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Radiopharmaceutical management of ^{90}Y/^{111}In labeled antibodies: shielding and quantification during preparation and administration

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Background: The combined application of potent β-emitting isotopes for therapy with γ-emitting isotopes for scintigraphy requires a profound regimen concerning team member safety and radionuclide quantification. ***Methods:*** We have developed materials and methods for a proper and easy manipulation of ^{90}Y during preparation and administration of ^{90}Y/^{111}In pharmaceuticals used for radioimmunotherapy. ***Results:*** The efficacy of the shielding measures is documented. Protocols for the calibration of γ-dose calibrators with respect to ^{90}Y are extended to the assessment of quench-corrected liquid scintillation counting of ^{90}Y. The contribution of ^{90}Y backscatter to ^{111}In counting is quantified. Newly developed shielding equipment allows an adequate administration of relatively large volumes (100 m*l*) of ^{90}Y/^{111}In labeled pharmaceuticals to patients. ***Conclusions:*** The procedures described combine pharmaceutical (Good Manufacturing Practice) and radiation safety requirements with an accurate logging of relevant data.

Key words: radiopharmaceutical, radioimmunotherapy, radiation protection, radionuclide calibration, quench correction

INTRODUCTION

The β-emitting isotope ^{90}Y is presently in focus for its radiotherapeutic potency. After binding of $^{90}Y^{3-}$ to a tumor-specific antibody, the resulting complex targets some of the specified tumor cells. Cytotoxic effects in these and the surrounding cells are induced by the damage due to ^{90}Y irradiation. Evidence is accumulating that antibodies against CD20 may serve as a vehicle for the radioimmunotherapy of non-Hodgkin's lymphoma.[1,2] Likewise, radiolabeled anti-CEA (carcinoembryonic antigen) antibodies have been shown to affect epithelial ovarian cancer,[3] medullary thyroid carcinoma[4] and many others.[5] Recently, an inventory has been given of logistic,[6] dosing[7] and safety[8,9] aspects of ^{90}Y-Ibritumomab Tiuxetan (Zevalin) for the treatment of patients with non-Hodgkin's lymphoma. In this study, we continue these considerations focusing on the consequences for daily practice.

^{90}Y emits pure β^--radiation with a maximum energy of 2.28 MeV and has a half-life of 64.1 hours.[10] Compared to ^{131}I, ^{90}Y radiation has a much higher β^- energy and shorter half-life, but lacks the γ-emission required for scintigraphic imaging. Particularly at the trial stage of investigations, a portion of the antibody may therefore be labeled with ^{111}In, a pure γ-emitter (245 and 171 keV) with a half-life of 67.3 hours, in order to trace scintigraphically the fate of the antibody *in vivo*. Dual-label protocols that combine ^{90}Y with ^{111}In require a well-considered regime of Perspex and lead shielding in order to minimize the personnel radiation exposure of β- and γ-emissions, as well as bremsstrahlung.[11]

Electrons, with a velocity that exceeds the velocity of light in the medium, dissipate this excess energy during collisions as blue-light photons (Cerenkov radiation[12]), which are readily detectable by the photomultipliers of a liquid scintillation counter. However, a red substance like hemoglobin is a potent absorber of blue light and serum samples may differ with respect to the extent of hemolysis. Therefore, the availability of a quench curve is a prerequisite for an estimation of the counting efficiency. Gamma emitters like ^{111}In are unable to induce a significant count

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rate in a Cerenkov liquid scintillation system. By contrast, ^{90}Y-induced radiation does interfere with ^{111}In counting in a γ-counter. By means of a cross-over table (Sharkey and coworkers (pers. comm.)), the count rate of ^{111}In can be corrected for the ^{90}Y backscatter.

Before the actual administration to a patient, ^{90}Y-pharmaceuticals are diluted into a large volume (100 m*l*) in order to avoid putative radiolysis of the protein. Since infusion of 100 m*l* is time-consuming compared to injection of small volumes, we have developed appropriate shielding materials in order to protect the assisting personnel from irradiation.

The objectives of this report were to integrate relevant but scattered knowledge of ^{90}Y management with some newly developed applications and to apply these in the setting of routine production of radiopharmaceuticals. As a result, we have implemented procedures for efficient shielding during preparation, accurate ^{90}Y/^{111}In dual isotope determination for wide ranges of radioactivity, and the safe administration of ^{90}Y/^{111}In-labeled radiopharmaceuticals to patients in large volumes.

MATERIALS AND METHODS

For reasons of clarity, we first provide an inventory of relevant equipment used for daily routine, and separately, we specify the adaptations made for the management of ^{90}Y.

Laboratory equipment for daily routine

Manipulations are performed in a class A laminar flow cabinet (Clean Air Techniek B.V., Woerden, the Netherlands) placed in a class D environment. The cabinet was constructed with 3 mm lead protection in the walls and 6 mm lead in the base (Veenstra Instruments, Joure, the Netherlands). Front protection consists of a 2 cm thick rolling lead glass window (equivalent to 6 mm lead).

Amounts of radioactivity in the range of 1 MBq to 50,000 MBq are routinely measured in a VDC-405 radionuclide dose calibrator (Veenstra Instruments, Joure, the Netherlands). The predefined isotope-specific calibration factor for ^{111}In measurement in the dose calibrator was found to be appropriate using a certified 150 MBq $^{111}InCl_3$ source obtained from Tyco Healthcare, Mallinckrodt Medical, Petten, the Netherlands. Amounts of less than 1 MBq are determined in a 5650 AutoGamma counter (γ-emitting isotopes) or in a 1600CA liquid scintillation counter (β-emitting isotopes), both from Packard. Procedures for the determination of count rate efficiencies are described below. A Rados RDS-110 (Rados Technology Oy, Turku, Finland) radiation monitor is used to measure levels of radiation. Instruments are maintained and their performance controlled on a regular basis.

For radiochemical purity control, the preparations under investigation are spotted on ITLC-SG strips (1 × 6.5 cm, Gelman, Ann Arbor, USA) at a 1 cm mark. The strips are then developed in a mobile phase of 0.9% NaCl (anti-CD20) or of 10 mmol/*l* Na_2EDTA (anti-CEA) until the solvent front has reached the 5–6 cm marks. After chromatography, the labeling efficiencies are determined by means of a miniGITA scanning device controlled by the GITA v1.64 computer program (Raytest, Hamburg, Germany), using a high voltage of 757 V and a 15–200 keV energy window.

Additional shielding requirement for ^{90}Y

For manipulations with ^{90}Y in the laminar flow cabinet, a 2 cm Perspex shield was applied to the inside of the front protection in order to avoid the generation of an excess of bremsstrahlung. In case of high levels of radioactivity, extra removable L-shaped shields consisting of 1 cm Perspex and 3 mm lead provided additional shielding as required during incubations. For patient administration of ^{90}Y-radiopharmaceuticals by infusion, a 1.6 cm Perspex container with a Teflon lid was developed to hold the 100 m*l* infusion bottle. The shielded bottle is hung upside down in a large-mesh wire-netting. In this position, an additional lead cover was added to give more shielding against ^{111}In irradiation and ^{90}Y-bremsstrahlung (see Fig. 1).

Calibration and measurement of ^{90}Y radioactivity

Radionuclide dose calibrators are routinely used for preparations of γ-emitting radiopharmaceuticals. They may also be employed for the quantification of nuclides emitting β-spectra provided that absorption of low-energy electrons and conversion of high-energy electrons into γ-radiation is taken into account.[13] Vials containing $^{90}YCl_3$ in aqueous solution were obtained from either MDS Nordion (Fleures, Belgium) or from CIS Biointernational (Gif-sur-Yvette, la France) in amounts certified for calibration or authorized for preparation. An 1830 MBq certified ^{90}Y source was used for checking and adjusting the predefined isotope-specific calibration factor Y-90**v** (the setting for ^{90}Y in the standard **v**ial) until the read-out equaled 1830 MBq (corrected for decay). A portion was then removed from the vial by means of a syringe, and the vial was re-measured in order to determine the amount of radioactivity in the syringe. The syringe's content was adjusted to a predefined volume and measured in the dose calibrator in order to adjust the isotope-specific calibration factor Y-90**s** (the setting for ^{90}Y in this particular type of **s**yringe containing the predefined volume). These manipulations were performed for each vial and each syringe volume required for the generation of a well-calibrated patient syringe. These settings were monitored at each therapy occasion using the calibrated amount of ^{90}Y certified for preparation.

For the determination of the ^{90}Y count rate in gamma and liquid scintillation counters, the content of a syringe, calibrated as described, was transferred quantitatively (measuring the full and empty syringe) in a preweighed

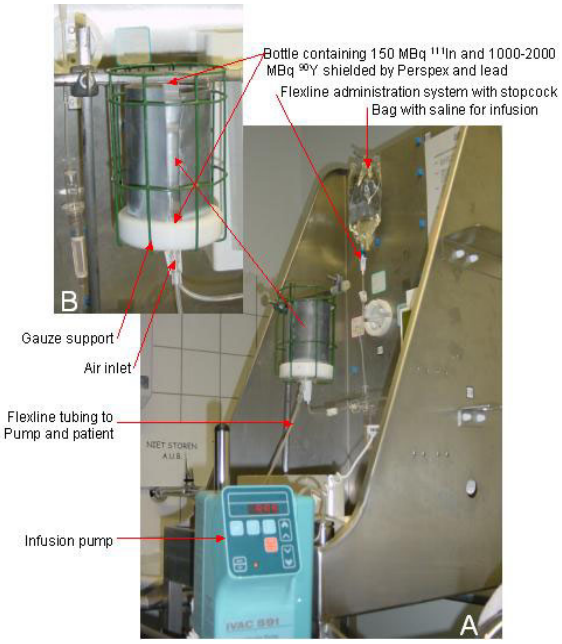

Fig. 1 Administration of ^{90}Y/^{111}In labeled pharmaceuticals to patients. The 100 m*l* infusion bottle is hung upside down in a Perspex/lead shield (A). Single-use tubing is applied for connection with a saline bag at one end and the infusion pump at the other end (B). Coach-work and pump are routinely applied for the administration of therapeutic quantities of ^{131}I-MIBG.

vial resulting in a well-known amount of ^{90}Y-radioactivity per unit of volume. Using this stock solution, a series of accurate dilutions will render calibration samples in the (k)Bq range for use in gamma and liquid scintillation counters.

Quench correction of ^{90}Y Cerenkov counting

For liquid scintillation counting, a quench correction curve was constructed as follows. 1 m*l* of blood was mixed with 9 m*l* of warm water and centrifuged. 1 m*l* supernatant was added to 9 m*l* of freshly prepared serum and this solution (designated "serum with 10% hemolysis") was used as the quenching agent. A series of samples with decreasing quenching capacity were made by accurate serial dilution of this stock solution with freshly prepared serum as described above. A small but well-known amount of ^{90}Y was added to each of a series of counting vials and the vials were counted in the liquid scintillation counter. Spectral analysis indicated a 0–50 keV window as appropriate for the Cerenkov counting of ^{90}Y. The counting confirmed that indeed all vials of the series contained identical amounts of ^{90}Y radioactivity. Quenching was then introduced by adding an equal volume of each dilution sample of the quenching agent to each vial. The vials were counted again in the liquid scintillation counter according to its instruction manual for the generation and storage of quench curves. The well-known amount of ^{90}Y in kBq must be converted into dpm before feeding into the machine's program. Upon storage, the quench curve obtained can be applied at each subsequent occasion of ^{90}Y Cerenkov counting.

Preparation and radiochemical purity control of ^{90}Y-pharmaceuticals

Purified DTPA-hMN-14 conjugate (anti-CEA IgG) and ibritumomab tiuxetan (anti-CD20 IgG) were made available by Immunomedics Inc. and Schering AG, respectively. Binding of ^{90}Y or ^{111}In to the modified antibodies may involve incubation at 45°C (anti-CEA) or at room temperature (anti-CD20). A Peltier-directed Thermostat-*Plus* (Eppendorff) hotplate facilitates control of the 45°C incubation. A tight-fitting brass pig (thickness 3 mm) was made to provide both an efficient heat transfer from plate to vial and shielding from radiation. The L-shaped Perspex and lead shield provided additional radiation protection on demand. A dual-input thermocouple thermometer with data logging (Fluke 54II) was used in order to record the temperature course on the inside of a "phantom" vial. The second probe was put in ice for "real-time" calibration. Radiochemical purity control was performed as described above for the daily routine production of radiopharmaceuticals.

Administration to patients

The equipment regularly used for patient administration of therapeutic quantities of ^{131}I-MIBG (GE Healthcare, Amersham Health B.V., Cygne Centre, Eindhoven, the Netherlands) was adapted for the infusion of ^{90}Y-pharmaceuticals into patients. An overview is given in Figure 1A. The insert (Fig. 1B) shows the 100 m*l* infusion bottle upside down in its Perspex shield with lead cover. The Teflon lid leaves a small opening for connection with a single-use administration system (BBBO/C Flexline, Medisize, Hillegom, the Netherlands) to a saline infusion bag and a similar line through the infusion pump (Ivac model 591, San Diego, California, USA) into the patient's body. The pump can be set to stop when the infusion is nearly completed. The bottle is refilled upon opening of the stopcock in order to rinse the final traces of the ^{90}Y-pharmaceutical into the infusion line. When the stopcock is in the closed position, the pump takes the liquid from the bottle.

RESULTS

Shielding measures for ^{90}Y

The efficacy of shielding against ^{90}Y-irradiation was assessed by measuring the levels of radiation from an unprotected vial containing 1830 MBq of ^{90}Y, and with the various shielding measures (Table 1). The distance between radiation source and radiation monitor was kept

Table 1 Effect of shielding against ^{90}Y radiation

	Radiation level (%)
Unprotected ^{90}Y vial	100
Laminar flow cabinet underneath	0.3
Cabinet plus 2 cm perspex in front window	3
Brass heating pig 3 mm	35
Perspex shield 10 mm	35
Perspex shield 10 mm with 3 mm leaden shield	9
Perspex flask container 16 mm	23
Perspex flask container with 3 mm leaden shield	5

Levels of residual radiation are expressed as a percentage of the radiation level of the unprotected source vial containing 1830 MBq ^{90}Y. For each shielding situation, the distance between radiation source and measuring monitor has been kept to a minimum. Build-up effects were not taken into account.

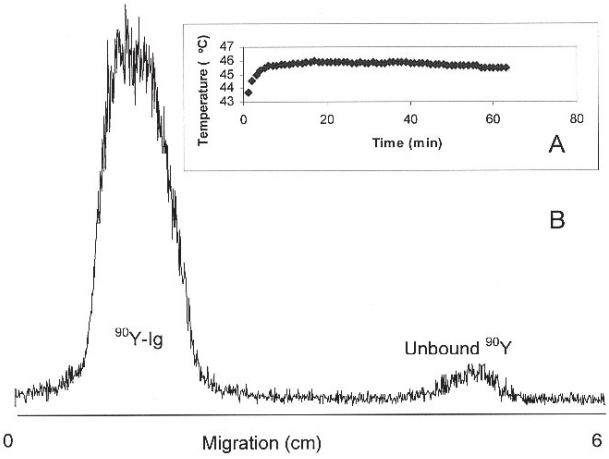

Fig. 2 Temperature monitoring during preparation and radiochemical purity control of ^{90}Y-carrying proteins. Logged data of the temperature course (A) can be archived together with the main data files. The labeling percentage of this preparation is 91% (B).

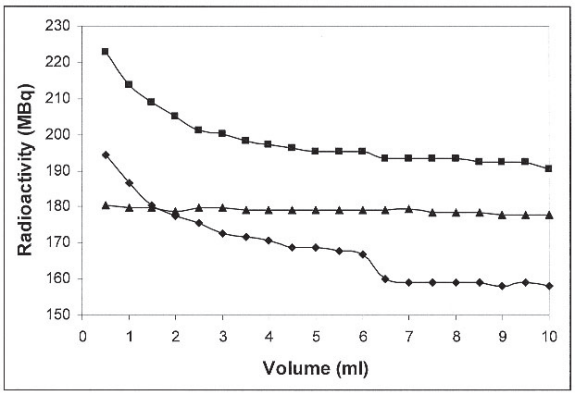

Fig. 3 Calibration curves of identical amounts of ^{90}Y in thin-wall (*squares*) and thick-wall (*diamonds*) glass vials, and in 10 m*l* syringes (*triangles*) for increasing volumes. Note: the dip in the diamond curve at 6 m*l* is an artifact.

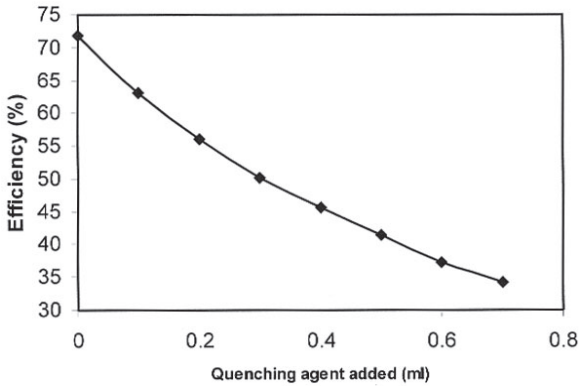

Fig. 4 Quench curve for ^{90}Y Cerenkov scintillation counting. A window of 0–50 keV was set for unquenched samples. Counting efficiency (%cpm/dpm) is plotted against the proportion of quenching agent. The highest point of quenching corresponds to serum with approximately 10% hemolysis (*see text*).

as close as physically possible, reflecting the radiation to which body parts would be maximally exposed. For instance, the distance between the unprotected vial and monitor (the 100% level of radiation) was zero, but this distance was about 50 cm when the vial was placed on the floor of the laminar flow cabinet and the monitor held underneath the cabinet (0.3% level of radiation). Brass with a thickness of 3 mm showed a shielding capacity equal to 10 mm of Perspex and an extra lead shield is therefore recommended. The same holds for the Perspex flask container (thickness 16 mm). No effort was undertaken to identify the physical character of the radiation. It is anticipated, that the majority represents bremsstrahlung perhaps with the exception of the unprotected vial. The ^{90}Y-specific shielding measures can easily be removed for other daily purposes.

Calibration, preparation and quantification

Isotope-specific calibration factors of dose calibrators were adapted until the read-out equaled the amount of MBq in a certified ^{90}Y or ^{111}In standard. This was performed for each type of container (vial or syringe) and every volume to be applied, separately. On this basis, ^{90}Y- and ^{111}In-labeled immunoconjugate doses were prepared and controlled for their radiochemical purity (Fig. 2). After appropriate calibration, the doses were diluted to 100 m*l* for infusion into patients (see below).

As an alternative to the adaptation of isotope-specific calibration factors, correction for the volume dependence of ^{90}Y in a γ-dose calibrator can also be achieved by constructing volumetric calibration curves. The results for two different vials containing initially identical amounts of ^{90}Y (Fig. 3) show that the thickness and the quality (lead content) of the vial's glass, in addition to the solution's

absorption, determine the shape of the curve. A similar curve of ^{90}Y in a 10 m*l* syringe shows only minimal volume dependence of the count rate.[14] As a result, we were able to measure precisely the amount of ^{90}Y MBq in a stock solution and to estimate its volume simply by weight. Stock solutions calibrated in this way were subjected to a series of accurate dilution steps in order to obtain standards with known activities in the kBq range. These standards were used for the calibration of both liquid scintillation and γ-counters.

Cerenkov liquid scintillation counting of ^{90}Y

The Cerenkov energy spectrum of unquenched ^{90}Y fits into a 0–50 keV window. Differences in count rate among ^{90}Y samples due to photon capture are easily quantified by means of quench analysis. A quench curve was constructed as described above and is shown in Figure 4. Without addition of quenching agent, the counting efficiency of ^{90}Y amounts to approximately 72%. Stepwise addition of quenching agent induces a gradual reduction in counting efficiency from 72% to almost 30%. The sample with the highest level of quenching contained a mixture of clean serum (90% v/v) with completely hemolyzed blood (10% v/v). Consequently, traces of blood severely affect the count rate of the serum samples to be analyzed by means of Cerenkov scintillation counting and the quenching in whole blood samples may readily pass beyond the reach of a quench curve. Upon storage in the liquid scintillation counter, the quench curve obtained can be applied on each subsequent occasion. If present, ^{111}In does not contribute to the count rate of the samples during ^{90}Y Cerenkov counting, in view of the physical decay characteristics of ^{111}In.

Quantifying ^{111}In in the presence of ^{90}Y

Since ^{90}Y can be quantified in a γ-dose calibrator, a contribution of ^{90}Y-radiation to the overall count rate can also be expected to influence the determination of ^{111}In in a γ-counter. Indeed, double label counting of separate ^{111}In and ^{90}Y samples indicated the construction of so-called cross-over tables to discriminate between ^{111}In and ^{90}Y counts in dual label (mixed) samples. In short, a low-energy window A (i.e. 120–480 keV) is set to register all ^{111}In counts as well as an unknown portion of the ^{90}Y-induced count rate; a high-energy window B (i.e. 500–2000 keV) is set to register only ^{90}Y-related radioactivity. Counting a series of pure ^{90}Y samples in the absence of ^{111}In radioactivity generates the ^{90}Y count rate in window A as a proportion of the ^{90}Y-related count rate in window B. During mixed sample counting, the count rate of window B remains free of ^{111}In-related radioactivity and hence, the count rate in window A (^{111}In plus ^{90}Y) can proportionally be corrected on the basis of the ^{90}Y count rate in B. An example of a cross-over table for the estimation of dual labeled (^{111}In and ^{90}Y) samples is given in Table 2. ^{111}In counts are confined to the 120–480 keV window (A). When only ^{90}Y is present, the ratio A/B gives the cross-over or backscatter factor of ^{90}Y from B into A. In the presence of both nuclides (the serum sample), the count rate in B is multiplied by the backscatter factor and the product is subtracted from the count rate in window A to generate the sample's ^{111}In radioactivity in cpm. The method works quite reliably under a wide range of conditions, provided that the regular precautions concerning background and counting statistics are validated.

Counting of serial dilutions of properly calibrated ^{111}In standards indicates that the efficiency of ^{111}In counting amounts to 70% under these conditions. In addition, we have observed that the count rates of ^{90}Y samples in a

Table 2 Cross-over table: ^{90}Y contribution to ^{111}In γ-counting

Windows	A	B	C
LL (keV)	120	500	15
UL (keV)	480	2000	2000
^{111}In (cpm)	160895	524	167729
^{90}Y (cpm)	13899	16177	40788
Serum (cpm)	123160	40803	203395

Energy window settings for A and B are shown in the upper two rows; an extra open window (C) is added for control purposes (LL = lower window level; UL = upper window level). ^{111}In (cpm) and ^{90}Y (cpm) refer to the count rates of the individual isotopes, respectively. The serum sample contains both isotopes in the example. The A/B ratio of ^{90}Y provides the "backscatter" factor by which the serum count rate in B is multiplied in order to calculate the proportion of ^{90}Y counts in window A of the serum sample (*see text*). ^{111}In radioactivity in this serum sample amounts to 123160 − (40803∗13899/16177) = 88103 cpm. Notice the "forward scatter" in window B compared to window A in the pure ^{111}In sample.

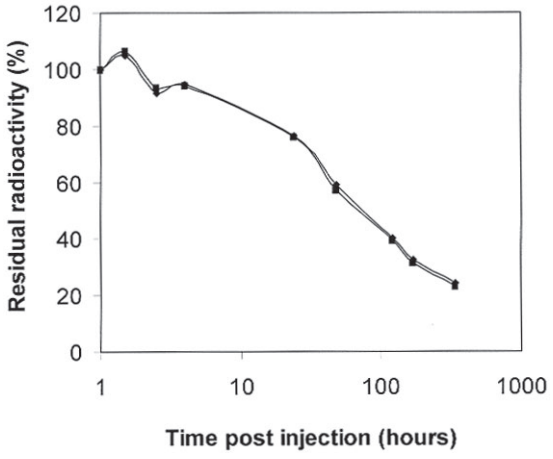

Fig. 5 Clearance of ^{111}In-Ig (*diamonds*) and ^{90}Y-Ig (*squares*) from a patient's serum. Serum samples were prepared at the time points indicated and stored frozen. After count rate determination, the data were corrected as mentioned in the text and are presented as a percentage of the initial value.

γ-counter are not affected by the presence of high levels of quenching agent. Samples displaying a 25%–70% difference in counting efficiency during Cerenkov counting generate identical cross-over tables upon assay in a γ-counter (data not shown).

Administration to patients

Complete administration of ^{90}Y/^{111}In-pharmaceuticals to the patient is attained via certified and single-use tubing and materials with the set-up as shown in Figure 1. After completing the administration of the radiopharmaceuticals and flushing the bottle and tubes twice, the remnants of radioactivity in the administration equipment were, approximately, 1–20 MBq as measured in the radionuclide dose calibrator. We concluded that at least 98% of the radiopharmaceutical was administered successfully.

After completion of the infusion, blood samples were taken from the patient during a period of 2 weeks for biodistribution purposes. Serum levels of ^{90}Y/^{111}In labeled antibodies were determined by means of the methods described above. An example is given in Figure 5 showing an exponential decrease of serum radioactivity to about 20% of the initial value during two weeks following injection. ^{90}Y- and ^{111}In-anti-CEA behave identically in this respect. This is not as evident as it seems to be. After subjection to *in vivo* degradation for as long as 14 days, ^{90}Y and ^{111}In ions (free or bound to remnants of the protein moiety) may behave differently in the patient's circulation. Apparently, this is not the case. Similar curves were obtained from other patients (not shown).

DISCUSSION

The results mentioned above illustrate that standard routine equipment can easily be adapted to the manipulation of ^{90}Y. The procedures described for the management of ^{90}Y are compatible with GMP guidelines for the production of radiopharmaceuticals for human use. The radiation safety measures described above contribute to the three main objectives, i.e. speed of action, distance to the radiation source and shielding. Although not completely, shielding results in acceptable exposure levels throughout the entire procedure without hampering the manipulations necessary for preparation and administration. After completion of patient administration of the ^{90}Y-immunoconjugate by infusion, protective measures concerning the patient and his/her environment are not recommended.[15]

The use of volumetric calibration curves instead of the adaptation of the isotope-specific calibration factors of the radionuclide dose calibrator allows an accurate and volume-independent determination of the amount of radioactivity. Use of these curves in future instances contributes to a reduction of manipulations and hence diminishes the radiation burden and as well as the likelihood of unintentional needlestick injuries.

The high energy of electrons emitted by ^{90}Y enables its quantification by means of liquid scintillation counting in a Cerenkov window.[12,16–18] The need of quench correction has, as far as we know, not yet been documented for these measurements. An advantage is the absence of a count rate contribution by γ-emitting isotopes. In a "classical" liquid scintillation system (using counting fluid), efficiencies of ^{90}Y-counting may reach up to 100%. In this scintillation system, however, ^{111}In is expected to interfere, since it has been reported that the unquenched spectrum of ^{99m}Tc (pure γ-emitter with an energy lower than that of ^{111}In) fits into a 0–150 keV window (^{14}C).[19]

We used 1000–2000 MBq of ^{90}Y-labeled antibody for patient therapy in combination with 120–150 MBq of ^{111}In-labeled antibody for imaging purposes. At these low ^{111}In/^{90}Y ratios, the main limitations for a reliable application of ^{111}In/^{90}Y cross-over tables are the conventional considerations regarding background contribution and counting statistics. At high ^{111}In v/^{90}Y ratios, the forward scatter and pileup of ^{111}In sets a limit to reliability, when its contribution to the count rate in energy window B reaches ^{90}Y count rate levels. One may try to suppress this phenomenon by setting the lower level of the high-energy window B at a higher position.

In conclusion, the procedures described above offer adaptations of local conditions for achieving safe and well-documented production and patient administration of combined ^{90}Y/^{111}In pharmaceuticals.

REFERENCES

1. Wiseman GA, White CA, Witzig TE, Gordon LI, Emmanoulides C, Raubitschek A, et al. Radioimmunotherapy of relapsed non-Hodgkin's lymphoma with Zevalin, a ^{90}Y-labeled CD20 monoclonal antibody. *Clin Cancer Res* 1999; 5: 3281s–3286s.
2. Witzig TE, White CA, Wiseman GA, Gordon LI, Emmanoulides C, Raubitschek A, et al. Phase I/II trial of Zevalin™ (^{90}yttrium ibritumomab tiuxetan; IDEC-Y2B8) radioimmunotherapy for treatment of relapsed or refractory CD20 positive B-cell non-Hodgkin's lymphoma. *J Clin Oncology* 1999; 17: 3793–3803.
3. Juweid ME, Swayne LC, Sharkey RM, Dunn R, Rubin AD, Herskovic T, Goldenberg DM. Prospects of radioimmunotherapy in epithelial ovarian cancer: results with ^{131}I-labeled murine and humanized anti-carcinoembryonic antigen monoclonal antibodies. *Gyneco Oncol* 1997; 76: 259–271.
4. Juweid ME, Hajjar G, Swayne LC, Sharkey RM, Suleiman S, Hersko T, et al. Phase I/II trial of ^{131}I-MN-14(F(ab)2 anti-carcinoembryonic antigen monoclonal antibody in the treatment of patients with metastatic medullary thyroid carcinoma. *Cancer* 1999; 85: 1828–1842.
5. Sharkey RM, Goldenberg DM, Murthy S, Pinsky H, Vagg R, Pawlyk D, et al. Clinical evaluation of tumor targeting with a high-affinity, anticarcinoembryonic-antigen-specific, murine monoclonal antibody, MN-14. *Cancer* 1993; 71: 2082–2096.

6. Zimmer AM. Logistics of Radioimmunotherapy with ^{90}Y Ibritumomab Tiuxetan (Zevalin). *Semin Nucl Med* 2004; XXXIV, 1 (Suppl): 14–19.
7. Spies MS. Imaging and Dosing in Radioimmunotherapy with ^{90}Y Ibritumomab Tiuxetan (Zevalin). *Semin Nucl Med* 2004; XXXIV, 1 (Suppl): 10–13.
8. Borghaei H, Schilder RJ. Safety and Efficacy of Radioimmunotherapy with ^{90}Y Ibritumomab Tiuxetan (Zevalin). *Semin Nucl Med* 2004; XXXIV, 1 (Suppl): 4–9.
9. Zhu X. Radiation Safety Considerations with ^{90}Y Ibritumomab Tiuxetan (Zevalin). *Semin Nucl Med* 2004; XXXIV, 1 (Suppl): 20–23.
10. Kossert K, Schrader H. Activity standardization by liquid scintillation counting and half-life measurement of ^{90}Y. *Appl Radiat Isot* 2004; 60: 741–749.
11. Zanzonico PB, Binkert BL, Goldsmith SJ. Bremsstrahlung radiation exposure from pure beta-ray emitters. *J Nucl Med* 1999; 40: 1024-1028.
12. Coursey BM, Calhoun JM, Cessna JT. Radioassays of yttrium-90 used in nuclear medicine. *Nucl Med Biol* 1993; 20: 693–699.
13. Coursey BM, Collé R, Zimmerman BE, Cessna JT, Golas DB. National radioactivity standards for β-emitting radionuclides used in intravascular brachytherapy. *Int J Radiation Oncology Biol Phys* 1998; 41: 207–216.
14. Zimmerman BE, Cessna JT, Millican MA. Experimental determination of calibration settings for plastic syringes containing solutions of ^{90}Y using commercial radionuclide calibrators. *Appl Radiat Isot* 2004; 60: 511–517.
15. Zhu X. Radiation safety considerations with therapeutic ^{90}Y Zevalin. *Health Phys* 2003; 85: S31–S35.
16. Parker RP, Elrick RH. The assay of beta-emitting radioisotopes using Cerenkov counting. *Int J Appl Radiat Isot* 1996; 17: 361–362.
17. Francois B. Detection of hard beta-emitting radionuclides in aqueous solutions using Cerenkov radiation: a review article. *Int J Nucl Med Biol* 1973; 1: 1–14.
18. L'Annunziata MF, Passo CJ. Cerenkov counting of yttrium-90 in the dry state; correlations with phosphorus-32 Cerenkov counting data. *Appl Radiat Isot* 2002; 56: 907–916.
19. Van Hemert FJ, Van Lenthe H, Schimmel KJM, Van Eck-Smit BLF. Preparation, radiochemical purity control and stability of ^{99m}Tc-mertiatide (Mag-3). *Ann Nucl Med* 2005; 19: 345–349.