	7.5
Ammonium sulfate	2	0	1	1	1.00	7.5
Chloroform	3	0	1	2	1.50	6.3
Dichloromethane	3	1	1	2	1.75	5.6
0.05 M DTPA	0	0	0	0	0.00	10.0
Ethanol	3	4	2	2	2.75	3.1
Ether	2	4	2	2	2.50	3.8
Ethyl acetate	2	4	0	2	2.00	5.0
0.001 N HCl*	1	0	1	1	0.75	8.1
Methanol	3	4	1	1	2.25	4.4
Methyl ethyl ketone	2	4	2	2	2.50	3.8
Methylene chloride	3	1	1	2	1.75	5.6
Monobasic potassium phosphate	0	0	0	1	0.25	9.4
Physiological saline	0	0	0	0	0.00	10.0
Sodium acetate, anhydrous	1	0	0	1	0.50	8.8
Tetrahydrofuran	2	3	2	1	2.00	5.0
Triethylamine	2	3	1	3	2.25	4.4
Water	0	0	0	0	0.00	10.0

EVALUATION OF RCP TESTING METHODS

Evaluation Principle for the RCP Testing Method which is Incomplete or Lacking Information

An RCP testing method that does not have information available concerning any of the evaluated items (either incomplete or lacking) will not earn a score for that category. This does not mean that the proposed RCP testing method is inadequate. Under the current selection criteria and scoring system, it is not possible to judge a QC method without the required information. However, if a subsequent publication should provide additional information with regard to the original method, the QC information from both the initial and supplemental methocs will be combined together and will be evaluated jointly according to our rating system.

Due to the fact both the package insert and the USP/NF are considered to be the authoritative sources, the "gold standard" RCP testing method(s) stated in either the package insert or the USP/NF will be automatically awarded the full scores for the items under statistical evaluation of accuracy (i.e., Range of Investigation, Validity of the Proposed Method, Accuracy of the Proposed Method, Measurement of % Bound, Replication of Trials, and Sample Size) even though supporting data may be absent.

Designation of an Alternative RCP Testing Method

Each of the compounded radiopharmaceuticals approved by the FDA from 1988 to 1997 will be reviewed and rated according to the scoring system as described previously. After evaluation of the RCP testing methods based upon our rating system, any published RCP testing method with the overall score higher than the method(s) described in the package insert or the USP/NF will be designated as an alternative QC method, and a brief description of the methodology will be provided in this manual for

easy reference. However, if there is no alternative QC method available for evaluation or none of the proposed RCP testing methods scored higher than the standard method(s), then there will be no designation of an alternative QC method and a brief description of the standard RCP testing method(s) will be provided for the compounded radiopharmaceutical.

Layout of the Alternative and Standard RCP Testing Methods

All compounded ^{99m}Tc-labeled radiopharmaceuticals approved by the FDA since 1988 will be listed first (in alphabetical order using the generic name of the labeled compound) followed by the compounded ^{111}In-labeled radiopharmaceuticals (also in alphabetical order). Since Cardiotec® (kit for the preparation of ^{99m}Tc-teboroxime, Squibb Diagnostics, Princeton NJ) and Myoscint® (kit for the preparation of ^{111}In-imciromab pentetate, Centocor, Inc., Malvern, PA) are no longer commercially available, both agents were not evaluated and are not included in this manual.

References

1. Package insert of Ceretec® (kit for the preparation of technetium Tc 99m exametazime injection). Arlington Heights, IL: Medi-Physics, Inc., May, 1995.

2. Package insert of TechneScan MAG3® (kit for the preparation of technetium Tc 99m mertiatide). St. Louis, MO: Mallinckrodt Medical, Inc., March, 1995.

3. Package insert of OctreoScan® (kit for the preparation of indium In 111 pentetreotide). St. Louis, MO: Mallinckrodt Medical, Inc., March, 1995.

4. Package of CEA-Scan™ (kit for the preparation of technetium Tc 99m arcitumomab). Morris Plans, NJ: Immunomedics, Inc., July, 1996.

5. Package insert of Verluma™ (kit for the preparation of technetium Tc 99m nofetumomab merpentan). Billerica, MA: Du Pont Pharma, August, 1996.

6. ProstaScint® (kit for the preparation of indium In 111 capromab pendetide). Princeton, NJ: Cytogen Corporation, August, 1997.

7. Robbins PJ. Chromatography of technetium-99m radiopharmaceuticals – a practical guide. New York, NY: The Society of Nuclear Medicine, 1984.

8. Standard system for the identification of the fire hazards of materials. NFPA 704-1990. Quincy, MA: National Fire Protection Association, 1990.

9. Baker SAF-T-DATA. The J.T. Baker catalog 1997/98. Phillipsburg, NJ: J.T. Baker, 1997

RCP TESTING PROCEDURES FOR COMPOUNDED ^{99m}Tc-LABELED RADIOPHARMACEUTICALS (1988-1997)

Ratings of the RCP Testing Methods for ^{99m}Tc-Arcitumomab [CEA-Scan™]

The standard RCP testing method for ^{99m}Tc-arcitumomab is only listed in the package insert for CEA-Scan™ (*1*) and is not contained in the USP/NF. There are no alternative QC methods published in the literature. Consequently, evaluation of the RCP testing methods for ^{99m}Tc-arcitumomab cannot be performed. However, there is a universal QC method for ^{99m}Tc labeled monoclonal antibodies which was proposed by Webber et al. (*2*) that may be useful. The proposed RCP testing method involves the use of the ITLC-SG chromatographic strip as the stationary phase and 0.9% NaCl solution as the mobile phase (*2*). However, this proposed method lacks the necessary information required to judge both the speed of the QC process and the statistical analysis of accuracy.

References

1. Package insert of CEA-Scan™ (kit for the preparation of technetium Tc 99m arcitumomab). Morris Plains, NJ: Immunomedics, Inc., July, 1996.

2. Webber DI, Zimmer AM, Kazikiewicz JM, Spies SM, Spies WG, Rosen ST. Rapid miniaturized chromatography systems for quality control of radiolabeled monoclonal antibodies. *J Nucl Med Technol* 1990; 18:141 (abstract).

Standard RCP Testing Method for ^{99m}Tc-Arcitumomab [CEA-Scan™]

[Note: The reader should refer to the package insert (1) for additional information.]

Materials and Methods

Stationary Phase:

- ITLC-SG
- 1.0 cm x 9.0 cm
  - *origin*: 1.0 cm*
  - *cut line*: 4.5 cm*
  - *solvent front*: 8.0 cm

* There is no specific information regarding the locations of the origin and cut line for the ITLC–SG strip used for the RCP determination of ^{99m}Tc-arcitumomab (*1*). The designated locations of the origin and cut line on the ITLC-SG strip as stated above are based on the common specifications for the miniaturized chromatography strip.

Mobile Phase: Acetone

Calculation: $\text{RCP}\,(\%) = \dfrac{\text{Top piece}\,(\mu\text{Ci})}{\text{Both pieces}\,(\mu\text{Ci})} \times 100$

RCP Acceptance Limit

90% (*1*)

References

1. Package insert of CEA-Scan™ (kit for the preparation of technetium Tc 99m arcitumomab). Morris Plains, NJ: Immunomedics, Inc., July, 1996.

Ratings of the RCP Testing Methods for ^{99m}Tc-Bicisate [Neurolite®]

RCP Testing Method	Fast (20)	ALARA (5)	Safe (10)	True (55)	Economical (5)	Reasonable (5)	Overall Score (100)
Package Insert (*1*)	0.0	5.0	5.0	55.0	4.0	5.0	74.0 (a)
USP/NF (2)	0.0	2.5	5.0	55.0	4.0	5.0	71.5 (b)
Budde et al. (*3*)	20.0	5.0	5.0	50.0	4.0	5.0	89.0 (c)
Amin et al. (*4*)	20.0	5.0	5.0	10.0	5.0	5.0	50.0 (d)

The Evaluation Behind the Ratings:

a. *Fast*: The RCP testing process involves solvent saturation in the developing tank (15-30 min), sample spot drying time (5-10 min), solvent developing time (~15 min), and TLC plate drying time (~2.5 min), totaling 40-60 min to complete (0 point). *Economical*: The dose calibrator can be used as a counting instrument (2 points). The Baker-Flex silica gel IB-F TLC plates come with the cold kit (2 points). The mobile phase of the QC system uses an HPLC-grade ethyl acetate (0 point). *Reasonable*: No heat activation process is required with the use of the TLC plates (2.5 points). Only one simple solvent is needed for the RCP evaluation (2.5 points)

b. *Fast*: Total time required for completion of the QC process is similar to that required for the package insert method (*1*). *Note*: The USP/NF method requires the preparation of four vials of ^{99m}Tc-bicisate and the RCP testing procedure to be performed on each vial (very expensive and time-consuming QC process). *ALARA*: ~5 µl x 4 = ~20 µl (2.5 points). *Economical*: The dose calibrator can be used as a counting instrument (2 points). The Baker-Flex silica gel IB-F TLC plates come with the cold kit (2 points). The HPLC-grade ethyl acetate is used as the mobile phase (0 point). *Reasonable*: No heat activation process is required for the use of the TLC plates (2.5 points), and the QC process requires only one simple chemical solvent (2.5 points).

c. *True*: Only three trials of triplicate measurements were conducted below the RCP acceptance limit; therefore, this method receives a score of zero for the subcategory of Sample Size.

d. *True*: Due to the absence of required information such as Range of Investigation, Validity of Proposed Method, Accuracy of Proposed Method, Replication of Trials, and Sample Size, no evaluation can be conducted using those criteria, and consequently no score is awarded.

References

1. Package insert of Neurolite® (kit for the preparation of technetium Tc 99m bicisate injection). Billerica, MA: Du Pont Merck Pharmaceutical Company; November, 1994.
2. Technetium Tc 99m bicisate injection. The United States Pharmacopeia, 23rd rev., and The National Formulary, 18th ed. Suppl 7. Rockville, MD: United States Pharmacopeial Convention; 1997:3934.
3. Budde PA, Hung JC, Mahoney SW, Wollan PE. Rapid quality control procedure for technetium-99m-bicisate. *J Nuc Med Technol* 1995; 23:190-194.
4. Amin KC, Saha GB, Go RT. A rapid chromatographic method for quality control of technetium-99m-bicisate. *J Nucl Med Technol* 1997; 25:49-51.

Alternative RCP Testing Method for ^{99m}Tc-Bicisate [Neurolite®]

[Note: The reader should refer to the published literature (1) for additional information.]

Materials and Methods

Stationary Phase:

- Whatman Grade 17 Chr (Whatman, Hillsboro, OR)
- 1.0 cm x 9.0 cm
  - *origin*: 2.0 cm
  - *cut line*: 5.5 cm
  - *solvent front*: 9.0 cm

Mobile Phase: HPLC grade ethyl acetate

Calculation: $\text{RCP}\,(\%) = \frac{\text{Top piece}\,(\mu\text{Ci})}{\text{Both pieces}\,(\mu\text{Ci})} \text{ X } 100$

RCP Acceptance Limit

90% (*2,3*)

References

1. Budde PA, Hung JC, Mahoney DW, Wollan PC. Rapid quality control procedure for technetium-99m-bicisate. *J Nucl Med Technol* 1995; 23:190-194.

2. Package insert of Neurolite® (kit for the preparation of technetium Tc 99m bicisate injection). Billerica, MA: Du Pont Merck Pharmaceutical Company; November, 1994.

3. Technetium Tc 99m bicisate injection. The United States Pharmacopeia, 23rd rev., and The National Formulary, 18th ed. Suppl 7. Rockville, MD: United States Pharmacopeial Convention; 1997:3934.

Ratings of the RCP Testing Methods for ^{99m}Tc-Exametazime [Ceretec®]

RCP Testing Method	Fast (20)	ALARA (5)	Safe (10)	True (55)	Economical (5)	Reasonable (5)	Overall Score (100)
Package Insert (*1,2*) and Hung et al. (*3*)	10.0	2.5	5.9	55.0	2.0	0.0	75.4 (a)
USP/NF (*4*)	10.0	2.5	5.9	55.0	1.0	0.0	74.4 (b)
Jurisson et al. (*5*) and Hung et al. (*6*)	20.0	5.0	3.8	40.0	5.0	5.0	78.8 (c)
Dutta et al. (*7*)	NA	NA	NA	NA	NA	NA	NA (d)
Mah et al. (*8*)	20.0	0.0	10.0	20.0	5.0	5.0	60.0 (e)
Webber et al. (*9*) and Hung et al. (*6*)	20.0	5.0	5.0	35.0	5.0	5.0	75.0 (f)

The Evaluation Behind the Ratings:

a. *Fast*: Although the package insert for Ceretec® indicates that the entire RCP testing procedure takes ~15 min to complete (*1,2*) (5 points), we have found that completion of the recommended 3-strip chromatography system (i.e., spotting sample, solvent migration, radioactivity measurement, and RCP calculation) takes ~5-7 min (*3*) (10 points). *ALARA*: Three sample spots for three QC strips (~ 15 µl) (*1,2*) (2.5 points). *Safe:* The rating of chemical safety is the average score of the three solvents (i.e., MEK, saline, and 50% acetonitrile) used in the 3-strip chromatography system (see Table 1 for the Safety Ratings of the QC Chemical Solvents). *Economical*: The counting equipment is not specified (*1,2*) (2 points). The 3-strip chromatography system involves the use of two ITLC-SG strips (0 point) and HPLC-grade MEK and 50% acetonitrile (0 point). *Reasonable*: Heat activation process is required with the use of the ITLC-SG strips (0 point). Additionally, the QC system requires three different chemical solvents (0 point).

b. *Fast*: Total time required for completion of the QC process is similar to that required for the package insert method (*1-3*) (10 points). *ALARA*: Three sample spots for three QC strips (~ 15 µl) (2.5 points). *Safe:* The rating of chemical safety is the average score of the three solvents (i.e., MEK, saline, and 50% acetonitrile) used in the 3-strip chromatography system (see Table 1 for the Safety Ratings of the QC Chemical

Solvents). *Economical*: The USP/NF specify the use of a scanner to determine the radioactive distribution of all three QC strips (0 point). Two ITLC-SG strips are needed as two stationary phases of the total three-strip QC system (0 point). There is no specification with regard to the use of HPLC-grade MEK and 50% acetonitrile as the mobile phases (1 point). *Reasonable*: Heat activation process is required with the use of the ITLC-SG strips (0 point). Additionally, the QC system requires three different chemical solvents (0 point).

c. .*Fast*: The solvent developing time is ~1.5 min (*6*). *True:* No replication of trials (e.g., duplicate or triplicate samples) were conducted (*5,6*) (0 point). Both the false positive and negative rates for this proposed method are 10.3% and 0%, respectively (*6*) (0 point). *Please note that the false positive rate has been revised. The previously reported false positive rate was 4% (6).*

d. Incomplete information.

e. *ALARA:* The reversed phase chromatography method requires a 0.1-ml sample to be loaded onto the cartridge (0 point). *True:* Six trials out of a total of 17-batch samples (35.3%) used ^{99m}Tc-exametazime preparations with RCP values below the acceptance limit (i.e., 80%, [*1,2,4*]) (15 points for the Range of Investigation). The correlation coefficient of the proposed method is ~0.9 (0.88, [*8*]), however the RCP results obtained by the proposed QC method requires some degrees of calibration (5 points for the Validity of Proposed Method). The proposed QC method has a 0% false positive rate; however, the false negative rate is 81.8% (0 point for the Accuracy of Proposed Method). The proposed Sep-Pak® method did not achieve complete separation of the hydrolyzed-reduced ^{99m}Tc and the secondary ^{99m}Tc-exametazime complex from the lipophilic ^{99m}Tc-exametazime complex (0 point for the Measurement of % Bound). No replication of trials was performed (0 point), and the total number of the tested samples with an RCP value less than 80% (*1,2,4*) is only 6 (0 point for the Sample Size).

f. *True:* No determination can be made with regard to the correlation coefficient for the proposed method from the original article by Webber et al. (*9*). However, a subsequent comparison study shows that the proposed RCP testing method yields a high correlation coefficient (r = 0.97) (*6*), however the RCP values measured by the proposed QC method does require calibration (5 points for the Validity of the Proposed Method). A false RCP acceptance rate of 25.6% is seen (*Please note that the false positive rate has been revised. The previously reported false positive rate of 40% [6])* and a 0% false negative rate are noted with the proposed QC method (0 point for the Accuracy of the Proposed Method) (*6*). No replication of trials were conducted (*6,9*) (0 point for the Replication of Trials). The original number of samples tested with below-the-acceptable limit RCP value was 12 (*9*) (0 point for the Sample Size). However, a later study evaluated 39 samples with RCP values below 80% (i.e., the minimal acceptance value for ^{99m}Tc-exametazime, [*1,2,4*]) (*6*) (5 full points for the Sample Size category).

References

1. Package insert of Ceretec® (kit for the preparation of technetium Tc 99m exametazime injection). Arlington Heights, IL: Medi-Physics, Inc., May, 1995.
2. Package insert of Ceretec™ (kit for the preparation of technetium Tc 99m exametazime injection). Arlington Heights, IL: Amersham Corporation, November, 1990.
3. Hung JC, Wilson ME, Silberstein EB. Pitfalls in the standard radiochemical purity testing for technetium-99m-exametazime. *J Nucl Med Technol* 1994; 22:229-231.
4. Technetium Tc 99m exametazime injection. The United States Pharmacopeia, 23rd rev., and The National Formulary, 18th ed. Suppl 6. Rockville, MD: United States Pharmacopeial Convention; 1997:3732-3733.
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6. Hung JC, Taggart TR, Wilson ME, Owens TP. Radiochemical purity testing for $^{99}Tc^{m}$-exametazime: a comparison study for three-paper chromatography. *Nucl Med Commun* 1994; 15:569-574.
7. Dutta A, Wang TST, Bohdiewicz PJ, Alderson PO. Improved miniaturized chromatography for Tc-99m HM-PAO. *J Nucl Med Technol* 1988; 16:Ab5 (abstract).
8. Mah G, Reilly RM, Wong GLM, Houle S. A comparison of three methods to determine the radiochemical purity of $^{99}Tc^{m}$-hexamethylpropylene amine oxime ($^{99}Tc^{m}$-HMPAO). *Nucl Med Commun* 1989; 10:733-740.
9. Webber DI, Zimmer AM, Geyer MC, Spies SM. Use of a single-strip chromatography system to assess the lipophilic component in technetium-99m exametazime preparations. *J Nucl Med Technol* 1992; 20:29-32.

Alternative RCP Testing Method for ^{99m}Tc-Exametazime [Ceretec®] – *Method 1*

[Note: The reader should refer to the published literature (1,2) for additional information.]

Materials and Methods

Stationary Phase:

- Solvent Saturation Pads (Gelman Science, Ann Arbor, MI)
- 1.0 cm x 8.5 cm
  - *origin*: 1.5 cm
  - *cut line*: 5.0 cm
  - *solvent front*: 8.5 cm

Mobile Phase: Ether

Calculation: $\text{RCP}(\%) = \frac{\text{Top piece}\ (\mu\text{Ci})}{\text{Both pieces}\ (\mu\text{Ci})} \times 100$

RCP Acceptance Limit

80% (3-5)

References

1. Jurisson S, Schlemper EO, Troutner DE, Canning LR, Nowotnik DP, Neirinckx RD. Synthesis, characterization, and X-ray structural determinations of technetium(V)-oxo-tetradentate amine oxime complexes. *Inorg Chem* 1986; 25:543-549.

2. Hung JC, Taggart TR, Wilson ME, Owens TP. Radiochemical purity testing for $^{99}Tc^{m}$-exametazime: a comparison study for three-paper chromatography. *Nucl Med Commun* 1994; 15:569-574.

3. Package insert of Ceretec® (kit for the preparation of technetium Tc 99m exametazime injection). Arlington Heights, IL: Medi-Physics, Inc., May, 1995.

4. Package insert of Ceretec™ (kit for the preparation of technetium Tc 99m exametazime injection). Arlington Heights, IL: Amersham Corporation, November, 1990.

5. Technetium Tc 99m exametazime injection. The United States Pharmacopeia, 23rd rev., and The National Formulary, 18th ed. Suppl 6. Rockville, MD: United States Pharmacopeial Convention; 1997:3732-3733.

Ratings of the RCP Testing Methods for ^{99m}Tc-Mertiatide [TechneScan MAG3®]

RCP Testing Method	Fast (20)	ALARA (5)	Safe (10)	True (55)	Economical (5)	Reasonable (5)	Overall Score (100)
Package Insert (*1*)	10.0	0.0	5.9	55.0	3.0	0.0	73.9 (a)
USP/NF *Method 1* (*2*)	0.0	2.5	6.9	45.0	3.0	2.5	59.9 (b)
USP/NF *Method 2* (*2*)	0.0	2.5	6.3	55.0	0.0	0.0	63.8 (c)
DuCret et al. (*3*)	NA	NA	NA	NA	NA	NA	NA (d)
Taylor et al. (*4*)	NA	NA	NA	NA	NA	NA	NA (e)
Crombez et al. (*5*)	0.0	2.5	5.8	10.0	0.0	0.0	18.3 (f)
Chen et al. 1990 (*6*) and Chen et al. 1993 (*7*)	0.0	5.0	6.0	0.0	3.0	2.5	16.5 (g)
Hung et al. (*8*)	20.0	2.5	6.6	55.0	5.0	2.5	91.6 (h)
Fueger et al. (*9*) and Chen et al. 1993 (*7*)	20.0	2.5	7.5	0.0	2.0	5.0	37.0 (i)
Chen et al. 1993 (*7*)	5.0	2.5	5.7	37.5	1.0	0.0	51.7 (j)
Zimmer 1996 (*10*)	0.0	2.5	5.6	10.0	5.0	2.5	25.6 (k)

The Evaluation Behind the Ratings:

a. *Fast*: The complex cartridge analysis system typically takes 8-10 min to complete (*7*) (10 points). *ALARA:* The Sep-Pak® C18 cartridge method requires a 0.1-ml sample for analysis (0 point). *Safe:* The rating of chemical safety is the average score of the three solvents (i.e., saline, 0.001 N HCl, and 1:1 ethanol/saline solution) used in the Sep-Pak® QC system (see Table 1 for the Safety Ratings of the QC Chemical Solvents). *Economical*: It is not a paper chromatography or solvent extraction method (0 point). *Reasonable*: It is not a paper chromatography, solvent extraction, or centrifugation method (0 point). The QC process involves the use of three different chemical solvents (0 point).

b. *Fast*: The RCP testing method uses a 20-cm paper strip as the stationary phase, and the developed strip has to be dried before scanning with a radiochromatogram scanner (total QC time estimated >20 min) (0 point). *ALARA*: A sample spot of ~5-10 μl (2.5 points).). *Safe:* The rating of safety is the average score of the two chemical solvents (i.e., a mixture of acetonitrile and water, 60:40) (see Table 1 for the Safety Ratings of the QC Chemical Solvents). *True:* The paper chromatography method only measures the % hydrolyzed-reduced ^{99m}Tc (0 point for the Measurement of % Bound). *Economical*: The USP/NF specify the use of a scanner to determine the radioactive distribution of the QC strip (0 point). *Reasonable*: The mobile phase is made of a mixture of acetonitrile and water (60:40) (0 point).

c. *Fast:* The USP/NF *Method 2* is an HPLC method that requires the solvents to be filtered and degassed. The system also needs to be equilibrated for 15 min before use. The retention time for ^{99m}Tc-mertiatide is between 10 and 14 min (0 point). *ALARA*: The HPLC procedure requires a 20-μl test sample (2.5 points). *Safe:* The safety rating was calculated by averaging the scores of the three chemical solvents used in the HPLC system (i.e., monobasic potassium phosphate solution, triethylamine, and THF) (see Table 1 for the Safety Ratings of the Chemical Solvents). *Economical*: The QC method uses an HPLC analytical system (0 point for each of the three items under the Economical category). *Reasonable*: HPLC (0 point) with two chemical mixtures that require special manipulations (i.e., pH adjustment, filtration, and degassing) (0 point).

d. Incomplete information.

e. Incomplete information.

f. *Fast*: The RCP value is determined by a combination of ITLC-SG and HPLC (total QC time > 20 min) (0 point). *ALARA*: ~5 μl (ITLC-SG) + 20μl (HPLC) = 25 μl test sample (2.5 points). *True:* The only information available for this criteria is the proposed method that can theoretically determine the % bound of ^{99m}Tc-mertiatide (10 points). *Economical and Reasonable:* HPLC system and three different chemical solvents (i.e., acetone, ethanol, and phosphate buffer) (0 point for each of the two criteria).

g. *Fast:* Long performance time (*7*). *ALARA*: Single strip (~5 μl sample) (5 points). *Safe:* The safety rating was calculated by averaging the scores of the three QC solvents (i.e., ethyl acetate, water, and ethanol, 5:5:2 [*6*] or 5:6:2 [*7*]) (see Table 1 for the Safety Ratings of the QC Chemical Solvents). *True:* Non-reproducible separation of ^{99m}Tc-mertiatide from free ^{99m}Tc (*7*) (0 point). *Economical:* Does not use dose calibrator as a counting device (0 point). *Reasonable:* Mobile phase uses a mixture of three different chemical solvents (0 point).

h. *Fast:* The average time for performing the proposed RCP testing method takes 2-3 min to complete (20 points). *ALARA:* Dual-strip QC method (~5 μl x 2 = ~ 10μl test sample) (2.5 points). *Safe:* The safety rating was calculated by averaging the scores of the four solvents in two mobile phases (i.e., mobile phase 1: chloroform, acetone, and THF, 1:1:2; mobile phase 2: saline) (see Table 1 for the Safety Ratings of the Chemical Solvents). *True:* The proposed method meets all of the criteria listed under the True category, with the exception of the criteria for multiple measurements. The proposed QC method evaluated each tested RCP value with a single measurement only (0 point for the

Replication of Trials). The proposed 2-strip chromatography system has a false positive rate of 2.8% and a false negative rate of 0% (10 points for the Validity of the Proposed Method). *Reasonable:* Multiple solvents for the two mobile phases (0 point).

i. *Fast:* No information regarding the QC time for this proposed dual-paper chromatography system (*7*) (0 point). The original is published in German language (*8*), and the article cannot be located in any library. Reference 7 has a very brief description of the proposed QC method (*7*). *ALARA:* Dual strip (~5 µl x 2 = ~10 µl sample) (2.5 points). *Safe:* The safety rating of the QC chemical solvents was calculated by averaging the scores of the two solvents (i.e., acetone and saline) (see Table 1 for the Safety Ratings of the QC Chemical Solvents). *True:* No information available for evaluation (0 point). *Economical:* The only available information is the proposed QC method that uses a 2-strip paper chromatography system (2 points) (*7*). *Reasonable:* Paper chromatography system (2.5 points) and relatively simple solvents (i.e., acetone and saline) (2.5 points).

j. *Fast:* The time required to perform the analysis is <20 min (5 points). *ALARA:* Dual-strip QC method (~5 µl x 2 = ~ 10µl test sample) (2.5 points). *Safe:* The safety rating was calculated by averaging the scores of the four chemical solvents used in the two mobile phases (i.e., mobile phase 1: MEK and ethyl acetate, 2:3; mobile phase 2: acetonitrile and water, 1:1) (see Table 1 for the Safety Ratings of the QC Chemical Solvents). *True:* Seven of the total of 51 trials (13.7%) were conducted with the use of test samples that were below the acceptable purity level (i.e., 90%) (*1,2*) (7.5 points for the Range of Investigation and 0 point for the Sample Size). There were no false positive and negative rates noted to be associated with the proposed QC method (10 points for the Accuracy of the Proposed Method). Single measurement for each tested RCP value (0 point for the Replication of Trials). *Reasonable:* Multiple solvents for the two mobile phases (0 point).

k. *Fast:* No information regarding the QC time for this proposed dual paper chromatography system (*7*) (0 point).). *ALARA:* Dual-strip QC method (~5 µl x 2 = ~ 10µl test sample) (2.5 points). *Safe:* The safety rating was calculated by averaging the scores of the three solvents in two mobile phases (i.e., mobile phase 1: methylene chloride and acetone, 1:1; mobile phase 2: distilled water) (see Table 1 for the Safety Ratings of the QC Chemical Solvents). *True:* The proposed dual paper chromatography system can determine the % bound of ^{99m}Tc-mertiatide (10 points for the Measurement of % Bound). None of the other information regarding the Range of Investigation, Validity of the Proposed Method, Accuracy of the Proposed Method, Replication of Trials, and Sample Size is not available (0 point for each of the aforementioned criteria). *Reasonable:* Multiple solvents for the two mobile phases (0 point).

References

1. Package insert of TechneScan MAG3® (kit for the preparation of technetium Tc 99m mertiatide). St. Louis, MO: Mallinckrodt Medical, Inc., March, 1995.
2. Technetium Tc 99m mertiatide injection. The United States Pharmacopeia, 23rd rev., and The National Formulary, 18th ed. Suppl 3. Rockville, MD: United States Pharmacopeial Convention; 1995:2984-2984
3. duCret RP, Boudreau RJ, Gonzalez R, Carpenter R, Tennison J, Kuni CC. Clinical efficacy of ^{99m}Technetium mercaptoacetylglycine kit formulation in routine renal scintigraphy. *J Urol* 1989; 142:19-22
4. Taylor A, Ziffer JA, Steves A, Eshima D, Delaney VB, Welchel JD. Clinical comparison of I-131 orthoiodohippurate and the kit formulation of Tc-99m mercaptoacetyltriglycine. *Radiol* 1989; 170:721-725.
5. Crombez D, Van Nerom C, Gormans G, De Roo M, Verbruggen A. Comparison of purity and biological behaviour in mice of kit-formulated and HPLC-purified Tc-99m MAG3. In: Schmidt HAE, Van der Schoot JE, eds. *Proceedings of the third congress of the European Association of Nuclear Medicine*, Amsterdam 1990. Stuttgart: Schattauer, 1991.
6. Chen F et al. Preparation of a new renal function imaging agent. *Chinese J Nucl Med* 1990; 10:27-29.
7. Chen F, Decristoforo C, Rohrbacker B, Riccabona G. A simple two-strip method to determine the radiochemical purity of technetium-99m mercaptoacetyltriglycine. *Eur J Nucl Med* 1993; 20:334-338.
8. Hung JC, Wilson ME, Brown Manuel. Rapid preparation and quality control of technetium-99m MAG3™. *J Nucl Med Technol* 1991; 19:176-179.
9. Fueger G. Qualitatskontrolle durch die Nutzer. In: *Qualitatskontrolle II – Radiopharmaka Fortbildungstagung für das technische Personal an Nuklearmedizinischen Stationen*, Linz, 1992.
10. Zimmer AM. Faster and easier radiochemical methods. In: *Continuing Education Course Manual –1996.* Reston, VA: Society of Nuclear Medicine; 1996:609-610.

Alternative RCP Testing Method for ^{99m}Tc-Mertiatide [TechneScan MAG3®]

[Note: The reader should refer to the published literature (1) for additional information.]

Materials and Methods

Stationary Phases:

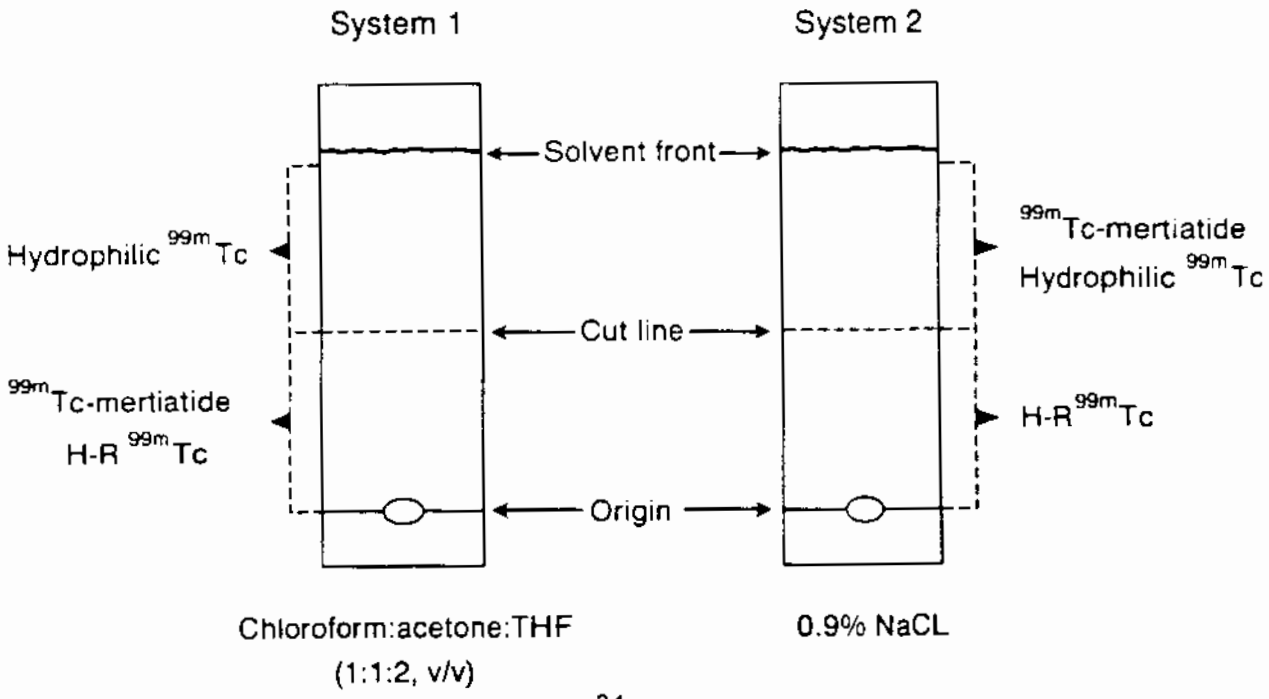
Systems 1 and 2

- Solvent Saturation Pads (Gelman Sciences, Ann Arbor, MI)
- 1.0 cm x 8.5 cm
  - *origin*: 1.5 cm
  - *cut line*: 5.0 cm
  - *solvent front*: 8.5 cm

Mobile Phases:

System 1: chloroform: acetone: tetrahydrofuran (1:1:2, v/v)

System 2: 0.9% NaCl



Calculation:

$$\text{Free } ^{99m}\text{Tc } (\%) = \frac{\text{Top piece of System 1}(\mu\text{Ci})}{\text{Both pieces of System 1}(\mu\text{Ci})} \text{ X } 100$$

$$\text{H-R } ^{99m}\text{Tc } (\%) = \frac{\text{Bottom piece of System 2}(\mu\text{Ci})}{\text{Both pieces of System 2}(\mu\text{Ci})} \text{ X } 100$$

(H-R ^{99m}Tc: hydrolyzed-reduced ^{99m}Tc)

$$\text{RCP } (\%) = 100 - (\%\text{ Free } ^{99m}\text{Tc} + \%\text{ H/R } ^{99m}\text{Tc})$$

RCP Acceptance Limit

90% (2,3)

References

1. Hung JC, Wilson ME, Brown Manuel. Rapid preparation and quality control of technetium-99m MAG3™. *J Nucl Med Technol* 1991; 19:176-179.

2. Package insert of TechneScan MAG3® (kit for the preparation of technetium Tc 99m mertiatide). St. Louis, MO: Mallinckrodt Medical, Inc., March, 1995.

3. Technetium Tc 99m mertiatide injection. The United States Pharmacopeia, 23rd rev., and The National Formulary, 18th ed. Suppl 3. Rockville, MD: United States Pharmacopeial Convention; 1995:2984-2984

Ratings of the RCP Testing Methods for ^{99m}Tc-Nofetumomab Merpentan [Verluma™]

The RCP testing method for ^{99m}Tc-arcitumomab is not listed in the USP/NF. However, the package insert for Verluma™ describes a recommended RCP testing procedure for ^{99m}Tc-nofetumomab merpentan (*1*). No alternative QC methods for ^{99m}Tc-nofetumomab merpentan can be found in the literature. Thus, evaluation of the RCP testing methods for ^{99m}Tc-arcitumomab cannot be performed. However, There is a universal QC method for ^{99m}Tc labeled monoclonal antibodies which was proposed by Webber et al. (*2*) that may be useful. The proposed RCP testing method involves the use of an ITLC-SG chromatographic strip as the stationary phase and 0.9% NaCl solution as the mobile phase (*2*). However, this proposed method lacks the information required to evaluate the speed of the QC process and the statistical analysis of accuracy.

References

1. Package insert of Verluma™ (kit for the preparation of technetium Tc 99m nofetumomab merpentan). Billerica, MA: DuPont Merck Pharmaceutical Company, August, 1996.

2. Webber DI, Zimmer AM, Kazikiewicz JM, Spies SM, Spies WG, Rosen ST. Rapid miniaturized chromatography systems for quality control of radiolabeled monoclonal antibodies. *J Nucl Med Technol* 1990; 18:141 (abstract).

Standard RCP Testing Method for ^{99m}Tc-Nofetumomab Merpentan [Verluma™]

[Note: The reader should refer to the package insert (1) for additional information.]

Materials and Methods

Stationary Phase:

- ITLC-SG*
- 2.0 cm x 10.0 cm
  - *origin*: 1.2 cm
  - *cut lines*: 3.8 cm and 7.4 cm†
  - *solvent front*: 9.0 cm

* Allow the sample spot to dry prior to beginning chromatographic development (*1*).

† The middle section of the ITLC-SG strip may be used to verify the complete separation between the bound compound and impurities. There should be less than 5% of total ^{99m}Tc activity remaining on this section of the strip (*1*).

Mobile Phase: 12% (w/v) trichloroacetic acid (stock reagent is stable for at least 30 days when stored refrigerated) (*1*)

Calculation: $\text{RCP}\,(\%) = \dfrac{\text{Bottom piece}\,(\mu\text{Ci})}{\text{Three pieces}\,(\mu\text{Ci})} \times 100$

RCP Acceptance Limit

85% (*1*)

Reference

1. Package insert of Verluma™ (kit for the preparation of technetium Tc 99m nofetumomab merpentan). Billerica, MA: DuPont Merck Pharmaceutical Company, August, 1996.

Ratings of the RCP Testing Methods for ^{99m}Tc-Labeled Red Blood Cells [UltraTag® RBC]

The RCP testing method for ^{99m}Tc-labeled red blood cells is stated in either the package insert for UltraTag® RBC (*1*) or the USP/NF (*2*), and the two recommended methods are identical. No rating evaluation can be conducted since there is no other alternative methods published in the literature for the determination of the labeling efficiency of ^{99m}Tc-labeled red blood cells.

Both standard methods use the centrifugation process to separate the radiolabeled red blood cells from the unbounded impurities (*1,2*). Although the time period for the centrifugation process is mentioned in both the package insert and the USP/NF, there is no specification of speed or g-force for the centrifugation (*1,2*). One can refer to reference 3 for more information regarding the optimal centrifugation parameters for the determination of labeling efficiency of ^{99m}Tc-labeled red blood cells labeled with the use of UltraTag® RBC.

References

1. Package insert of UltraTag® RBC (kit for the preparation of technetium Tc 99m-labeled red blood cells). St. Louis, MO: Mallinckrodt Medical, Inc., February, 1996.

2. Technetium Tc 99m red blood cells injection. The United States Pharmacopeia, 23rd rev., and the National Formulary, 18th ed. Suppl 3. Rockville, MD: United States Pharmacopeial Convention; 1995:2985-2986

3. Chowdhury S, Hung JC. Optimal centrifugation: parameters for labeling efficiency determination of technetium-99m labeled red blood cells. *J Nucl Med Technol* 1993; 21:114-115 (abstract).

Standard RCP Testing Method for ^{99m}Tc-Labeled Red Blood Cells [UltraTag® RBC]

[Note: The reader should refer to the published literature (1-3) for additional information.]

1. Transfer 0.2 ml of ^{99m}Tc-labeled red blood cells (RBC) to a centrifuge tube containing 2 ml of 0.9% NaCl solution.

2. Centrifuge the ^{99m}Tc-labeled RBC sample at 150 g for 1 min (*3*).

3. Carefully pipette off the plasma supernatant and measure the radioactivity in the plasma and the ^{99m}Tc-labeled RBC pellet separately in a dose calibrator.

4. Calculate the labeling efficiency of ^{99m}Tc-labeled RBC as follows:

$$\% \text{ RBC labeling} = \frac{\text{RBC activity}}{\text{RBC activity} + \text{Plasma activity}} \times 100$$

RCP Acceptance Limits

95% (*1*)
90% (*2*)

References

1. Package insert of UltraTag® RBC (kit for the preparation of technetium Tc 99m-labeled red blood cells). St. Louis, MO: Mallinckrodt Medical, Inc., February, 1996.

2. Technetium Tc 99m red blood cells injection. The United States Pharmacopeia, 23rd rev., and the National Formulary, 18th ed. Suppl 3. Rockville, MD: United States Pharmacopeial Convention; 1995:2985-2986

3. Chowdhury S, Hung JC. Optimal centrifugation: parameters for labeling efficiency determination of technetium-99m labeled red blood cells. *J Nucl Med Technol* 1993; 21:114-115 (abstract).

Ratings of the of RCP Testing Methods for ^{99m}Tc-Sestamibi [Cardiolite®, Miraluma™]

RCP Testing Method	Fast (20)	ALARA (5)	Safe (10)	True (55)	Economical (5)	Reasonable (5)	Overall Score (100)
Package Insert (*1,2*)	0.0	2.5	3.1	55.0	3.0	2.5	66.1 (a)
USP/NF *Method 1* (3)	0.0	5.0	5.2	55.0	1.0	0.0	66.2 (b)
USP/NF *Method 2* (*3*)	0.0	2.5	3.8	55.0	0.5	0.0	64.0 (c)
Proulx *Method 1* (*4*)	0.0	2.5	7.4	20.0	3.0	2.5	35.4 (d)
Proulx *Method 2* (*4*) and Hung et al. (*5*)	20.0	2.5	8.2	15.0	5.0	5.0	55.7 (e)
Hung et al. (*5,6*)	20.0	5.0	5.7	50.0	5.0	2.5	88.2 (f)
Hammes et al. (*7*) and Hung et al. (*5*)	20.0	0.0	3.1	40.0	2.0	5.0	70.1 (g)
Zimmer et al. (*8*)	20.0	5.0	5.0	10.0	5.0	5.0	50.0 (h)
Reilly et al. (*9*)	20.0	0.0	10.0	20.0	3.0	2.5	55.5 (i)
Varga et al. (*10*)	20.0	0.0	8.2	10.0	4.0	5.0	47.2 (j)
Patel et al. (*11*)	20.0	2.5	5.0	10.0	5.0	5.0	45.0 (k)
Hirsch et al. (*12*)	20.0	2.5	3.1	30.0	3.0	2.5	61.1 (l)

The Evaluation Behind the Ratings:

a. *Fast*: The completion of the recommended QC process involves the following steps: drying the sample spot (~15 min), equilibrating the TLC tank (~10 min), developing the QC strip (~10-15 min) (5), and sample counting time (~1-2 min) 90 point). *ALARA*: The recommended TLC method requires the application of 2 drops of test sample onto the QC plate (~5 μl x 2 = ~10 μl) (2.5 points). *Economical*: It is not a paper

chromatography or solvent extraction method (0 point). *Reasonable*: It is not a paper chromatography, solvent extraction, or centrifugation method (0 point).

b. *Fast*: Similar procedure to the QC method stated in the package insert (*1, 2*) (0 point). *Note*: The USP/NF method requires the preparation of four vials of ^{99m}Tc-sestamibi and the RCP testing procedure to be performed on each vial. Additionally, the mixture of the four QC solvents must be freshly prepared (not more than 4 hr) (very expensive and time-consuming QC process). *ALARA*: Only takes a sample spot of ~1-2 μl for the TLC plate. However, the USP/NF RCP testing method requires a QC performance with 4 vials of ^{99m}Tc-sestamibi (~1-2 μl x 4 = ~4-8 μl) (5 points for the use of the smaller required volume, i.e., ~4μl). *Safe*: The rating of chemical safety is the average score of the four chemical solvents (i.e., a mixture of acetonitrile, methanol, 3.85% ammonium acetate, and THF, 4:3:2:1) (see Table 1 for the Safety Ratings of the QC Chemical Solvents). *Economical*: The USP/NF QC method specifies the use of TLC plate (0 point) and a scanner to determine the radioactive distribution (0 point). *Reasonable*: Use a reverse-phase TLC plate as the stationary phase (0 point). The mobile phase is made of a mixture of four different chemical solvents (0 point).

c. Since the hydrolyzed-reduced ^{99m}Tc-colloid is retained in the HPLC column, the percentage for the colloid must be obtained from the USP/NF *Method 1*. Consequently, the ratings for the USP/NF *Method 2* were calculated by averaging the scores from *Methods 1* and *2*. *Fast*: The USP/NF *Method 2* is an HPLC method that requires the solvents to be filtered and degassed. The system needs to be equilibrated before use. The retention time for ^{99m}Tc-sestamibi is ~5-10 min (0 point and 0 point from *Method 1*). *ALARA*: Each HPLC procedure requires a 5-μl test sample. Four samples will take 20 μl ([2.5 points + 5 points from *Method 1*] ÷ 2 = 3.8 points). *Safe*: The safety rating was calculated by averaging the scores of the three chemical solvents used in the HPLC system (i.e., methanol, 0.05 M ammonium sulfate solution, and acetonitrile, 45:35:20) (see Table 1 for the Safety Ratings of the QC Chemical Solvents) (4.2 points for the chemicals used in *Method 2* and 5.2 points for the chemicals used in *Method 1*, average score is 4.7 points). *Economical*: The QC method uses an HPLC analytical system (0 point for each of the three items under the Economical category) (0 point for *Method 2* and 1 point for *Method 1*, average score is 0.5 point). *Reasonable*: HPLC (0 point) with three chemical mixtures that require special manipulations (i.e., filtration and degassing) (0 point for either methods).

d. *Fast*: The time required for completing the RCP evaluation is not stated in the article (0 point). *ALARA*: The 2-strip QC method will need ~10 μl of test sample (2.5 points). *Safety*: The average score for acetone and saline is 7.4 (please refer to Table 1 for the Safety Ratings of the QC Chemical Solvents). *True*: The relative front (R_f) values for the three major radiochemical species are different. Thus, the proposed QC method is able to measure the % bound of ^{99m}Tc-sestamibi (10 points). No information is available for the other criteria listed under the *True*

category (0 point). *Economical and Reasonable:* The proposed RCP testing method uses two ITLC-SG strips as the stationary phase (0 point for each of the two categories that favor the use of either a paper chromatography, solvent extraction, or centrifugation process).

e. *ALARA:* The chemical extraction method requires a few drops of the test sample (2.5 points). *Safety:* The average score for two QC chemical solvents (i.e., chloroform and water) is 8.2 (please refer to Table 1 for the Safety Ratings of the QC Chemical Solvents). *True:* Thirty percent of the QC trials (i.e., [6 ÷ 20] x 100 = 30%) were conducted when RCP values of the test samples were below 90% (*1-3,5*) (15 points for the Range of Investigation). The relative front (R_f) values for the three major radiochemical species are different. Thus, the proposed QC method is able to measure the % bound of ^{99m}Tc-sestamibi (10 points). No information is available for the other criteria listed under the *True* category (0 point). *Economical and Reasonable:* The proposed RCP testing method uses two ITLC-SG strips as the stationary phase (0 point for each of the two categories that favor the use of either a paper chromatography, solvent extraction Incomplete information.

f. *Safe:* The safety rating for the QC chemical solvents was calculated by averaging the scores of the two solvents (i.e., chloroform and THF) (see Table 1 for the Safety Ratings of the QC Chemical Solvents). *True:* The proposed QC method has a 0% false positive rate (*5,6*), and the false negative rate is 10% (Two samples that have acceptable RCP as measured by the recommended TLC method [*1*] have unacceptable RCP by the proposed QC method) (*5*) (10 points for the Accuracy of the Proposed Method). No duplication of trials was conducted for the proposed RCP testing method (0 point for the Replication of Trials). *Reasonable:* The single strip QC system uses two chemical solvents (0 point for the item of Simple chemical solvent).

g. *Fast:* The proposed method can be completed in less than 5 min (7) (20 points). ALARA: The proposed reversed phase Sep-Pak chromatography method requires a 0.1 ml test sample (0 point). *True:* More than 20% of trials were conducted by another laboratory to evaluate ^{99m}Tc-sestamibi samples with a purity level below the acceptance limit (i.e., 90%, [*1-3*]) (*5*) (15 points for the Range of Investigation and 5 points for the Sample Size). The correlation coefficient of the proposed method was determined to be 0.88 (~0.9) (10 points for the Validity of the Proposed Method) (*5*). Although the false positive rate for the proposed Sep-Pak method is 0, the false negative rate is >20% (0 point for the Accuracy of the Proposed Method) (*5*). No replication of trials was performed for the proposed RCP testing method (0 point for the Replication of Trials). *Economical*: It is not a paper chromatography or solvent extraction method (0 point). *Reasonable*: It is not a paper chromatography, solvent extraction, or centrifugation method (0 point).

h. *True:* The proposed single strip paper chromatography can migrate the ^{99m}Tc-sestamibi to the solvent front – with some streaking (*8*) (10 points for the Measurement of % Bound). There is no information available for the other criteria listed under the True category (0 point).

i. *Fast:* The time required to complete the QC process is not stated in the original article by Reilly et al. (9). According to the experience during the comparison study (*5*), the entire QC procedure can be completed within 5 min (20 points). ALARA: The proposed QC method requires a

0.05-0.1 ml of test sample to be loaded onto the Sep-Pak alumina N cartridge (0 point). *True:* More than 20% of the trials evaluating test samples with RCP levels below the acceptance limit were performed by another laboratory (*5*) (15 points for the Range of Investigation and 5 points for the Sample Size). The correlation coefficient of the proposed method to measure the levels of free ^{99m}Tc is very high (r=0.998) (*9*). However, other study has shown that the proposed QC method significantly overestimates the RCP values of ^{99m}Tc-sestamibi (*5*). Even when the RCP results obtained by the recommended TLC method (*1,2*) are at the lower levels (i.e., 26.8% and 21.8%), the proposed Sep-Pak method still produced high RCP values (i.e., 91.4% and 91.9%) (*5*) (0 point for the Validity and Accuracy of the Proposed Method). The proposed method can only measure the % free ^{99m}Tc (0 point for the Measurement of % Bound). No replication of trials was performed for the proposed RCP testing method (0 point for the Replication of Trials). *Economical*: It is not a paper chromatography or solvent extraction method (0 point). *Reasonable*: It is not a paper chromatography, solvent extraction, or centrifugation method (0 point).

j. *ALARA:* There is no information regarding the amount of sample to be used for the proposed QC method (0 point). *Safe:* The safety rating for the QC chemical solvents was calculated by averaging the scores of the two solvents (i.e., chloroform and saline) (see Table 1 for the Safety Ratings of the QC Chemical Solvents). *True:* The proposed QC method uses chloroform to extract the bound ^{99m}Tc-sestamibi (10 points for the Measurement of % Bound). However, all of the other required information for the evaluation of True category is not available (0 point).

k. *True*: The proposed single strip paper chromatography can migrate ^{99m}Tc-sestamibi to the solvent front – with some streaking (R_f range of ^{99m}Tc-sestamibi is 0.55-0.75) (*11*) (10 points for the Measurement of % Bound). There is no information available for the evaluation of the other criteria listed under the True category (0 point).

l. *Fast:* The proposed method is similar to the Sep-Pak method proposed by Hammes et al. (<5 min to complete) (*7*) (20 points). *ALARA:* The proposed alumina-N Sep-Pak method requires two drops (~10 μl) of test sample to be loaded on the conditioned cartridge (2.5 points). *Safety*: For measurement of the % bound ^{99m}Tc-sestamibi, the proposed method requires only the use of 95% ethanol. *True:* Fifty-eight percents of the trials were conducted using ^{99m}Tc-sestamibi samples with purity levels below 90% (*1-3*) (15 points for the Range of Investigation and 5 points for the Sample Size). The proposed QC method can determine the % bound of ^{99m}Tc-sestamibi (10 points for the Measurement of % Bound). However, all of the other required information for the evaluation of True category is not available (0 point). *Economical*: It is not a paper chromatography or solvent extraction method (0 point). *Reasonable*: It is not a paper chromatography, solvent extraction, or centrifugation method (0 point).

References

1. Package insert of Cardiolite® (kit for the preparation of technetium Tc 99m sestamibi injection). Billerica, MA: Du Pont Merck Pharmaceutical Company, February, 1996.
2. Package insert of Miraluma™ (kit for the preparation of technetium Tc 99m sestamibi injection). Billerica, MA: Du Pont Merck Pharmaceutical Company; May, 1997.
3. Technetium Tc 99m sestamibi injection. The United States Pharmacopeia, 23rd rev., and The National Formulary, 18th ed. Suppl 2. Rockville, MD: United States Pharmacopeial Convention; 1995:2680-2681.
4. Proulx A, Ballinger JR, Gulenchyn KY. Routine determination of radiochemistry purity of ^{99m}Tc-MIBI. *Appl Radiat Isot* 1989; 40:95-97.
5. Hung JC, Wilson WE, Gebnard MW, Gibbons RJ. Comparison of four alternative radiochemical purity testing methods for $^{99}Tc^{m}$-sestamibi. *Nucl Med Commun* 1995; 16:99-104.
6. Hung JC, Wilson ME, Brown ML, Gibbons RJ. Rapid preparation and quality control method for technetium-99m-2methoxy isobutyl isonitrile (technetium-99m-sestamibi). *J Nucl Med* 1991; 32:2162-2168.
7. Hammes R, Kies S, Koblenski D, Julin C. A better method of quality control for technetium-99m sestamibi. *J Nucl Med Technol* 1991; 19:232-235.
8. Zimmer AM, Spies SM. Quality control procedures for newer radiopharmaceuticals. *J Nucl Med Technol*1991; 19:210-214.
9. Reilly RM, So M, Polihronis J, Houle S. Rapid quality control of $^{99}Tc^{m}$-sestamibi. *Nucl Med Commun* 1192; 13:664-666.
10. Varga L, Láng J. New, rapid QC method for $^{99}Tc^{m}$-sestamibi. *Eur J Nucl Med* 1992; 19:740 (abstract).
11. Patel M, Sadek S, Jahan S, Owunwanne A. A miniaturized rapid paper chromatographic procedure for quality control of technetium-99m sestamibi. *Eur J Nucl Med* 1995; 22:1416-1419.
12. Hirsch JI, Watson MW. Rapid quality control of technetium-99m-2-methoxy isobutyl isonitrile (technetium-99m-sestamibi). *J Nucl Med* 1996; 24:114-118.

Alternative RCP Testing Method for ^{99m}Tc-Sestamibi [Cardiolite®, Miraluma™] – *Method 1*

[Note: The reader should refer to the published literature (1) for additional information.]

Materials and Methods

Stationary Phase:

- Solvent Saturation Pads (Gelman Sciences, Ann Arbor, MI)
- 1.0 cm x 8.5 cm
  - *origin*: 1.0 cm
  - *cut line*: 4.5 cm
  - *solvent front*: 8.0 cm

Mobile Phase: chloroform: tetrahydrofuran (1:1, v/v)

Calculation: $\text{RCP}\,(\%) = \frac{\text{Top piece}\,(\mu\text{Ci})}{\text{Both pieces}\,(\mu\text{Ci})} \text{X}\,100$

RCP Acceptance Limit

90% (2-4)

References

1. Hung JC, Wilson ME, Brown ML, Gibbons RJ. Rapid preparation and quality control method for technetium-99m-2methoxy isobutyl isonitrile (technetium-99m-sestamibi). *J Nucl Med* 1991; 32:2162-2168.

2. Package insert of Cardiolite® (kit for the preparation of technetium Tc 99m sestamibi injection). Billerica, MA: Du Pont Merck Pharmaceutical Company, February, 1996.

3. Package insert of Miraluma™ (kit for the preparation of technetium Tc 99m sestamibi injection). Billerica, MA: Du Pont Merck Pharmaceutical Company; May, 1997.

4. Technetium Tc 99m sestamibi injection. The United States Pharmacopeia, 23rd rev., and The National Formulary, 18th ed. Suppl 2. Rockville, MD: United States Pharmacopeial Convention; 1995:2680-2681.

Alternative RCP Testing Method for ^{99m}Tc-Sestamibi [Cardiolite®, Miraluma™] – *Method 2*

[Note: The reader should refer to the published literature (1) for additional information.]

1. Slowly push 5 ml of ethanol (100% ethanol is preferable) through a fresh Water™ Sep-Pak® alumina N cartridge (Millipore Corporation, Milford, MA).

2. Load 0.05-0.1 ml of ^{99m}Tc-sestamibi on the long-neck side of the cartridge column, making sure it gets on the column and not in the tube neck.

3. With a disposable syringe, push 10 ml of ethanol through the column slowly, drop by drop and collect the eluate in a test tube. Follow with a few ml of air to collect all of the ethanol.

4. Place the Sep-Pak® cartridge in a second test tube.

5. Assay each tube in a dose calibrator.

6. Calculate the RCP value of ^{99m}Tc-sestamibi as follows:

$$\text{RCP (\%)} = \frac{\text{Ethanol tube } (\mu\text{Ci})}{\text{Both tubes } (\mu\text{Ci})} \text{ X } 100$$

RCP Acceptance Limit

90% (*2-4*)

References

1. Hammes R, Kies S, Koblenski D, Julin C. A better method of quality control for technetium-99m sestamibi. *J Nucl Med Technol* 1991; 19:232-235.

2. Package insert of Cardiolite® (kit for the preparation of technetium Tc 99m sestamibi injection). Billerica, MA: Du Pont Merck Pharmaceutical Company, February, 1996.

3. Package insert of Miraluma™ (kit for the preparation of technetium Tc 99m sestamibi injection). Billerica, MA: Du Pont Merck Pharmaceutical Company; May, 1997.

4. Technetium Tc 99m sestamibi injection. The United States Pharmacopeia, 23rd rev., and The National Formulary, 18th ed. Suppl 2. Rockville, MD: United States Pharmacopeial Convention; 1995:2680-2681.

Rating of the RCP Testing Methods for ^{99m}Tc-Tetrofosmin [Myoview™]

RCP Testing Method	Fast (20)	ALARA (5)	Safe (10)	True (55)	Economical (5)	Reasonable (5)	Overall Score (100)
Package Insert (*1*)	0.0	5.0	5.3	55.0	3.0	0.0	68.3(a)
USP/NF	NA	NA	NA	NA	NA	NA	NA (b)
Geyer et al. (*2*)	20.0	5.0	5.3	10.0	3.0	0.0	47.3 (c)
McKay et al. (*3*)	20.0	5.0	5.0	22.5	5.0	5.0	62.5 (d)

The Evaluation Behind the Ratings:

a. *Fast*: The recommended RCP testing method (2 cm x 20 cm Gelman ITLC-SG strip) requires almost 30 min for completion (*2*) (0 point). *Safe:* The rating of the chemical safety is the average score of the two chemical solvents (i.e., 35:65 v/v mixture of acetone and dichloromethane) (see Table 1 for the Safety Ratings of the QC Chemical Solvents). *Economical*: It is not a paper chromatography or solvent extraction method (0 point). *Reasonable*: It is not a paper chromatography, solvent extraction, or centrifugation method (0 point).

b. Neither the current USP/NF nor its supplements have the monograph for ^{99m}Tc-tetrofosmin.

c. *Fast:* The miniaturized strip takes ~4 min for developing the ITLC-SG strip (1 cm x 10 cm) (20 points). *ALARA:* 5-µl sample (5 points). *Safe:* The rating of the chemical safety is the average score of the two chemical solvents (i.e., 35:65 v/v mixture of acetone and methylene chloride) (see Table 1 for the Safety Ratings of the QC Chemical Solvents). *True:* None of the 112 trials used the test samples that had RCP values below the acceptance limit (i.e., 90%, [*1*]) (0 point for each of the following categories: Range of Investigation, Accuracy of the Proposed Method, and Sample Size). The data points that appear in the linear regression graph of the original article (Fig. 6, *2*) seem to be quite spread out; therefore, the correlation coefficient may be less than 0.9 (0 point for the Validity of the Proposed Method). A similar migration of radiochemical components is found for both the proposed method (*2*) and the recommended QC method stated in the package insert (*1*) (10 points for the Measurement of % Bound). No replication of sample testing was done in the original trial (0 point for the Replication of Trials).

Economical: It is not a paper chromatography or solvent extraction method (0 point). *Reasonable*: It is not a paper chromatography, solvent extraction, or centrifugation method (0 point).

d. *Fast:* The RCP result is available within 3 min (20 points). *True:* Three out of the 23 samples had RCP values below 90% (7.5 points for the Range of Investigation). The correlation coefficient is not available (*3*). Additionally, the data points in the linear regression graph of the original article (Fig. 4, *3*) seem to be spread out, and thus the correlation coefficient may be less than 0.9 (0 point for the Validity of the Proposed Method). Only one data point was collected in the critical range. Therefore, there is not adequate information to judge the Accuracy of the Proposed Method (0 point). The proposed RCP testing method can separate the bound ^{99m}Tc-tetrofosmin from other radiochemical impurities (10 points for the Measurement of % Bound). There were no replication of trials (0 point).

References

1. Package insert of Myoview™ (kit for the preparation of technetium Tc 99m tetrofosmin for injection). Arlington Heights, IL: Medi-Physics, Inc., February, 1996.
2. Geyer MC, Zimmer AM, spies WG, Spies SM, Hendel RC. Rapid quality control of technetium-99m-tetrofosmin: comparison of miniaturized and standard chromatography systems. *J Nucl Med Technol* 1995; 23:186-189.
3. McKay BF, Spies SM. Rapid chromatographic quality control procedure for Tc-99m tetrofosmin. *J Nucl Med* 1996; 24:165 (abstract).

Standard RCP Testing Method for ^{99m}Tc-Tetrofosmin [Myoview™]

There is no alternative RCP testing method for ^{99m}Tc-tetrofosmin since the QC method stated in the package insert (*1*) has the highest overall score.

[Note: The reader should refer to the published literature (1) for additional information.]

Materials and Methods

Stationary Phase:

- ITLC-SG (Gelman Sciences, Ann Arbor, MI)
- 2.0 cm x 20.0 cm
  - *origin*: 3.0 cm
  - *cut lines*: 6.0 cm and 15 cm
  - *solvent front*: 18.0 cm

Mobile Phase: acetone: dichloromethane (35:65, v/v)

Calculation: $\text{RCP}\,(\%) = \dfrac{\text{Center piece}\,(\mu\text{Ci})}{\text{Three pieces}\,(\mu\text{Ci})} \times 100$

RCP Acceptance Limit

90% (*1*)

Reference

1. Package insert of Myoview™ (kit for the preparation of technetium Tc 99m tetrofosmin for injection). Arlington Heights, IL: Medi-Physics, Inc., February, 1996.

RCP TESTING PROCEDURES FOR COMPOUNDED ^{111}In-LABELED RADIOPHARMACEUTICALS (1988-1997)

Ratings of the RCP Testing Methods for ^{111}In-Capromab Pendetide [ProstaScint®]

The only published RCP testing method for ^{111}In-capromab pendetide is stated in the package insert for ProstaScint® (*1*). This recommended method is similar to the common QC method for ^{111}In labeled monoclonal antibodies proposed by Zimmer (*2*).

References

1. Package insert of ProstaScint® (kit for the preparation of indium In 111 capromab pendetide). Princeton, NJ: Cytogen Corporation, August, 1997.

2. Zimmer AM. An update of miniaturized chromatography procedures for newer radiopharmaceuticals. In: Hladik WB III, editor. Correspondence continuing education courses for nuclear pharmacists and nuclear medicine professionals. Albuquerque, NM: University of New Mexico, 1994; 3(5):10.

Standard RCP Testing Method for ^{111}In-Capromab Pendetide [ProstaScint®]

[Note: The reader should refer to the published literature (1) for additional information.]

Materials and Methods

Stationary Phase:

- ITLC-SG (Gelman Sciences, Ann Arbor, MI)
- 1.0 cm x 8.0 cm*
  - *origin*: 1.0 cm*
  - *cut line*: 4.0 cm*
  - *solvent front*: 7.0 cm*

* There is no specific information regarding the size of the ITLC-SG strip and the locations of the origin, cut line, and solvent front for the ITLC –SG strip to be used for the RCP determination of ^{111}In-capromab pendetide (*1*). The designated numbers are based upon the common specifications employed for QC procedure involving the use of the miniaturized chromatography strip.

Mobile Phase: 0.9% NaCl solution

Note: Prior to the application of the test sample onto the ITLC-SG strip, mix equal (several drops of each) of ^{111}In-capromab pendetide with 0.05 M DTPA solution and allow the mixture to stand at room temperature for 1 min.

Calculation: $\text{RCP}\,(\%) = \dfrac{\text{Bottom piece}\,(\mu\text{Ci})}{\text{Both pieces}\,(\mu\text{Ci})} \times 100$

RCP Acceptance Limit

90% (*1*)

Reference

1. Package insert of ProstaScint® (kit for the preparation of indium In 111 capromab pendetide). Princeton, NJ: Cytogen Corporation, August, 1997.

Ratings of the RCP Testing Methods for ^{111}In-Pentetreotide [OctreoScan®]

RCP Testing Method	Fast (20)	ALARA (5)	Safe (10)	True (55)	Economical (5)	Reasonable (5)	Overall Score (100)
Package Insert (*1*)	20.0	0.0	7.2	55.0	3.0	2.5	87.7 (a)
USP/NF Method 1 (*2*)	0.0	5.0	6.6	55.0	0.0	0.0	66.6 (b)
Zimmer et al. (*3*)	0.0	0.0	10.0	10.0	3.0	2.5	25.5 (c)

The Evaluation Behind the Ratings:

a. *Fast*: There is no information regarding the required time to complete the recommended method. According to the experience of performing the QC process with the Waters Sep-Pak® C18 cartridge, the entire QC procedure should only take ~5 min (20 points). *ALARA* The recommended method requires a 0.05-0.1 ml test sample for the evaluation (0 point). *Safe:* The rating of the chemical safety is the average score of the two chemical solvents (i.e., methanol and distilled water) (see Table 1 for the Safety Ratings of the QC Chemical Solvents). *Economical*: It is not a paper chromatography or solvent extraction method (0 point). *Reasonable*: It is not a paper chromatography, solvent extraction, or centrifugation method (0 point).

b. *Fast*: The recommended HPLC method is very time-consuming (e.g., solvent treatments, maintaining the column temperature at 35°C, equilibrating the HPLC system for at least 15 min, 30-min incubation time after test sample is reconstituted, etc.) (0 point). *ALARA:* The recommended method requires a volume of test sample having an activity of 0.5-15 MBq (14-400 μCi). Using the lower end of the activity range, the required sample volume could be less than 5 μl (5 points). *Safe:* The rating of the chemical safety is the average score of the two chemical solvents (i.e., sodium acetate and methanol) (see Table 1 for the Safety Ratings of the QC Chemical Solvents). *Economical* and *Reasonable*: HPLC testing procedure (0 point).

c. *Fast:* The proposed QC method does not specify the required time to complete the RCP testing process (0 point). *ALARA* The proposed method requires the mixing of 50 μl of test sample with 25 μl of 0.05 M DTPA solution (0 point). *Safe:* The proposed ITLC-SG method uses 0.9% NaCl solution as the mobile phase (10 points) (see Table 1 for the Safety Ratings of the QC Chemical Solvents). *True:* Following

solvent migration, the bound ^{111}In-pentetreotide remains at the origin (R_f = 0.0), while unbound and/or weakly bound ^{111}In, such as a DTPA chelate, migrates with to the solvent front (R_f = 1.0). (10 points for the Measurement of % Bound). There is no information available for the other criteria listed under the True category (0 point). *Economical*: It is not a paper chromatography or solvent extraction method (0 point). *Reasonable*: It is not a paper chromatography, solvent extraction, or centrifugation method (0 point).

References

1. Package insert of OctreoScan® (kit for the preparation of indium In 111 pentetreotide). St. Louis, MO: Mallinckrodt Medical, Inc., March, 1995.
2. Indium In-111 pentetreotide injection. The United States Pharmacopeia, 23rd rev., and the National Formulary, 18th ed. Suppl 6. Rockville, MD: United States Pharmacopeial Convention; 1997:3683-3684.
3. Zimmer AM. An update of miniaturized chromatography procedures for newer radiopharmaceuticals. In: Hladik WB III, editor. Correspondence continuing education courses for nuclear pharmacists and nuclear medicine professionals. Albuquerque, NM: University of New Mexico, 1994; 3(5):10.

Standard RCP Testing Method for ^{111}In-Pentetreotide [OctreoScan®]

Since the recommended QC method stated in the package insert has the highest score, please refer to the package insert for OctreoScan® for the RCP testing method of ^{111}In-pentetreotide (*1*).

[Note: The reader should refer to the published literature (1) for additional information.]

1. Slowly push 10 ml of methanol through the longer end of a fresh Water™ Sep-Pak® C18 cartridge (Millipore Corporation, Milford, MA). Similarly, rinse the cartridge with 10 ml water and then with another 5 ml water. Discard the eluates.

2. Load 0.05-0.1 ml of ^{111}In-pentetreotide on the longer end of the cartridge column, making sure the test sample migrates onto the column and not in the tube neck.

3. With a disposable syringe, slowly push (in dropwise manner) 5 ml of water through the longer end of the cartridge, using a test tube (tube 1) to collect the eluate. Similarly, elute the cartridge with 5 ml methanol drop by drop and collect the eluate in a test tube (tube 2).

4. Place the Sep-Pak® cartridge in a test tube (tube 3).

5. Assay each tube in a dose calibrator.

6. Calculate the RCP value of ^{111}In-pentetreotide as follows:

$$\text{RCP}\,(\%) = \frac{\text{Tube 2}\,(\mu\text{Ci})}{\text{Three tubes}\,(\mu\text{Ci})} \times 100$$

RCP Acceptance Limit

90% (*1*)

Reference

1. Package insert of OctreoScan® (kit for the preparation of indium In 111 capromab pendetide). Princeton, NJ: Cytogen Corporation, August, 1996.

Rating of the RCP Testing Method for ^{111}In-Satumomab Pendetide [OncoScint® CR/OV]

There is no recommended RCP testing method for ^{111}In-satumomab pendetide published in the package insert for OncoScint® CR/OV (*1*). However, the USP/NF has recently listed a monograph for ^{111}In-satumomab pendetide (*2*), and a recommended QC method is included in the monograph. The USP/NF RCP test method is similar to the universal QC method for ^{111}In labeled monoclonal antibodies which was proposed by Zimmer (*3*).

References

1. Package insert of ProstaScint® (kit for the preparation of indium In 111 capromab pendetide). Princeton, NJ: Cytogen Corporation, August, 1996.

2. Indium In 111 satumomab pendetide injection. The United States Pharmacopeia, 23rd rev., and The National Formulary, 18th ed. Suppl 8. Rockville, MD: United States Pharmacopeial Convention; 1998:4219-4220.

3. Zimmer AM. An update of miniaturized chromatography procedures for newer radiopharmaceuticals. In: Hladik WB III, editor. Correspondence continuing education courses for nuclear pharmacists and nuclear medicine professionals. Albuquerque, NM: University of New Mexico, 1994; 3(5):10.

Standard RCP Testing Method for ^{111}In-Satumomab Pendetide [OncoScint® CR/OV]

[Note: The reader should refer to the published literature (1) for additional information.]

Materials and Methods

Stationary Phase:

- ITLC-SG
- 1.0 cm x 8.0 cm
  - *origin*: 1.0 cm
  - *cut line*: 1.6 cm
  - *solvent front*: 7.0 cm

Mobile Phase: 0.9% NaCl solution

Note: Prior to the application of the test sample onto the ITLC-SG strip, mix equal (several drops of each) of ^{111}In-satumomab pendetide with 0.05 M DTPA solution in a glass vial. Allow the spot of test sample on the strip to air-dry before development of the solvent.

Calculation: $\text{RCP}\,(\%) = \frac{\text{Bottom piece}\,(\mu\text{Ci})}{\text{Both pieces}\,(\mu\text{Ci})} \times 100$

RCP Acceptance Limit

90% (*1*)

Reference

1. Indium In 111 satumomab pendetide injection. The United States Pharmacopeia, 23rd rev., and The National Formulary, 18th ed. Suppl 8. Rockville, MD: United States Pharmacopeial Convention; 1998:4219-4220.

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