Manual on the proper use of

radium dichloride (Ra-223) injection

First Edition

Japan Radiological Society

Japanese Society of Nuclear Medicine

The Japanese Urological Association

Japanese Society of Radiological Technology

Japanese Society for Therapeutic Radiology and Oncology

11/28/2018

Background

Radioactive radium dichloride ($^{223}RaCl_2$) injection (hereafter referred to as “this drug”) has been developed as radiopharmaceutical for the treatment of castration-resistant prostate cancer (CRPC) and associated bone metastases. Radiation therapy using such an unsealed radionuclide is called “internal radiation therapy”. When administering this drug, it is essential to thoroughly comply with the Medical Care Act and other laws and regulations related to radiation protection, as well as the relevant public notices and notices. Moreover, it is very important to pay attention to appropriate clinical use of this drug based on its formulation and characteristics, in addition to handling it as a radionuclide. To present the contents appropriately and for the convenience of the user, this manual is divided into two parts, i.e., a part about safety that focuses on the precautions for handling this drug as a radionuclide (Radiation safety guide) and a part that focuses on clinical use (Clinical guide).

The Radiation safety guide was devised to achieve absolute compliance with regard to correct handling of this radioactive drug, such as avoiding exposure of the general public to radiation and ensuring safe treatment with a radiopharmaceutical based on the ICRP and other international recommendations, as well as the relevant Japanese laws and regulations including the “Release of Patients who have been Administered a Radiopharmaceutical” (Notice No. 70 from the Safety Division, Pharmaceutical and Medical Safety Bureau (PMSB), Ministry of Health, Labour and Welfare (MHLW), dated 30 June 1998, as amended by the Notice of the Head of the Regional Medical Care Planning Division, Health Policy Bureau (HPB), MHLW, No. 0511/1, 11 May 2016).

The Clinical guide covers use of this radiopharmaceutical, which was developed for treatment of CRPC patients with bone metastases and other metastases. It was compiled with reference to Japanese and international guidelines on appropriate use, including the above-mentioned “Considerations for Release of Patients Administered Radiopharmaceuticals” and the “Precautions” section in the package insert of this drug.

In relation to clinical use, it is desirable for medical care professionals to have a thorough knowledge of the characteristics of this drug and the relevant laws and regulations, so that team medicine (involving comprehensive consultation/collaboration among various medical fields) achieves the maximum benefit for patients. In addition, this manual should be used to ensure the safety of family members, caregivers, and the general public.

This manual was jointly prepared by the Japan Radiological Society (JRS), the Japanese Society of Nuclear Medicine (JSNM), the Japanese Urological Association (JUA), the Japanese Society of Radiological Technology (JSRT), the Japanese Society for Therapeutic Radiology and Oncology (JASTRO), and the Japan Radioisotope Association (JRIA) (Subcommittee for Internal Isotope Therapy of the Medical Science and Pharmaceutical Committee), based on "Research on Radiological Protection in Medicine" supported by a 2010 Grant-in-Aid for Health and Labour Sciences (Research Program to Promote the Development of Community Medicine) and on investigation by the working group involved in preparation of the Clinical guide part of the manual.

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- Radiation safety guide-

1 Objectives of the safety guide

This Radiation safety guide deals with the use and handling of radioactive radium dichloride ($^{223}RaCl_2$) injection (hereafter referred to as “this drug”), which is an effective treatment for castration-resistant prostate cancer (CRPC) patients with bone metastases. It strictly complies with the “Release of Patients who have been Administered a Radiopharmaceutical” (Notice No. 70 from the Safety Division, PMSB, MHLW, dated 30 June 1998 [hereafter referred to as “PMSB Notice No. 70”], as amended by the Notice of the Head of the Medical Care Planning Division, HPB, MHLW, No. 0511/1, 11 May 2016[1)]) and it was compiled for the purpose of ensuring safe handling of this drug.

For treatment of CRPC patients with bone metastases using this superior low-invasive drug (hereafter referred to as “this therapy”) to become very widespread, safe handling of this radiopharmaceutical is essential based on thorough application of procedures for prevention of radiation exposure as well as pollution control. With respect to radiation safety, it is extremely important to not only consider the patients, relatives, and other concerned parties, but also the general public.

This manual incorporates the essential recommendations and other references about radiation protection set forth in the Medical Care Act and in the standards of international organizations.[2-8)] It is necessary for the personnel of hospitals and clinics using this therapy (hereafter referred to as “hospitals, etc.”) to ensure radiation safety in accordance with this manual. It should be noted that this drug differs from conventional therapeutic radiopharmaceuticals because it is an alpha emitter, which is a type of radionuclide that has not been dealt with by medical institutions to date. For that reason, it is essential for the personnel of hospitals, etc. using this therapy to become familiar with the physical and chemical properties of Ra-223. Accordingly, the following points are covered in the Radiation safety guide part of this manual.

(1) Facility management guide

(2) Protection against radiation exposure

(3) Storage and waste management of medical radioactive contaminated objects

In addition, hospitals, etc. where this therapy is performed are required to meet the following criteria regarding the standards for facilities in order to ensure radiation safety for ordinary citizens.

① Hospitals, etc. where this therapy is performed must meet the standards for facilities laid down by the relevant laws and ordinances, and must have obtained the necessary permits specified by these laws and ordinances.

② Hospitals, etc. where this therapy is performed must employ full-time physicians and radiological technologists who have specified training with regard to handling of radiopharmaceuticals, etc. and who possess sufficient knowledge and experience in this field. In addition, the hospital must employ physicians who have sufficient knowledge and experience with regard to treating urologic cancer patients.

③ The Ra-223 radiation safety supervisor and Ra-223 radiation safety officers concerned with this therapy must have completed the specified training and courses as defined in this manual.

For information on the clinical aspects of this therapy, refer to the Clinical guide part of this manual.

Paragraph (3) of “5 Precautions” in the “Guideline for Release of Patients Administered Radiopharmaceuticals” (annex to “Release of Patients who have been Administered a Radiopharmaceutical”; PMSB Notice No. 70[9)]) states as follows: “Refer to guidelines, etc. prepared by scientific societies and other organizations in the radiation field for further safety measures such as appropriate protection corresponding to the physical characteristics of radionuclides and relevant instructions for patients and caregivers.” This manual was approved

by the relevant scientific societies in the radiation field and is considered to an equivalent to guidelines as defined by the above-mentioned Guideline.

The Radiation safety guide of this manual was designed on the basis of using this drug for treatment of CRPC patients with bone metastases. Because it adequately covers the basic procedures for radiation safety, it can also be applied if clinical trials carried out in the future using radioactive radium dichloride ($^{223}RaCl_2$) injection for other cancers. However, consideration needs to be given to the characteristics of the patients, the method of drug use, and the dosage, etc. in each clinical trial, and a review of suitability, handling, and compliance should be carried out.

2 Requirements for hospitals, etc. where internal radiation therapy with this drug is performed

In view of the special nature of this drug, this therapy is performed by a medical team that includes personnel such as hospital physicians and radiological technologists (involved in handling of radiopharmaceuticals and radiation safety management) as well as other caregivers involved in nursing and assisting the patients. For this reason, hospitals where this therapy is performed must fulfill the requirements specified in 2.1 through 2.3 of this paragraph.

2.1 Requirements related to buildings and installations of hospitals, etc. implementing this therapy

Hospitals, etc. that are eligible to implement this therapy are institutions where the facilities used for the therapy and the other buildings and installations, etc. specified in the Ordinance for Enforcement of the Medical Care Act [Article 30, sections (8), (9), and (11)] have been approved by the relevant local Governor as being in conformity with the standards specified in Article 30, paragraphs 13-30, section (26) of the same regulations.

2.2 Safety management systems in hospitals, etc. implementing this therapy

In order to ensure safe handling of this drug and radiation safety, managers of hospitals, etc. where this therapy is performed must confirm that their Ra-223 radiation safety supervisors and Ra-223 radiation safety officers involved in this therapy have attended a “Training course on safe handling and appropriate use of internal radiation therapy with radium dichloride (Ra-223) injection” (hereafter referred to as a “safe handling training course”) sponsored by the Japanese Society of Nuclear Medicine and related societies. In addition, this therapy must be performed at facilities that are capable of arranging an organized management system for medical safety, such as is described below, that is specifically purposed for “internal radiation therapy using Ra-223 injection.”

2.2.1 Selection and role of Ra-223 radiation safety supervisors in performing this therapy

Directors of hospitals, etc. where this therapy is performed must nominate an Ra-223 radiation safety supervisor for this therapy from among physicians who have attended a safe handling training course and whose expertise in this therapy has been certified. The Ra-223 radiation safety supervisor has the task of training the facility’s physicians, etc. participating in this therapy, as well as controlling and supervising this therapy.

2.2.2 Selection and role of Ra-223 radiation safety officers in performing this therapy

Managers of hospitals, etc. where this therapy is performed must nominate at least one Ra-223 radiation safety officer, depending on the hospital’s situation, from among radiological

technologists or other staff who have attended a safe handling training course and whose expertise in this therapy has been certified. The Ra-223 radiation safety officers carry out work related to ensuring the safety of this therapy and radiation safety management, etc. under the direction of the Ra-223 radiation safety supervisor.

2.3 Conditions for implementing this therapy according to this manual

The following conditions must be met for performing this according to this manual.

(1) This drug is administered for medical treatment to a CRPC patient with bone metastases.

(2) An expert on radiation safety management has explained the precautions for this therapy to the patient and family members (caregivers), and it has been concluded that following these precautions are possible and the patient as well as the family members (caregivers) have agreed that conforming to the requirements is feasible.

(3) The patient's residence must have appropriate sewerage facilities and a water closet.

(4) The patient should be able to lead an active and independent life.

(5) Contact between patient and children or pregnant women must be minimized for 2 ~ 3 days after administration of this drug.

3 Characteristics of Ra-223

3.1 Radioactive decay of Ra-223

Figure 1 shows the principal decay series of radium-223 (Ra-223). The decay products of Ra-223 have a rather short physical half-life. The stable nuclide lead-207 (Pb-207) is reached after emission of 4 alpha and 2 beta decays. In the decay series of radionuclides starting from Ra-223, emission of alpha and beta particles is also associated with gamma radiation.

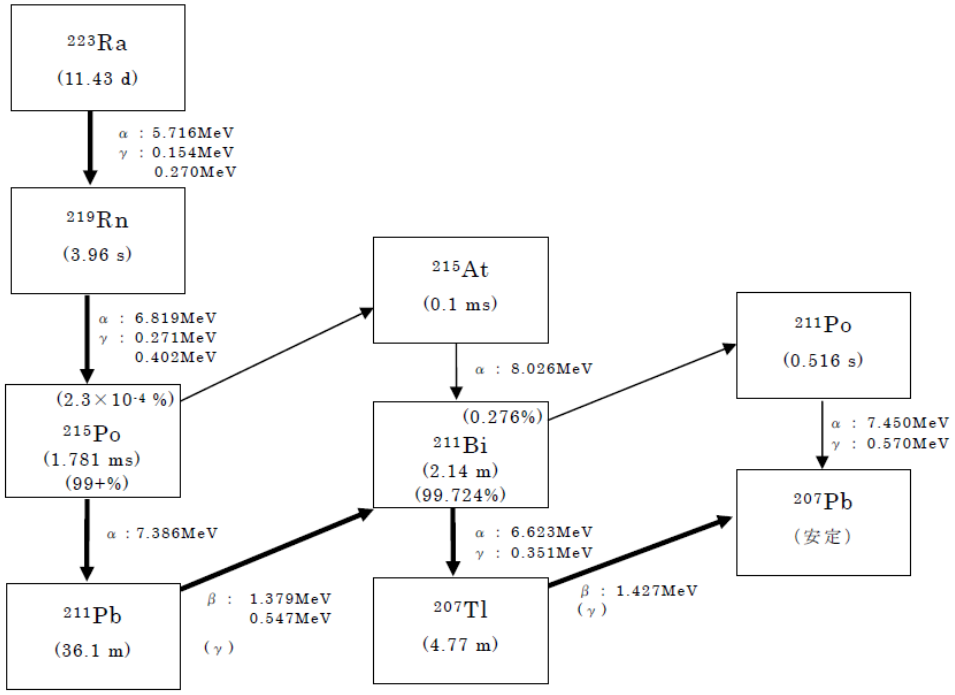

Figure 1: Radioactive decay of Ra-223

(Excerpt from the Isotope Pocket Data Book [11th Edition], Japan Radioisotope Association, 2011)

3.2 Physical properties of Ra-223 and Rn-219

Ra-223 undergoes alpha decay and produces the noble gas radon-219 (Rn-219). Therefore, the volatility of Rn-219 in solution needs to be considered.

Radon is the heaviest element among the noble gases. Rn-219 is a radionuclide of Rn-222 that exists most abundantly in nature, and its characteristics are identical to those of radon. According to the International Chemical Safety Card (ICSC No. 1322) for Rn-222, its boiling point is -62°C, its melting point is -71°C, and its density is 9.73 g/L. In addition, radon is soluble in water at 22.68 mL/100 mL at 25°C (0.2268 mL/mL),[10] showing remarkably high solubility compared to the other two noble gases (xenon and krypton), as well as compared to oxygen.

3.2.1 Rn-219 content of the drug product

The Rn-219 content per 1 MBq of Ra-223 injection (M) can be calculated as follows.

Ra-223 has a physical half-life of 11.43 days, while its decay product Rn-219 has a half-life of only 3.96 seconds (Fig. 1). If a parent nuclide has an extremely long physical half-life compared its progeny, as in this case, the following relationships hold at secular equilibrium.

$\lambda_1 N_1 = \lambda_2 N_2$ (1)

$A_1 = A_2$ (2)

$N_1/T_1 = N_2/T_2$ (3)

where

λ_1: Decay constant of the parent nuclide = $0.693/T_1$.

λ_2: Decay constant of the progeny = $0.693/T_2$.

N_1 or N_2: Number of atoms of the parent nuclide or progeny, respectively, at radioactive equilibrium.

A_1 or A_2: Radioactivity of the parent nuclide or progeny, respectively, at time t.

T_1 or T_2: Physical half-life of the parent nuclide or progeny, respectively.

The number of atoms of Rn-219 at the secular equilibrium of 1 MBq Ra-223 can be obtained from equation (4), which is a modification of equations (1) - (3).

$A_1 = \lambda_2 N_2$, $N_2 = A_1/\lambda_2$, $N_2 = A_1 \times T_2 / 0.693$ (4)

$N_2 = 1 \times 10^6 \times (3.96/0.693) = 5.71 \times 10^6$ [particles]

Furthermore, the volume of 5.71×10^6 [particles] of Rn-219 in an ideal state is,

$M = (5.71 \times 10^6$ [particles] $/ 6.02 \times 10^{23}$ [particles/mol] $/ \times 22.4$[L/mol]$\times 1000$[mL/L]$= 2.13 \times 10^{-13}$ [mL]

Here 6.02×10^{23} [particles/mol]: number of atoms in 1 mol of Rn-219 (Avogadro constant)

22.4 [L/mol]: the volume of 1 mol of Rn-219 in an ideal state

In this way, it can be calculated that the volume of Rn-219 per 1 MBq of Ra-223 is 2.13×10^{-13} mL at radioactive equilibrium. This quantity is a small fraction ($1/1.1 \times 10^{12}$) of the amount of Ra-223 soluble in water at 25°C (0.2268 mL/mL). Hence, it can be concluded that Rn-219 gas is completely dissolved in the Ra-223 injection solution. Regarding possible volatilization of Rn-219 gas from the injection solution, when vapor from the surface of the solution was adsorbed by water and charcoal for 3 hours and gamma-radiation was measured, it was found to be at background level. This suggests that almost no volatilization occurs. Concerning polonium-215 (Po-215), the progeny of Rn-219, polonium is usually tetravalent and stable, existing as an oxide. Therefore, unless this drug is shaken excessively, Ra-223 and its progeny will remain in solution and there is little risk of volatilization into the atmosphere. Thus, considering the nature of Rn-219 as a progeny of Ra-223, it can be concluded from the above that a dispersion rate of 0.001[11)] is applicable for evaluation of the concentration limit, etc. of a liquid or solid in this drug based on the Medical Care Act.

3.2.2 In vivo behavior of Ra-223 and its progeny

Like calcium, radium belongs to the alkaline earth metals in the periodic table. Consequently, it shows similar in vivo behavior to calcium and the major part of an administered dosage of Ra-223 accumulates in the bones, including sites affected by metastasis. After Ra-223 accumulates in the bones, it decays to form Rn-219 with a physical half-life of 11.43 days, following which Rn-219 decays to Po-215 with a short physical half-life of 3.96 seconds (Figure 1). Compared with the diffusion time of Rn-219 from solution, its physical half-life of 3.96 seconds is rather short. On the other hand, polonium has a strong affinity for many tissues and organs. Therefore, it is expected that Ra-223 will persist in the bones as the progeny Po-215 and eventually decay to Pb-207, a stable isotope. This supposition is supported by the results of in vitro dissolution tests using the bones of animals administered Ra-223, which have shown that progeny are eluted into aqueous solution in extremely small quantities not exceeding a few percent.[12)] Accordingly, it is speculated that most of the administered Ra-223 and its progeny remains in the bones for an extended period[13)] and a comparatively small amount escapes to expiration of administrated patients.

4 Laws and regulations controlling the use of this drug

The following laws and regulations are related to prevention of radiation hazards when using pharmaceuticals for medical purposes as specified Article 2 (1) of the Act Ensuring the Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (hereafter referred to as the "Pharmaceuticals and Medical Devices Act").

① Medical Care Act[2] (Ordinance for Enforcement of the Medical Care Act[14]): MHLW

② Pharmaceuticals and Medical Devices Act: MHLW

③ Medical Practitioners Act: MHLW

④ Pharmacists Act: MHLW

⑤ Radiology Technicians Act: MHLW

⑥ Act Governing Clinical Laboratory Technicians, etc.: MHLW

⑦ Industrial Safety and Health Act (Ordinance on Prevention of Ionizing Radiation Hazards[15] [hereafter referred to as the "Ionizing Radiation Ordinance"], Work Environment Measurement Act): MHLW

⑧ National Public Service Act (Rules and Directives of the National Personnel Authority 10-5)[16]: National Personnel Authority

According to the provisions of the Ordinance for Enforcement, Article 1, paragraph 1 (2), of the "Act on Prevention of Radiation Hazards due to Radioisotopes, etc. (hereafter referred to as the 'Radiation Hazard Prevention Act')" under the jurisdiction of the Nuclear Regulatory Authority ("Substances that are pharmaceuticals as specified in the Pharmaceuticals and Medical Devices Act, Article 2, paragraph 1, as well as their raw materials or ingredients existing at manufacturing sites approved according to Article 13, paragraph 1 of the same act"), this drug is excluded from regulation under the Radiation Hazard Prevention Act. For this reason, it is independently controlled as a "Radionuclides for medical application (hereafter medical radionuclide)" as stipulated in Article 24, paragraph 1 (8) of the Ordinance for Enforcement of the Medical Care Act.[14, 17] Hospitals, etc. can only use this drug by providing Public Notice under the Medical Care Act.

4.1 Standards for facilities, etc. where medical radionuclides are used (see Appendix a)

Hospitals, etc. where this drug and other medical radionuclides are used (hereafter referred to as "nuclear medicine practices") must have facilities in which the medical radionuclides are used, as well as buildings and installations for storage and waste management of medical waste that meet the standards specified in Article 30, sections (8), (9), and (11) of the Ordinance for Enforcement of the Medical Care Act.

4.2 Standards for concentration limits in facilities, etc. where medical radionuclides are used

In hospitals, etc. where nuclear medicine practices are performed, the facilities set forth in paragraph 4.1 as well as the other buildings and installations must meet the standards for concentration limits, etc. shown in Table 1.

Table 1: Criteria for dose limits and concentration limits in rooms where medical radionuclides are used

Room where medical radionuclides are used	Medical Care Act
Rooms where medical radionuclides are used	Room where medical radionuclides are used [*1)]
	Storage facilities[*2)]
	Disposal facilities[*3)]
Dose limits and concentration limits in controlled areas, etc.[*4)]	• Effective dose of external radiation [*5)]: Not exceeding 1.3 mSv per three months • Concentration of radionuclides in the air [*5)]: Average concentration over 3 months not exceeding 1/10 of the concentration limit of radionuclides in the air • Surface contamination: not exceeding 1/10 of the surface density limit – radionuclides that emit alpha particles: 0.4 Bq/cm^2, radionuclides that do not emit alpha particles: 4 Bq/cm^2
Dose limits and concentration limits at places in facilities using medical radionuclides where people are constantly entering[*1-3)]	• Effective dose on the walls etc. not exceeding 1 mSv per week • Concentration of radionuclides in the air: Average concentration over 1 week is equal to the concentration limit of radionuclides in the air[*5)] • Surface contamination: surface density limit – radionuclides that emit alpha particles: 4 Bq/cm^2, radionuclides that do not emit alpha particles: 40 Bq/cm^2
Dose standards at boundaries in a hospital or other medical facility (including areas in the hospital that might be accessed by treated patients) [*6)]	Effective dose not exceeding 250 μSv per 3 months[*5)]
Exposure dose for inpatients[*7)]	Effective dose not exceeding 1.3 mSv per 3 months

*1) Ordinance for Enforcement of the Medical Care Act, Article 30 (8): Rooms where medical radionuclides are used

*2) Ordinance for Enforcement of the Medical Care Act, Article 30 (9): Storage facilities

*3) Ordinance for Enforcement of the Medical Care Act, Article 30 (11): Disposal facilities

*4) Ordinance for Enforcement of the Medical Care Act, Article 30 (16): Controlled Areas

*5) Ordinance for Enforcement of the Medical Care Act, Article 30 (26): Concentration limit

*6) Ordinance for Enforcement of the Medical Care Act, Article 30 (17): Protection at site boundaries

*7) Ordinance for Enforcement of the Medical Care Act, Article 30 (19): Prevention of patient exposure

4.3 Restrictions on the locations of use, etc. (Ordinance for Enforcement of the Medical Care Act, Article 30 (14))

Medical radionuclides must be used inside rooms where medical radionuclides are used. However, this restriction shall not apply in case of temporary use in operating rooms, use inisolation rooms (rooms for patients administered radiopharmaceuticals) for patients whose transport is difficult, or temporary use in intensive care units or coronary care units after appropriate protective measures and contamination control measures have been taken.[4-1)]

Note 4-1: The “appropriate protective measures and contamination control measures” in this provision are explicitly stated in PFSB Notice No. 188 (Notice No. 188 of the Pharmaceutical and Food Safety Bureau [PFSB] dated March 12, 2001)[11)] (hereafter referred to as “PMSB Notice No. 188”), 2. Specific Matters (4), Matters related to Management Obligations 1. (11).

5 Release of patients after administration of this drug

Paragraph 1 of the Ordinance for Enforcement of the Medical Care Act, Article 30 (15) (Restrictions on the admission of patients to hospital) stipulates the following: “Managers of hospitals or clinics must only admit to isolation rooms for patients who are receiving treatment by continuous insertion of medical radiation devices or medical radiation instruments into the body, or patients who are receiving treatment with medical radionuclides or medical radionuclides for positron emission tomography (PET)”.[5-1)] This is aimed at reducing the radiation exposure of third parties other than the patient. On the other hand, the same article states that “this shall not apply if appropriate protective measures and contamination control measures[5-2)] have been taken” and that, taking into account the patient’s QOL, admission to a sickroom for patients administered radiopharmaceuticals is not always compulsory if a certain level of radiation protection is ensured. This is the objective of the safety guideline “Release of patients administered radiopharmaceuticals”.

Note 5-1: With regard to “receiving treatment”, PFSB Notice No. 188 points out that there is a possibility of radiation exposure exceeding 1.3 mSv per 3 months to patients other than those receiving radiotherapy if patients are undergoing radiation therapy by continuous insertion of medical radiation devices or medical radiation instruments into the body or by administration of medical radionuclides (radiopharmaceuticals and radioactive investigational drugs [drugs undergoing clinical trials as stipulated in paragraph 2 (17) of the Pharmaceuticals and Medical Devices Act]) or medical radionuclides for PET.

Note 5-2: “Appropriate protective measures and contamination control measures" are specified in A) through C) below.

A) If a patient is released from a sickroom for patients administered radiopharmaceuticals to a general ward of the hospital, the effective dose to other patients must be less than 1.3 mSv per 3 months.

B) Appropriate measures must be taken if a medical radiation device or medical radiation instrument falls out when a patient is receiving treatment by insertion of such a device or instrument into the body.

C) Upon release of patients who have been administered radiopharmaceuticals from a sickroom for patients administered radiopharmaceuticals, etc., instructions for the patients and caregivers as well as release records must be prepared in conformity with the release criteria of PMSB Notice No. 70.

5.1 Release criteria

The release criteria (PMSB Notice No. 70) were issued to ensure the QOL of patients receiving radiopharmaceutical treatment, as well as the radiation safety of the general public and caregivers. They were published to provide interpretation of the “provisions” specified in the Ordinance for Enforcement of the Medical Care Act, Article 30 (15) paragraph 1. The essential points of the release criteria are as follows.

1) Scope of application: When patients who have been administered radiopharmaceuticals are released from room where medical radionuclides are used, isolation rooms, etc. within the hospital and discharged home.

2) Release criteria: The “Standards for dose suppression” were established as safety standards. As a result, 1 mSv per year was determined for the general public[5-3] and 5 mSv per patient[5-4)] was established for caregivers, by taking into consideration the benefits for both the patient and the caregiver.[5-5]

   Concretely, release from hospital and discharge of the treated patient home will be approved if the patient fits any of the release criteria (1) to (3) set out below.

   (1) Dosage-based release criteria

   Release from hospital and discharge home will be approved if the dosage or the amount of residual radioactivity in the patient does not exceed the amount of radioactivity shown in the following table. These reference values were calculated on the basis of dosage, physical half-life, an occupancy factor of 0.5, and a 1 cm dose equivalent rate constant at 1 m from the patient’s body surface.

Acceptable radioactivity at release from hospital and discharge home of patients administered radiopharmaceuticals

Nuclide used for treatment	Dosage or residual radioactivity in the body (MBq)
Strontium-89	200[*1)]
Iodine-131	500[*2)]
Yttrium-90	1184[*1)]

*1: Maximum dosage.

*2: The radioactivity of iodine-131 is the dose obtained by combining internal exposure due to inhalation of iodine-131 discharged in the patient’s breath and external exposure due to radiation from the patient’s body.

   (2) Release criteria based on the measured dose rate

   Release from hospital and discharge home will be approved if the dose rate measured at 1 m from the patient’s body surface does not exceed the value shown in the following table. These reference values were calculated on the basis of dosage, physical half-life, an occupancy factor of 0.5, and a 1 cm dose equivalent rate constant at 1 m from the patient’s body surface.

Acceptable dose rate at release from hospital and discharge home of patients administered radiopharmaceuticals

Radionuclide used for treatment	1 cm dose equivalent rate (μSv/h) at 1 m from the patient’s body surface
Iodine-131	30[*)]

*: The dose equivalent rate is the dose obtained by combining internal exposure due to inhalation of iodine-131 discharged in the patient’s breath and external exposure due to radiation from the patient’s body.

(3) Release criteria based on the patient's cumulative dose

Based on the cumulative dose calculated for each patient, release from hospital and discharge home will be approved in the following (and similar) cases.

(a) When taking into account the effective half-life and other factors, in addition to the condition of the patient, and calculating the cumulative dose at 1 m from the patient's body surface, the cumulative dose caregivers are exposed to does not exceed 5 mSv and the cumulative dose does not exceed 1 mSv for the general public.

(b) In this case, records regarding calculation of the cumulative dose must be kept. The above release criteria are treated as conforming in the following cases.

Release criteria based on the patient's cumulative dose

Radionuclides used for treatment	Scope of application	Dosage (MBq)
Iodine-131	Treatment of patients to eradicate residual thyroid cancer (ablation) after total thyroidectomy for differentiated thyroid carcinoma without distant metastases*1)	1110*2)
Radium-223	Treatment of CRPC patients with bone metastases*3)	12.1*4) (72.6*5))

*1: Implementation conditions: Restricted to implementation in accordance with the relevant guidelines prepared by the related scientific societies ("Ambulatory treatment with I-131 [1,110 MBq] for eradication of residual thyroid cancer").

*2: The radioactivity of iodine-131 is the dose obtained by combining internal exposure due to inhalation of iodine-131 discharged in the patient's breath and external exposure due to radiation from the patient's body.

*3: Implementation conditions: Restricted to patients who have received no more than 6 administrations of 55 kBq/kg of radium dichloride (Ra-223) injection at 4-week intervals in accordance with the relevant guidelines prepared by related scientific societies ("Manual for Appropriate Conduct of a Clinical Trial of Internal Therapy with Radium dichloride (Ra-223) Injection").

*4: Maximum dosage per 1 administration.

*5: Maximum dosage per 1 course of the treatment (6 administrations).

3) Release records

If release from hospital is approved, records with regard to the following points must be prepared and retained for 2 years after release of the patient.

(1) Dosage administered, date and time of release, and dose rate measured at release.

(2) Details of advice and instructions to breastfeeding mothers.

(3) If release from hospital was approved according to paragraph 2) point (3), the method of calculating the cumulative dose to approve release.

4) Important points

(1) If release from hospital and return of the patient to home have been approved, written as well as oral advice and instructions for daily life, etc. must be provided in order to minimize unnecessary exposure of third parties as much as possible.

(2) If the patient is breastfeeding a baby, sufficient explanation, advice, and instructions must be given.

(3) Refer to the guidelines, etc. prepared by scientific societies and other organizations in the radiation field for further safety measures, such as protection corresponding to the physical characteristics of radionuclides and relevant instructions for patients and caregivers.

Note 5-3: Dose limit for the general public: 1 mSv/year

The limit recommended in ICRP Publication 60 (1990)[4)] is used as the dose limit for the general public (1 mSv per year). However, higher values are permitted in single years under special circumstances, if the average exposure over 5 years does not exceed 1 mSv per year. Although not currently incorporated into the national laws and ordinances, the applicable limit in the new ICRP Publication 103 (2007)[18)] also follows the above recommendation from 1990.

Note 5-4: Cumulative dose limit for caregivers: 5 mSv

With regard to the exposure of caregivers, volunteers etc., ICRP Publication 73 (1996), "Radiological Protection and Safety in Medicine"[5)], Clause 95, classifies the exposure of friends and relatives who assist in nursing patients as "medical exposure" and suggests that "dose constraints in the order of several mSv per case are reasonable". On the other hand, the IAEA's International Basic Safety Standards (1996)[7)] recommend practical values concerning dose constraints and dose limits for consolers and visitors to patients: "The dose limits established in this section are not applicable to consolers of patients, i.e. individuals knowingly exposed to radiation while voluntarily (not on an employment or work-related basis) helping with nursing, attending and soothing patients who receive medical checkups or therapies, or to visitors of these patients. Nevertheless, the dose of any consoler or visitor should be constrained so as not to exceed 5 mSv per activity during the patient's checkups or therapies. The dose of children visiting patients who took in radioactive substances must be reduced to less than 1 mSv in the same way."

Note 5-5:

In a memorandum (Data related to calculation of release criteria: PMSB/SD, MHLW, June 30, 1998)[19)] issued at the same time as PMSB Notice No. 70, the cumulative doses of radiopharmaceuticals frequently used in Japan at the time were calculated (radiation from inside the body of the treated patient: cumulative dose at a distance of 1 m from the radiation source when only considering the physical half-life). Among 8 radiopharmaceuticals, only I-131 (dosage of 1,110 MBq, occupancy factor = 1) exceeded 20 mSv, while the cumulative doses for the other diagnostic radiopharmaceuticals ranged from 0.02 to 0.28 mSv (occupancy factor = 1).

5.1.1 Factors relating to evaluation of release criteria

1) Occupancy factor[5-6)]: The duration of contact with the patient and the distance from the patient (radiation source) are factors influencing exposure to radiation. Consequently, the "occupancy factor", which is taken into account when assessing the exposure of third parties to be set by considering each individual's involvement with the patient.

(1) Occupancy factor for caregivers: 0.5

Based on measured exposure doses after patients were administered radiopharmaceuticals, an occupancy factor of 0.5 has been reported to be reasonable in cases where careful nursing is required.[20)] The results of surveys conducted in Japan to determine the exposure dose from treated patients also suggest that a factor of 0.5 is appropriate.[21)] Accordingly, use of an occupancy factor of 0.5 to assess the dose to

caregivers after release of patients from hospital and discharge home has been established.

(2) Occupancy factor for the public: 0.25

Based on the measured exposure doses to patients' families in average households, an occupancy factor of 0.25 has been reported to be appropriate.[20] Accordingly, use of an occupancy factor of 0.25 for family members (apart from caregivers) and the general public after release of patients from hospital and discharge to home has been established.

Note 5-6: Occupancy factor: Ratio of the estimated dose actually received from a patient by a third party to the cumulative dose that would be received after remaining at 1 m from the point source (patient) for an infinite time (the time until complete decay of the radionuclide).

5.2 Calculation of the external exposure dose to third parties

The external exposure dose to third parties (other than patients) is calculated by using the following formula.

$I = A \times C \times Fa \times t/L^2$

where

I: Effective dose at the point of calculation (μSv), A: Radioactivity (MBq), C: Effective dose rate constant of the radiation source (μSv × m2 × MBq-1 × h-1), Fa: Effective dose transmission rate (in case of multiple shielding, the overall product is taken as the transmission rate), t: Time of use (h), L: Distance from the radiation source to the point of calculation (m).

The effective dose rate constant (C) is a total value calculated by assuming that Ra-223 is at radioactive equilibrium, as shown in Table 2. When assessing external radiation due to γ-rays etc. released from Ra-223 inside the patient's body, it was assumed that the administered Ra-223 remains inside the patient at radioactive equilibrium and external radiation decreases according to the longest physical half-life of the radionuclides.

The cumulative dose to which a third party is exposed from patients receiving this drug is assessed by combining the cumulative doses due to external and internal exposure.

Table 2: Effective dose rate constant of Ra-223 at radioactive equilibrium

(Effective dose rate constant of each radionuclide: According to the Isotope Pocket Data Book, 11th edition)

Radionuclide	Effective dose rate constant (minimum 10 keV) ($\mu Sv \times m^2 \times MBq^{-1} \times h^{-1}$)
Ra-223 and Rn-219 at equilibrium	0.0294
Po-215	2.51E-05
Pb-211	0.00882
Bi-211	0.00683
Tl-207	3.09E-04
Total	0.0454*)

*: The total effective dose rate constant for Ra-223 and its progeny is 0.0454. At-215 and Po-211 (see Figure 1) are not considered when calculating this value. The contribution of At-215 (decay rate: 1 %) and Po-211 (decay rate: 0.27 %) to the total effective dose rate constant of all radionuclides at radioactive equilibrium amounts to only three ten millionths (3×10^{-6}) of the effective dose rate constant. Therefore, in these guidelines, the effective dose rate

constant of Ra-223 and its progeny at radioactive equilibrium is the sum of Ra-223/Rn-219, Po-215, Pb-211, Bi-211, and Tl-207.

5.2.1 Assessment of the cumulative external exposure dose received by caregivers and the general public from patients administered this drug

The cumulative external exposure dose received by caregivers or the public at a distance of 1 m from patients administered this drug was determined as follows.

1) Exposure of caregivers

Cumulative external exposure dose = 3.85 [MBq/administration] × 0.0454 [μSv × m^2 × MBq^{-1} × h^{-1}] × 1.443 × 24 [h/d] × 11.43 [d] × 0.5 × 6 [administrations/course of therapy] = 207.6 [μSv/course of therapy][5-7]

where

3.85 [MBq/administration]: Average dosage for 1 administration of this drug per patient

0.5: Occupancy factor for caregivers

0.0454 [μSv × m^2 × MBq^{-1} × h^{-1}]: Effective dose rate constant of Ra-223 at radioactive equilibrium

11.43 [d]: Physical half-life of Ra-223

6 [administrations/course of therapy]: Frequency of administration to the treated patient

2) Public exposure

Cumulative external exposure dose = 3.85 [MBq/administration] × 0.0454 [μSv × m^2 × MBq^{-1} × h^{-1}] × 1.443 × 24 [h/d] × 11.43 [d] × 0.25 × 6 [administrations/ course of therapy] = 103.8 [μSv/course of therapy]

where

0.25: Occupancy factor for the general public

Note 5-7: The dosing regimen of this drug is 55 kBq per kg of body weight, with a maximum of 6 administrations at 4-week intervals. According to the 2012 “National Health and Nutrition Survey,” the average body weight of adults aged 20 years or older is 65.9 ± 10.8 kg (mean ± standard deviation). Accordingly, this manual assumes that the body weight of a treated patient is 70 kg and sets the administered radioactivity of this drug as 3.85 MBq (55 kBq/kg × 70 kg/1000 [kBq/MBq] ＝ 3.85 MBq) per dose. For indications based on NIST standards, see below:

Since early development of this drug, during launch outside Japan in 2013, and up to the present day, the quantity and concentration of radioactivity in this drug has been calibrated based on a standard established by the National Institute of Standards and Technology (NIST). However, a change to the NIST standard value was announced in March 2015. Under the new NIST standard, the quantity and concentration of radioactivity in the prepared drug and the dose administered to the patient will be displayed as approximately 10% higher than before the change. However, the change to the NIST standard only affects displayed values, and the quantity and concentration of radioactivity in the prepared drug and the actual dose administered to the patient remains the same before and after the change to the NIST standard. In order to avoid confusion in the countries and regions where Ra-223 is already in circulation, once the time needed to apply for a change in the approved dose used in these countries and regions has passed, all preparations of Ra-223 used in any country worldwide that are manufactured from April 4, 2016 onwards will display values based on the new NIST standard. Since the drug will launch in Japan after the change to displayed values has been implemented throughout the world, this manual and the package inserts to be used inside Japan will show values based on the new NIST standard (e.g.: dose = 55 kBq/kg), even though the values shown in articles and other materials that were published before the NIST change will still be based on the old NIST standard (e.g.: dose = 50 kBq/kg). Accordingly, caution is required when referring to reports and other materials related to research conducted before this change was made to the NIST standard.

(Clinical guide, p. 19, footnote 1)

5.2.2 Assessment of the internal exposure doses received by caregivers and the general public from patients administered this drug

1) Estimation of the internal exposure dose by using a model

Excreta of patients administered this drug will enter river systems via waste water treatment plants. Considering the chemical properties of radium, it is presumed that most Ra-223 excreted by patients will exist as insoluble compounds. However, there is also the possibility of soluble compounds due to chelating substances. Consequently, when estimating the internal exposure dose to third parties due to ingestion, trial calculations were performed by assuming that the whole dosage was discharged into a river and that Ra-223 existed in a soluble form. The Yodogawa River system with its high utilization of purified waste water was used as the model.

* Average flow rate of water in the Yodogawa River system: Approx. 4.1 [TL/year]
* Population of the Osaka region using the system for drinking water: Approx. 12.80 million people (Osaka + Nara + Wakayama prefectures + 1/2 of Hyogo prefecture)
* Total Japanese population: Approx. 125 million people (1995)
* Percentage of the total population of Japan residing in the Osaka region: 10.2 %
* Number of patients in Japan expected to develop bone metastases of prostate cancer (2015-2019): 12,152/year
* Assuming that 30-40 % of eligible patients are administered this drug.

→ 12,152 [patients/year] × 0.4 ≒ 4,800 [patients/year]

* Number of treated patients in the Osaka region: 4,800 [patients/year] × 0.102 ≒490 [patients/year] (calculated from the population share)

It was assumed that the dosage of Ra-223 administered to 1 patient each time is 3.85 MBq and the number of administrations is 6 per year.

* Total dose of Ra-223 administered in the Osaka region: 3.85 [MBq/administration] × 6 [administrations/patient] × 490 [patients/year] ＝ 11.32 [GBq/year]

It was assumed that all of the Ra-223 administered is discharged into the Yodogawa River system and exists in a soluble form.

* Ra-223 concentration in the Yodogawa River system: 0.01132 [TBq/year] ÷ 4.1 [TL/year] ＝ 2.76×10^{-3} [Bq/L]

* Annual intake of Ra-223 by a member of the public (drinking 2 liters of water per day):[23] 2.76×10^{-3} [Bq/L] × 2 [L/day] × 365 [days/year] ＝ 2.02 [Bq/year]

* Trial calculation of the annual internal exposure dose: 2.02 [Bq/year] × 1×10^{-4} [mSv/Bq] ＝ 2.02×10^{-4} [mSv/year] ≒ 0.20 [μSv/year]

  However, 1×10^{-4} [mSv/Bq] was reported to be the effective dose coefficient in case of Ra-223 ingestion.[22]

* The annual internal exposure dose of 0.20 μSv ICRP is 1/5000 of the dose limit for the public specified in ICRP recommendations (1 mSv per year).

2) Estimation of the internal exposure dose by using the uptake coefficient

On the other hand, evaluation of the internal exposure of third parties due to radioactive contamination from treated patients has been performed by using an uptake coefficient. As a result, the internal exposure of third parties due to contamination was assumed to not exceed $1/10^6$ of the radioactivity administered to patients.[24]

Based on this report, the internal exposure dose received by third parties (other than the patient) was calculated as follows.

* Trial calculation of the internal exposure dose: 3.85 [MBq/administration] × 10^6 [Bq/MBq] × 10^{-5} × 1×10^{-4} [mSv/Bq] × 6 [administrations/course of therapy] × 10^3 [μSv/mSv] ＝ 23.1 [μSv/ course of therapy]

where

10^{-5}: Uptake coefficient for third parties of radioactivity administered to patients assumed in NUREG-1556[24]

Though the reported internal exposure of third parties was assumed to not exceed $1/10^6$ of the radioactivity administered to patients, 10^5 was used for calculation.

1×10^{-4} [mSv/Bq]: Effective dose coefficient after treatment with Ra-223[22]

* The annual internal exposure dose of 23.1μ Sv per 1 treated patient received by third parties amounts to 1/44 of 1 mSv per year, which is the dose limit for the public.

If a patient who has been administered this drug returns home immediately after treatment, 23.1 μSv is the base dose for internal exposure when performing combined evaluation. It provides safe assessment among the methods of calculating the internal exposure of third parties.

5.2.3 Assessment of combined external and internal exposure doses received by caregivers and the public from patients administered this drug

Exposure dose to caregivers = 207.6 [μSv] ＋23.1 [μSv] ＝230.7 [μSv]

Exposure dose to the public = 103.8 [μSv] ＋23.1 [μSv] ＝126.9 [μSv]

Accordingly, the cumulative doses to which caregivers and the general public are exposed when a patient is administered 3.85 MBq of this drug are less than the relevant doses for suppression (caregivers: 5 mSv/patient, public: 1 mSv/year). When calculated in the same way, the exposure doses to caregivers and the public do not exceed 5 mSv and 1 mSv respectively, if the patient's body weight is assumed to be 550 kg (30.25 MBq of administered radioactivity). On the other hand, the amount of radioactivity per 1 vial of this drug is listed as 6.16 MBq/5.6 mL, which is the amount of radioactivity equivalent to the dosage for a patient with a body weight of about 110 kg. The usual dosage of this drug for 1 patient is up to 2 vials. Even by assuming that a patient has a body weight of 220 kg (administered radioactivity = 12.1 MBq per dosage), it seems applicable to the vast majority of patients in Japan. In this case, if each individual dosage is ≤ 12.1 MBq, it can be assumed that the release criteria for patients administered this drug will be fulfilled. Therefore, release of treated patients from special facilities for radionuclide management, etc. and discharge home immediately after administration of this drug are regarded as possible because the patients conform to the safety guidelines with regard to release.

If release of a patient from hospital and returning home are approved, written as well as oral advice and instructions must be given to ensure radiation safety in daily life, etc. In addition, records of these explanations to the patient and family members and records of their consent must be stored.

5.3 Precautions for patients and family members (caregivers)

A very low level of radioactivity is found in body fluids (mainly blood), urine, and feces after administration of this drug. Therefore, it is necessary to provide a written explanation of the important points listed in 5.3.1 to patients and family members (caregivers) before administration and to ensure their understanding of measures for reducing radiation exposure of third parties and preventing pollution.

5.3.1 Precautions to be observed for 1 week after administration of this drug (the first week after each dose)

[Precautions in daily life]

① If bleeding occurs, wipe up the blood completely with toilet paper and flush it away in the toilet.

② Wear disposable rubber gloves if there is a risk of contact with the patient's urine or feces or if clothing, etc. soiled with urine/feces is handled.

③ Thoroughly wash the affected parts immediately using soap after contact of the hands or skin with a patient's blood or other body fluids.

④ Refrain from sexual activity.

⑤ Minimize contact of the patient with children and pregnant women for 2-3 days after administration of this drug.

⑥ The patient should preferably take a bath at the end of the day. In addition, the bath tub should be cleaned thoroughly after the patient bathes by brushing with detergent, etc.

[Precautions for handling laundry]

Wash clothing, etc. worn by the patient separately from those of other family members, etc. Carefully rinse sheets or underclothes that have been soiled with blood or urine.

[Precautions when urinating/defecating or vomiting]

① Men must urinate in a sitting position.

② Flush the toilet twice after use.

③ If urine or feces are spilled on the toilet, the floor, etc. wipe up completely with toilet paper and flush away in the toilet.

④ Be sure to wash the hands thoroughly using soap after defecation or urination.

⑤ Be sure to wash the hands and skin thoroughly using soap without delay after coming into contact with the patient's excreta or vomitus.

5.4 Precautions for the patient after administration of this drug

About 63 % of the administered dosage of this drug is discharged in the feces within 1 week after administration. In a domestic phase I clinical study of Japanese CRPC patients with bone metastases, the average cumulative fecal excretion rate at 72 hours after a single dose of this drug was 64 %, the average cumulative urinary excretion rate at 48 hours after a single dose of this drug was 0.9 %.

5.4.1 Radiation safety management for patients using diapers and/or urinary catheters

For patients using diapers and/or urinary catheters, the following precautions are necessary during the initial stage after administration (up to 1 week).

Similar to the precautions for prevention of biohazards, disposable gloves must be worn when handling diapers, urinary catheters, and urine bags.

[Precautions when using diapers, urinary catheters, etc. (at home and in hospital)]

① Use of plastic sheets is recommended for patients with urinary incontinence and patients using diapers.

② When the patient has a urinary catheter, the urine bag must be emptied into the toilet. Flush the toilet twice and wash the hands thoroughly afterwards.

③ Catheter urine collection packs of inpatients must be replaced before leaving hospital.

[Precautions when disposing of diapers, urinary catheters, etc.]

① Because most of the Ra-223 dose administered is excreted in the feces, the patient's diapers must be put into a plastic bag and sealed so that the fecal contents, etc. do not leak out, and then disposed of as general waste.

② When diapers, etc. used in a hospital or other facility are treated as infectious waste, refer to "Handling of Diapers, etc. from Patients Administered Radiopharmaceuticals (Guidelines for Health Care Providers Performing Nuclear Medicine Practices)"[25] (see paragraph 11 of this guide).

6 Formalities pertaining to notifications, etc. under the Medical Care Act

As stipulated in Article 24 (8) of the Ordinance for Enforcement of the Medical Care Act with regard to Article 15 (3) of the Medical Care Act on the use of medical radionuclides, when this drug is used in hospitals, etc. "Written notification must be presented acknowledging the items stated in Article 28, paragraph 1 (1-5) of the Ordinance for Enforcement of the Medical Care Act."[6-1] In this case, the standards for concentration limits, etc.[6-7] related to buildings and installations (facilities in which medical radionuclides are used[6-2], facilities for storage[6-3] and disposal[6-4], boundaries of controlled area[6-5], and others[6-6]) must be compatible or potentially

compatible with the standards related to airborne radiation doses and atmospheric concentrations. Similarly, when a sickroom for patients administered radiopharmaceuticals[6-8] is set up or has been set up, it must be compatible with the standards for concentration limits, etc.[6-9] related to the buildings and installations of such sickrooms. As described above, it is necessary for the management of the health care center to apply for a written notification, etc. acknowledging compatibility with the specified legal standards for buildings and installations, in order to gain approval for use of radionuclides.

It should be noted that the method for notification of the use of medical radionuclides, etc. is sometimes determined independently by the prefecture, and it is therefore desirable to consult the health authorities where the hospital, etc. is located.

Note 6-1: Ordinance for Enforcement of the Medical Care Act, Article 28, paragraph 1

(1) Name and location of the hospital or clinic.

(2) Types, forms, and quantities (showing Becquerel data) of medical radionuclides or medical radionuclides for PET that are scheduled to be used in the relevant year.

(3) Estimated maximum amount stored (showing Becquerel data) of each type of medical radionuclide or medical radionuclide for PET, estimated maximum amount used in 1 day, and estimated maximum amount used in 3 months.

(4) Overview of the buildings and installations, as well as the protective measures for radiation hazard prevention, in the rooms for use of medical radionuclides, rooms for use of medical radionuclides for PET, storage facilities, transport containers, and disposal facilities, as well as the wards in hospitals where patients receive therapy using medical radionuclides or medical radionuclides for PET.

(5) Names of the physicians and dentists using medical radionuclides or medical radionuclides for PET, as well as their experience with diagnosis and treatment using radionuclides.

Note 6-3: Ordinance for Enforcement of the Medical Care Act, Article 30, paragraph 9

Note 6-4: Ordinance for Enforcement of the Medical Care Act, Article 30, paragraph 11

Note 6-5: Ordinance for Enforcement of the Medical Care Act, Article 30, paragraph 16

Note 6-6: Ordinance for Enforcement of the Medical Care Act, Article 30, paragraph 17

Note 6-7: Ordinance for Enforcement of the Medical Care Act, Article 30, paragraph 26

Note 6-8: Ordinance for Enforcement of the Medical Care Act, Article 30, paragraph 12

Note 6-9: Ordinance for Enforcement of the Medical Care Act, Article 30, paragraph 19

6.1 Notification, etc. regarding the use of medical radionuclides

If a hospital, etc. that has already received permission is planning to set up a new radiation facility or if it is necessary to modify the buildings and installations of an existing radiation facility or to change the permitted items because of using new radiation equipment or radionuclides etc., a written application stating the required items must be submitted to the health authorities, etc. Furthermore, for notifications regarding the use of medical radionuclides, in addition to the other items required, supporting material must be included to indicate that the buildings and installations meet the legal standards and this must be attached to the notification. The basic items to be prepared are shown in (1)-(4) below.

(1) Permission-related items

① Application pertaining to permission for establishment (Medical Care Act, Article 7 [1], Ordinance for Enforcement of the Medical Care Act, Article 1 [14]) or application for changing items pertaining to permission for establishment

② Examination before use, etc. (Medical Care Act, Article 27)

(2) Notification-related items

① Notification after establishment (Ordinance for Enforcement of the Medical Care Act, Article 4 [2], Ordinance for Enforcement of the Medical Care Act, Article 3 [1])

② Notification about equipment for medical radionuclides (Ordinance for Enforcement of the Medical Care Act, Article 24 [8]) and Article 28 [1])

③ Notification about modifications, etc. (Ordinance for Enforcement of the Medical Care Act, Article 29 [1]) and [2])

(3) Application for permission to establish a facility (attach the building permit [copy])

(4) Attached papers (e.g., in the format required by the health authorities, etc.)

① License (copy) and details of experience if the establisher is a physician or dentist.

② Articles of incorporation, endowment act, or regulations and registration certificate if the establisher is a corporation.

③ Certificate of registered matters for the estate and building, and cadastral map (attach the lease agreement in case of leasing the estate or building [copy]).

④ Site plan.

⑤ Sketch map of the site surroundings.

⑥ Ground plan of the building (scale of 1:200 or more).

⑦ Drawings of the radiation protection facilities in the X-ray therapy rooms, etc. (ground plan and side view on a scale 1:50 or more, thicknesses of walls, lead shielding, etc.).

⑧ Documents indicating compatibility with the standards for external radiation exposure as well as radiation levels in the room air, discharged air, and waste water (documents mentioned in item 6.3).

6.2 Notification regarding the amount of medical radionuclides to be used

Regarding the “Amount of medical radionuclides to be used,” Article 28 of the Ordinance for Enforcement of the Medical Care Act stipulates notification of (1) the estimated maximum amount used in 1 day, (2) the estimated maximum amount used in 3 months, (3) the estimated annual maximum amount used, and (4) the estimated maximum amount in storage. Use of medical radionuclides in excess of the reported amount in hospitals, etc. is not acceptable (Articles 28 and 29 [2] of the Ordinance for Enforcement of the Medical Care Act, PFSB Notice No. 188 [11][6-10]). Also, the use of medical radionuclides must be determined in consideration of compatibility with the standards for facilities or buildings and installations based on the Ordinance for Enforcement of the Medical Care Act. Examples of how to determine the amounts for general notification are given next.

(1) Estimated maximum amount used in 1 day: Maximum dosage per patient × maximum number of patients treated per day. Since the packaging units of radiopharmaceuticals are roughly based on the quantity required per patient, the estimated maximum amount used in 1 day can be determined from the number of tests or treatments performed per day and per week, by taking into consideration the expected number of treatments per week or month based on the dosing regimen.

(2) Estimated maximum amount used in 3 months: Estimated maximum dose administered during 1 week (estimated maximum number of patients treated in 1 week × maximum dosage per patient) × 13 (weeks/3 months). It is stipulated in the Medical Care Act that the 3-month periods of a year commence on April 1st, July 1st, October 1st, and January 1st.

(3) Estimated annual maximum amount used: Estimated maximum amount used in 3 months × 4.

(4) Estimated maximum amount in storage: Several times the estimated maximum amount of a radionuclide used in 1 day.

The estimated quantities can be easily determined by taking into account the packaging units of each radiopharmaceutical.

Note 6-10: Report of changes, etc. of notification items regarding the use of medical radionuclides as stipulated in the Ordinance for Enforcement of the Medical Care Act, Article 29, paragraph 2, if items are to be changed

6.3 Preparing documents on the conformity with standards for buildings, facilities etc. concerning the use of medical radionuclides

Regarding the conformity with standards for external radiation doses and concentrations in room air, discharged air and drain water, the "Outline of buildings and installations as well as protective measures for the prevention of radiation hazards" as stipulated in the Ordinance for Enforcement of the Medical Care Act, Article 28, paragraph 1 (4) is applicable. As to the evaluation of external radiation doses and concentration limits etc. in discharged air and drain water (in the Medical Care Act, dose limits and concentration limits for use facilities are collectively referred to as "concentration limits etc."), a calculated evaluation based on reported amounts (estimated maximum use in 1 day, estimated maximum use during 3 months and estimated maximum storage) is required (see PFSB Notice No. 188, Notification No. 2 (6), 1 (1), 2-4), because the notification on the use of medical radionuclides has been defined as advance notification by said Article 28. The calculated evaluation is outlined in the following. Furthermore, for details of the calculation method, see "Guidelines for the evaluation of concentration limits in facilities practicing nuclear medicine".[26)]

6.3.1 Conformity with standards concerning external radiation

When calculating the effective dose of external radiation in 1 week, based on Ordinance for Enforcement of the Medical Care Act, Article 30 (8) paragraph 1 (3), Article 30 (9) paragraph 1 (2) and Article 30 (11) paragraph 1 (1), the effective dose of each nuclide is determined by assuming the average handling time of the radiation source in 1 week according to the estimated maximum use of the reported nuclide in 1 day, the distance between radiation source and worker and by using the effective dose rate constant of each nuclide. Next, add the effective dose of all reported nuclides. Standards for facilities are met when a 1-week-dose does not exceed 1mSv at evaluation point of the facility used. A document with this calculated evaluation is to be attached to the written statement. Also, the calculation of the effective dose at the boundaries of the controlled area and the site etc. is based on the handling time of the radiation source in 1 day according to the estimated maximum use of the reported nuclide in 3 months and the distance between radiation source and evaluation point at the boundaries of the controlled area and the hospital site etc. Standards are met when a 3-months-dose does not exceed 1.3mSv/3 months (controlled area) and 250 μSv/3 months (site boundaries etc.). With respect to controlled areas and site boundaries etc., a document with the calculation basis is attached to the written statement in the same way as in the case of use rooms etc.

6.3.2 Conformity with standards concerning room air, discharged air and drain water

The standards concerned assess and evaluate the suitability of Ordinance for Enforcement of the Medical Care Act, Article 30 (26), "Concentration limits as stipulated in Article 30 (11), No. 1 (2)1 and (3)1 assume the following 3 months average concentrations of radionuclides in drainage, drain water, discharged air or room air." The calculated evaluations comply with the

entries in “PFSB Notice No. 188, Notification No. 2 (6), Doses and Assessments etc., 4 Assessment of radionuclide concentrations regarding drain water and discharged air etc.” as well as with 6.3.2.1 for discharged air and 6.3.2.2 for drain water.

6.3.2.1 Calculation of the radionuclide concentrations in room air and discharged air

Based on the provisions of the Ordinance for Enforcement of the Medical Care Act, Article 30 (11), No. 1 (3)2, Article 30 (18), No. 1 (4), Article 30 (11), No. 1 (3)1 and Article 30 (22), No. 2 (2), the formula for calculating the radiopharmaceutical concentrations in room air or discharged air is used to determine the average concentration for each radionuclide during periods of 1 week or 3 months. Next, the percentage of each radionuclide is determined as the average concentration divided by the concentration limit shown in column 2 or 4 of annexed Table 3, and the sum of these percentages is calculated. It should be noted that the standards set forth in the law are met if the sum of the radionuclide percentages of the concentration limit is less than 1.

6.3.2.2 Calculation of the radionuclide concentrations in drain water

In accordance with PFSB Notice No. 188, Notification No. 2 (6), 4 (2), the method of calculation is as follows. ① The average concentration of each radionuclide for which use is reported during 3 months is determined. ② Then the concentration of each radionuclide is converted to a percentage of the concentration limit, with the average concentration at the drain water outlet for the target radionuclide. ③ The legal standard for drainage appliances is met if the sum of all reported radionuclide percentages of the concentration limit is less than 1. A document concerning this point is to be attached to the written statement. If the sum calculated in ③ exceeds 1, PFSB Notice No. 188 is applicable (“Taking into account the dilution capacity of the dilution tank, up to 10-fold dilution may be carried out before the sum of the final percentages is calculated.”), and the legal standard is met if the sum of the percentages calculated after up to 10-fold dilution is less than 1.

7 Safety management during use of this drug in radiation facilities

7.1 Management by record keeping, etc. (Ordinance for Enforcement of the Medical Care Act, Article 30 [23]).

This drug must be used in an appropriate way to ensure radiation safety. Management of radiation safety must be ensured, such as clarifying the location of radioactive materials by storing them at prescribed sites, etc. Therefore, it is mandatory to prepare and keep record books, etc. regarding the following points.[27)]

7.1.1 Records related to obtaining, using, storing, and disposing of this drug (Record Book for Use of Radiopharmaceuticals) (Ordinance for Enforcement of the Medical Care Act, Article 30 [23] paragraph 2; Notice No. 51 [1974] of the Ministry of Health and Welfare, Medical Affairs Bureau, PFSB Notice No. 188)

The following data must be entered in the record book:

① Product specification, ② date of receipt, ③ date of use, ④ amount used, ⑤amount remaining, ⑥ users, ⑦ names of treated patients, ⑧ date of storage or disposal, and ⑨ radioactivity at the time of storage or disposal.

Record books must be prepared for stored pharmaceuticals to periodically confirm that the amounts stored in the facility do not exceed the estimated maximum storage amount reported for each radionuclide.

7.1.2 Measuring and recording at locations with a high risk of radiation hazard (Ordinance for Enforcement of the Medical Care Act, Article 30 [22], Ordinance on Prevention of Ionizing Radiation Hazards, Article 54).

Measurement of radioactivity in the rooms etc. where radionuclides are used (the external walls, etc. of facilities in which medical radionuclides are used, such as radiation facilities, storerooms, disposal facilities [storage or disposal rooms as well as drainage appliances]), boundaries of controlled areas, areas that might be accessed by treated patients, isolation rooms, and site boundaries means that the level of radiation and the extent of contamination by radionuclides should be determined once before the start of treatment and once within 1 month after the start of treatment (within 6 months at specified locations). Records of the results must be kept for 5 years. Measurement of the level of radioactivity is carried out using the 1 cm dose equivalent (rate) or the 70 μm dose equivalent (rate) at locations which may exceed the 1 cm dose equivalent (rate) by 10-fold. Determination of the level of radioactivity and the extent of contamination by radionuclides is done with a radiation detector.[7-1] However, the values can be calculated if it is particularly difficult to use a radiation detector.[7-2]

Note 7-1: As a general rule, measurement using the 1 cm dose equivalent (rate) is done with a radiation detector that can adequately measure the amount of radiation emitted by the radionuclides used at the facility.

Note 7-2: Regarding the phrase “if it is particularly difficult to use a radiation meter,” PFSB Notice No. 188 indicates that this provision must not be applied without careful consideration. “It is limited to cases where measurement is particularly difficult due to physical constraints and determination by calculation is only approved in such cases.”

7.1.3 Measurement of the exposure dose to workers plus recording of calculations (Ordinance for Enforcement of the Medical Care Act, Article 30 (18); Ordinance on Prevention of Ionizing Radiation Hazards, Article 8).

The effective dose and equivalent dose for workers are measured with reference to the doses accrued by external and internal exposure. Based on these results, calculations are performed according to the stipulations of the Minister of Health, Labor and Welfare (Ministry of Health and Welfare Public Notice No. 398).[22)]

7.1.4 Individual ionizing radiation health check form (Ordinance on Prevention of Ionizing Radiation Hazards, Article 57)

The results of “ionizing radiation health checks” performed on workers who continuously provide radiation diagnosis and treatment are recorded in the “Individual Ionizing Radiation Health Check Form”.

7.2 Records on the release of patients administered radiopharmaceuticals (PMSB Notice No. 70)

If release of a patient from hospital and returning home has been approved, records of the following points must be made and stored for 2 years after release.

① Dosage administered, date and time of release, and dose rate measured at release.

② Details of advice and instructions for breastfeeding mothers.

8 Measurement of Radioactivity

8.1 General considerations when measuring Ra-223 radioactivity

Figure 1 shows the decay series by which Ra-223 is transformed to Pb-207, a stable nuclide. The types of radiation emitted by Ra-223 or its progeny and the energies related to radiation control measurements are shown in Table 3.

Table 3: Main types of radiation relevant to measuring emissions from Ra-223 and its progeny

(From: Japan Radioisotope Association, Isotope Pocket Data Book, 11th edition, 2011)

Ra-223, progeny[*1]	Half-life	Type of decay	Main α-particle energy (MeV) and emission rate	Main β-particle energy (MeV) and emission rate	Main γ(X)-ray energy (MeV) and emission rate
Ra-223	11.43 d	α	5.435 2.2 % 5.540 9.0 % 5.607 25.2 % 5.716 51.6 % 5.747 9.0 %		0.144 3.3 % 0.154 5.7 % 0.269 13.9 % 0.324 4.0 % 0.0831 41.7 %[*2] 0.0958 11.6 %[*2] 0.0132 24.1 %[*2]
Rn-219	3.96 s	α	6.819		0.271 0.402
Po-215	1.781 ms	α	7.386 99.9 %		
Pb-211	36.1 m	β^-		0.547 6.3 % 0.974 1.5 % 1.379 91.2 %	0.405 3.8 % 0.427 1.8 % 0.832 3.5 %
Bi-211	2.14 m	α	6.279 16.2 % 6.623 83.5 %		0.351 12.9 % 0.0724 2.0 % 0.0114 1.0 %
Tl-207	4.77 m	β^-		0.529 0.27 % 1.427 99.7 %	

*1: Decay via At-215 or Po-211 was excluded because of the low probability.

*2: Characteristic X-rays of Rn.

As shown in Table 3, alpha particles, beta particles, and gamma rays are emitted by Ra-223 and its progeny, and so can be determined by using effective measuring instruments for these types of radiation. That means, effective measuring instruments should be selected from among various models. Conversely, incorrect results will be obtained if it is not fully understood what kind of radiation the instrument is effective for measuring and if the types of radiation emitted by Ra-223 and its progeny are not known. Sometimes several types of radiation are counted and measurement becomes rather complicated. Naturally, to measure a particular type of radiation, it is necessary to know which instrument is efficient for counting it. If this is not known, the radiation dose and radioactivity cannot be determined.

This means that in addition to understanding the special characteristics of the instrument for measuring each type of radiation, the level of radioactivity cannot be determined unless one also knows what percentage of each type of radiation is emitted from the target specimen. If alpha or beta particles are measured, the data obtained from a specimen are greatly affected by self-absorption. Most of the SPECT radionuclides only emit gamma rays, but this difference in emissions must be adequately taken into account when measuring Ra-223. For example, if a specimen of Ra-223 is in a vial, only gamma rays penetrate the drug solution and the glass of the vial to be measured, but if surface contamination of floors or instruments occurs, alpha and beta particles are also emitted (from progeny) in addition to gamma rays.

During measurement, attention must be paid to maintaining the radioactive equilibrium of Ra-223 and its progeny. If Ra-223 and its progeny reach radioactive equilibrium, it is a secular equilibrium and the radioactivity of all progeny is the same as that of parent nuclide (Ra-223). If only alpha particles or gamma rays emitted from the parent nuclide (Ra-223) are measured, the radioactivity of Ra-223 can be determined whether radioactive equilibrium is established or not. However, if the radiation emitted from progeny is to be measured, the radioactivity of Ra-223 cannot be determined unless radioactive equilibrium is established.

As mentioned in 3.2.1, unless this drug is shaken vigorously or the like, there is only a low probability that Rn-219 in the drug solution will disperse into the atmosphere under normal conditions of use at room temperature. Hence it is conceivable that radioactive equilibrium is established under normal conditions and the radioactivity of Ra-223 can be calculated whatever radiation of Ra-223 or its progeny may be measured. However, it is possible, that Rn-219 may disperse from surface contamination, etc. for example, due to dried Ra-223 solution spilled on the floor, so special attention is needed when quantifying surface contamination because radioactive equilibrium may not be established.

8.2 Measurement of alpha particles, beta particles, and gamma rays

8.2.1 Detection of Ra-223 by measurement of alpha particles

When Ra-223 is used, alpha particles are rarely measured in the course of normal radiation management such as testing the air dose rate and surface contamination, or determination of radioactivity in the room air, discharged air, and drain water, etc. However, when examining surface contamination, it may be advantageous to make use of alpha particle measurement in addition to beta particle measurement. When comparing alpha particle measurement using a ZnS (Ag) scintillation counter with measurement of primarily beta particles using a GM counter, the former instrument has a low background count of about 1 cpm versus 50-100 cpm for the latter (with a GM tube diameter of 2 inches), which makes detection of contamination easy and testing with a low detection limit becomes possible. Moreover, if the alpha-emitting radionuclides used in the facility are limited to Ra-223, all of the radiation detected may be regarded as being derived from Ra-223.

Thus, it is certainly advantageous to measure alpha particles in surface contamination testing, but adequate attention must be paid to self-absorption. Because the penetrating power of alpha particles is extremely weak, as mentioned in 8.1, this can easily influence how much alpha radiation is emitted from the surface contamination source (source efficiency). Depending on the state of the surface contamination source, self-absorption of alpha particles may be high with almost no emission from the contamination. Even if the of contamination is thin, its surface may be covered by other matter. Therefore, care must be taken because the rate of alpha particle emission from the surface is typically low and gives a false low result. Even if alpha particles are emitted from the contamination source, absorption by air increases as the distance between the source and the detection unit becomes larger, which also leads to false low results. For measuring alpha particles, the distance between the surface of the incident window and the surface of the contamination source must be maintained at about 5 mm, and especially when determining radioactivity, the distance must be kept constant by using appropriate jigs. On the other hand, care must be taken because the detection unit can be contaminated and the incident window damaged if it is positioned too close to the

contamination source in order to reduce absorption by air. Accordingly, not only the positional relation (geometry) of the detection unit and source must be adequately understood when measuring alpha particles, but also the extent of absorption of alpha particles between the source and unit, and the counting efficiency must be evaluated for each measurement. Because the physical properties of the contamination source are not always constant, it is impossible to determine the counting efficiency for each measurement in routine contamination testing. Therefore, there are certainly advantages in measuring alpha particles to test for surface contamination by alpha-emitting radionuclides, as described above, but it is unlikely to be an appropriate method for routine surface contamination testing in clinical practice. Measurement of beta particles by using a GM counter, etc. is a more useful test.

8.2.2 Detection of Ra-223 by measurement of beta particles

Unlike alpha particles and gamma rays, the energy of beta particles is not monochromatic. Instead, it is a continuous energy spectrum extending from 0 to a radionuclide-specific maximum energy (E_{MAX}). This must be kept in mind when measurements are carried out. Even though high energy beta particles are emitted by Ra-223 or its progeny (E_{MAX}: 1.379 MeV and 1.427 MeV, see Table 3), there is a low-energy beta particle component as well. Though not to the same extent as alpha particles, such low-energy beta particles show marked attenuation by the sample itself, the sample container, the measuring jig, and the incident window of the measuring instrument (light-shielding film), etc. and the influence of such attenuation on detection efficiency must be understood. In addition, beta particles with a maximum energy of about 500 keV are also emitted at a low rate, and their effect must be considered as well.

8.2.3 Detection of Ra-223 by measurement of gamma rays

Because the beta particles produced by Sr-89 and Y-90 used in internal radiation therapy have a high maximum energy of about 1.5 MeV and 2.3 MeV, respectively, bremsstrahlung is emitted. Each radionuclide is a pure beta radionuclide, but instruments that measure gamma rays like well-type ionization chambers are employed to detect bremsstrahlung for dosage measurements, etc. The maximum energy of beta particles emitted by Ra-223 and its progeny is about 1.4 MeV and bremsstrahlung is also released. However, in contrast to Sr-89 and Y-90 that only emit beta particles, Ra-223 and its progeny also produce gamma rays. Hence, these gamma rays are a preferential target when carrying out measurements and the bremsstrahlung may be neglected.

Radiation detectors, monitors and other measuring instruments used in routine radiation control cannot be employed to perform high-precision spectral analyses. However, gamma rays represent radionuclide-specific monochromatic energy, so high-precision identification of radionuclides is possible if a Ge semiconductor detector or another high-resolution measuring instrument is used, as necessary.

When using Ra-223, ordinary beta particle measurement is performed for surface contamination testing. However, when other measurements are done as part of normal radiation management, such as determination of the air dose rate or the radiation levels in room air, discharged air, and drain water, measurement of gamma ray is typically performed in the same way as for SPECT radionuclides.

8.3 Types of radiation detectors and measurement principles for radiation management

In the places where medical radionuclides are used, the points to be considered regarding evaluation based on actual measured values as well as assessment based on values obtained by calculation are specifically listed in PFSB Notice No. 188, Notification No. 2 (3), 6 (6) [“When using medical radionuclides etc., contamination of the facilities due to matter contaminated by medical radionuclides or other radionuclides must be validated by measurement using suitable radiation measuring instruments.”] and in Notification No. 2 (6), 1 [“Evaluation methods for

radiation doses etc."] (see Appendix b). It is necessary to carry out measurements by selecting the appropriate instruments to evaluate radiation doses when performing practical radiation management.

Moreover, as mentioned in 7.1.2, the notification of PFSB Notice No. 188 states the following with regard to the phrase 'if it is particularly difficult to use a radiation detector, etc.': "It is limited to cases where measurement is particularly difficult due to physical constraints and determination by calculation is only approved in such cases." This emphasizes the importance of actual on-site measurements.[11)]

The types and general descriptions of effective radiation measuring instruments for radiation management and quality control during use of Ra-223 are categorized as follows:

① Testing surface contamination of facilities, apparatus, commodities, etc.

② Measurement of radiation levels in the room air, discharged air, and drain water.

③ Dosage measurements.

④ Air dose measurements at sites of use, boundaries of controlled areas, site boundaries, etc.

As a summary of the measuring instruments and monitors for general radiation protection, the "Guide to Facilities and Equipment for Radiation Protection"[28)], has been published by The Japan Radioisotope Association and can serve as a reference.

8.3.1 Surface contamination tests

Surface contamination tests are carried out by employing a direct measurement method in which the surface of the target is surveyed by a portable instrument, and an indirect measurement method in which the surface is wiped with filter paper, etc. and surface contamination is estimated quantitatively from the radioactivity attached to the filter paper, etc. To determine the radioactive surface contamination caused by Ra-223 and its progeny, alpha particles, beta particles, and gamma rays can all be measured, but beta particle measurement is typically the most suitable method for quantitation of surface contamination density. In general, the efficiency of counting gamma rays is low and the site of contamination from which site the gamma rays are derived remains unknown with direct measurement, unless the source of contamination is identified. This makes quantitative evaluation of the contaminated surface density by direct measurement of gamma rays very difficult. In contrast, quantitative evaluation of the contaminated surface density is simple with measurement of alpha particles or beta particles because the area of the contamination source can be considered as the effective area of the measuring instrument when direct measurement is done under normal conditions. However, as mentioned in 8.2.1, if evaluation of surface contamination is carried out by measurement of alpha particles, the results will be strongly influenced by the source efficiency (determined by the physical and chemical properties of the contamination source) and by attenuation caused by any matter that exists between the contamination source and the detection unit (air, etc.). Consequently, measurement of alpha particles requires careful attention and sufficient knowledge, and is not recommended for normal radiation management.

In general, for direct measurement of beta particles, GM counters, plastic scintillation detectors, and other survey meters are employed. While survey meters may also be used for indirect measurement, it is better to employ liquid scintillation counters, gas flow counters, GM counters, plastic scintillation counters, and other stationary counters to increase detection sensitivity. There is no problem with using indirect measurement of gamma rays for detection.

If direct measurement of alpha particles is carried out, a conventional ZnS (Ag) scintillation survey meter is used, while a liquid scintillation counter, gas flow counter, or some other stationary counter is effective for indirect measurement.

For a detailed description with regard to evaluation of radioactive surface contamination, see JIS Z 4504:2008 “Evaluation of surface contamination - Beta-emitters (maximum beta energy greater than 0.15 MeV) and alpha-emitters”.[29)]

8.3.2 Measurement of radiation levels in room air, discharged air, and drain water

1) Measurement of radioactivity in the room air

Portable monitors (room air monitors or room dust monitors) are generally employed for measurement of radioactivity levels in the room air at places regularly entered by persons within the facility. With a room air monitor, the room air is sampled by an aspirator (sampler) and the room air sample is taken into an airflow-type ionization chamber for measurement. In the case of a standard room dust monitor, dust in the air is collected on a filter and the radioactivity on the filter is measured. Since an air sample is introduced into the ionization chamber, a room air monitor shows high sensitivity to alpha and beta particles. It is also sensitive to gamma rays, but to a lesser extent. On the other hand, there are many commercial products referred to as room dust monitors that have plastic scintillation detectors. These are sensitive to gamma rays too, but the main measurement target is beta particles.

2) Measurement of radioactivity in discharged air

When measuring the level of radioactivity in discharged air, a method that employs a discharged air monitor (gas monitor, dust monitor) combined with a central monitoring system is commonly used. A gas monitor samples part of the discharged air and then automatically performs measurement. If the detection unit has an airflow-type ionization chamber, it is highly effective for detecting alpha and beta particles. Because of its low sensitivity to gamma rays, this type of gas monitor is referred to as a “beta particle gas monitor”. In addition to those with airflow-type ionization chambers, there are also beta-particle gas monitors available with plastic scintillation detectors. In contrast, NaI (Tl) scintillation detectors with a high sensitivity to gamma rays are frequently used in monitors designed for gamma ray measurement. Gamma-ray gas monitors with NaI (Tl) scintillation detectors have no sensitivity for alpha and beta particles.

With a dust monitor, like the above-mentioned room dust monitor, dust suspended in the discharged air is collected on a filter and the radioactivity measured. The widely used detectors are ZnS (Ag) scintillation detectors for alpha particles, plastic scintillation detectors and GM counters for beta particles, and NaI (Tl) scintillation detectors for gamma rays.

Since Ra-223 and its progeny emit alpha particles, beta particles, and gamma rays, all types of gas monitor and dust monitor are applicable.

3) Measurement of radioactivity in drain water

To measure radioactivity in drain water, a drain water monitor connected to a central monitoring system is commonly employed, in the same way as for the discharged air monitor. The drain water is sampled and measured continuously or by batch processing. Drain water monitors can be divided into beta monitors and gamma monitors. Many gamma drain water monitors use NaI (Tl) scintillation detectors, but some are equipped with wave height discriminators and can identify certain radionuclides. Most beta drain water monitors use a plastic scintillation detector. Since Ra-223 and its progeny emit alpha particles, beta particles, and gamma rays, each type of drain water monitor is applicable.

It takes some time and effort, but even if there is no automatic monitoring system, radioactivity in drain water is measured manually by collecting a sample from the drain water tank and using an appropriate radiation detector. This would be a stationary counter, such as a NaI(Tl) scintillation detector, a liquid scintillation counter, a gas flow counter, a GM counter, or a plastic scintillation detector. If gamma rays are measured, it may be done by simply collecting an appropriate water sample in a designated container for measurement.

However, when beta particles are measured, self-absorption within the specimen must be considered and appropriate treatment like evaporation to dryness must be carried out.

When measurement of discharged air, drain water, etc. is conducted, external companies that specialize in radiation control and such measurements can be entrusted with the task. Even if radiation measurements are outsourced, the Ra-223 radiation safety supervisors in the management systems organized by the hospital administrators must keep records of the results obtained, in order to have an accurate understanding of the radiation control situation and correctly manage the facilities.

8.3.3 Dosage measurement (radioactivity)

Measurement of the dosage of Ra-223 radioactivity is conducted by using a well-type ionization chamber (dose calibrator, etc.) in the same way as for Tc-99m, I-123, and other radioactive diagnostic agents or Sr-89, Y-90, and other radiopharmaceuticals, with gamma rays emitted by Ra-223 and its progeny as the target. Measurement is conducted similarly to conventional determination with radioactive diagnostic agents, etc., i.e., Ra-223 enclosed in a prescribed container (vial) is placed at the measuring position of a well-type ionization chamber using a sample holder. Since there is no operational experience with measuring Ra-223, the well-type ionization chamber may not have been calibrated for Ra-223 (no calibration constant for Ra-223). Therefore, before performing measurement for the first time, the instrument must be calibrated for Ra-223 or the instrument's manufacturer must be asked to set the calibration factor.

8.3.4 Dosimetry at sites of use, etc.

When using medical radionuclides, the radiation dose in air in places regularly entered by persons within the facility, at the boundaries of controlled areas, at site boundaries, in areas that might be accessed by treated patients, etc., as well as the radiation dose at the release of patients and the personal exposure dose of workers, must be measured regularly or as required (see 7.1.2). Dosimetry for radiation management of Ra-223 is conducted by measuring gamma rays. The dose in the room air is verified by using an instrument calibrated at a 1 cm dose equivalent H*(10) as the ambient dose, and exposure doses are measured with calibration at a 1 cm dose equivalent Hp(10) as the personal dose equivalent.

To measure radiation doses in air, a survey meter is used that has an ionization chamber or a scintillation detector, such as an NaI(Tl) scintillation detector, as the detection unit. Ionizing chambers are applicable to measurement at sites of use or other places with relatively high dose rates, while high-sensitivity NaI(Tl) scintillation survey meters are effective at low dose rate sites such as the boundaries of controlled areas or site boundaries. To evaluate the cumulative dose for a fixed period of time, such as 1 week or 3 months, the doses during the said period may be calculated adequately on the basis of momentary dose rates (typically expressed in μSv/h, but actually the cumulative dose over a period of a few seconds to tens of seconds) measured with the above-mentioned survey meter, but measuring instruments capable of the determining cumulative dose are used as well.

Some personal dosimeters display the actual exposure dose (direct reading type) and others calculate the exposure dose by using a reading device mounted for a fixed period (passive type). The passive type is usually sent to a personal dosimetry service agency for measurement of the exposure dose. Since a direct reading dosimeter is carried in a pocket, this type is also referred to as a "direct reading pocket dosimeter". Recently, many such devices have been developed utilizing Si and other semiconductors. Film badges used to be the main passive type of dosimeter, but fluoro-glass dosimeters and optically stimulated luminescent dosimeters have become rather popular lately.

9 Education and training

9.1 Education and training of Ra-223 radiation safety supervisors, etc. when implementing this therapy (physicians, radiological technologists, etc. with sufficient knowledge and experience of radiotherapy)

When performing this therapy, it is necessary to acquire knowledge regarding the safety of medical treatment with this radiopharmaceutical and the safe handling of radiation. Therefore, physicians, etc. participating in this therapy must previously attend a safe handling training course organized by relevant academic societies. Furthermore, education and training with the following contents based on safe handling training courses and this manual must be provided by medical institutions for physicians, etc. participating in this therapy who have not completed a safe handling training course. As a general rule, education and training at medical institutions are carried out under the guidance of the Ra-223 radiation safety supervisors for this therapy who have attended a safe handling training course organized by relevant academic societies, and the following items should be covered.

① Laws and regulations regarding radiation hazard prevention, points for notification, and release criteria of patients from hospital.

② Chemical and physical properties of the radiopharmaceutical (Ra-223) for internal radiation therapy and radiation protection.

③ Preventing exposure of workers, as well as instructions for patients and family members (caregivers).

④ Radiation measurement and safety management for radioactive waste.

Physicians, etc. who have acquired specialist knowledge through in-hospital education and training can be practitioners of this therapy. However, it is desirable for such physicians to be nominated by the management of the hospital, etc.

If the individuals who attended a “safe handling training course” organized by academic societies, move away from hospitals, etc. and are thus no longer available, an Ra-223 radiation safety supervisor must be selected from among the doctors, e.g. nuclear medicine physicians (radiology department) who have completed in-hospital education and training so that therapy can be continued for the time being. However, this Ra-223 radiation safety supervisor is required to attend a safe handling training course when one is held nearby. This exception only applies to facilities that have experience with this therapy, and not to those without experience.

Records of the implementation of in-hospital education and training must be prepared and kept for at least 2 years.

10 Measures to protect workers from radiation and radioactive contamination

10.1 Radiation protection measures for handling this drug

1) Preparation of protective devices

① Protective glasses (mandatory): When handling this drug, one must be prepared for the possibility that the solution may contaminate the eyes directly (Ra-223, the main component of this drug, is an alpha-emitting radionuclide and attention is required because its radiation weighting factor is 20-fold that of beta particles and gamma rays.)

② Protective gloves (mandatory): To avoid direct contamination of the fingers, etc. when handling this drug.

③ Water absorptive polyethylene sheets: Used to avoid spreading of contamination through absorption of water containing the radioactive material. The contaminable interiors of safety cabinets, working surfaces, lead blocks, etc. are covered with water absorptive polyethylene sheets.

④ Tweezers: Fixing silicone tubing, etc. to the tips of a pair of tweezers improves the grip and facilitates handling of vials, etc. with tweezers.

⑤ Vats of an appropriate size: If a water absorptive polyethylene sheet is placed on the interior base of a stainless steel vat of the appropriate size and dispensing, etc. is carried out on the sheet, radioactive contamination of the vat can be prevented and spread of contamination avoided.

2) Basics of handling radioactive materials

When handling radiopharmaceuticals, which are unsealed RI, attention must be paid to avoid both external exposure and internal exposure by intake into the body. It must also be considered that radiopharmaceuticals are often handled at relatively close proximity and that patients become radiation sources after administration. Consequently, when dealing with this drug, efforts must be made to reduce exposure by shortening the working time, maintaining a sufficient distance from the radiation source, and setting up shielding (the 3 principles of protection against external exposure).

(1) Cold runs (training in handling this drug)

Regarding the process of using vials containing this drug and dispensers, etc., practice in carrying out the procedures must be done in the same way as if using radioactive material, but without actually doing so. Such practice procedures are called cold runs. ① Operating procedures can be ascertained and understood by repeated performance until skill is acquired. ② The methods for preparation of the required equipment and materials as well as the protective measures can be ascertained. ③ Cold runs help to speed up operations with actual radioactive material and to avoid mistakes. In other words, handling of the actual radiation sources can become more rapid and both operational and procedural errors can be reduced.

Table 4 shows the distances from the radiation source and the actual measured dose rates without shielding.

Table 4: Distance from this drug (Ra-223)*) and dose rate

Distance from the vial surface	Dose rate (μSv/h/MBq)
1 m	< 0.1
10 cm	< 5
Surface	< 100

*: This drug is a colorless aqueous solution that contains 6.16 MBq of radioactivity per vial (test day), and the concentration of radioactivity is 1.1 MBq/mL.

(2) Precautions for controlled areas

With regard to precautions when entering or leaving controlled areas and laboratories etc., the matters for compliance according to the Medical Care Act, etc. are to be posted near all entrances and exits. Workers engaged in radiation-related work must be fully aware of these precautions. The main precautions are as follows.

① All entries into the room are recorded.

② Workers must change into slippers, sneakers, safety boots, etc. for exclusive use in controlled areas.

③ Workers must change into work clothes, etc. for exclusive use in controlled areas.

④ Men wear pocket dosimeters or other individual dosimeters on the chest, while women wear them on the abdominal region.

⑤ The operational status of ventilation exhaust equipment must be ascertained.

⑥ When handling radiopharmaceuticals, always wear protective glasses and protective gloves.

⑦ Radiopharmaceuticals or radioactive material discarded after use are transferred into rooms for storage or disposal immediately after the finish of work.

⑧ After use, radioactive contamination testing is carried out in the rooms, and decontamination is performed immediately if contamination is detected.

⑨ Hands must be washed using detergent and running water.

⑩ Contamination testing is performed for the hands, feet, cuffs, clothing surfaces, and footwear, etc.

⑪ If there is no contamination, the shoes and clothes are changed. If contamination is detected, decontamination is carried out in accordance with the instructions of the radiation administrators.

⑫ All exits from the room are recorded.

⑬ Personal exposure dosimeters are read and the data are recorded.

(3) Handling this drug

Dispensing this drug: It is desirable to carry out dispensing in a safety cabinet. ① It must first be ascertained that the safety cabinet is working reliably. ② The working surfaces inside the safety cabinet, including the front, back, and sides, must be covered with water absorptive polyethylene sheets. Moreover, lead plates, blocks, and other shielding materials must be used when handling radiopharmaceuticals in order to reduce exposure to workers, etc. ③ The floor near the safety cabinet must be covered with water absorptive polyethylene sheets to prevent the spread of contamination.

Procedures for waste disposal after handling and using this drug: Protective glasses must be worn when handling this drug, and work clothes, special gloves for handling RIs, and other protective gear must also be worn. Handling this drug must be done in a stainless steel vat or the like lined with water absorptive polyethylene sheets, etc. Contaminants are disposed of in the way mentioned above. If the facial skin or the eyes are accidentally contaminated by this drug, thorough washing must be performed immediately using a detergent and running water.

Workers must not leave the room or walk about while working with radioactive materials, as when preparing pharmaceuticals, etc. Waste must be separated and stored or disposed of immediately after finishing work.

Contamination testing and decontamination of rooms, etc. (walls, floors etc.) after using this drug: Potential contamination by Ra-223 must be tested along the flow path of this drug's use by measurement with a radiation meter.

Ra-223 emits alpha particles, beta particles, and gamma rays, so a suitable radiation detector must be used that is effective for detecting surface contamination by this drug (see 8.3.1). If multiple medical radionuclides are produced and dispensed simultaneously in a preparation room, etc., there is a risk of mutual contamination and a risk of administering the wrong drug. These risks must be avoided by all means possible to ensure the safety of medical care.

Radiation detectors: A survey meter can be used to clearly detect sites of contamination by Ra-223. If contamination is identified, a special instrument for measuring alpha particles can also be used for assessment. As mentioned in 8.3.1, it is difficult to find the actual sites of contamination because of the very short distance

travelled by alpha particles. Therefore, since Ra-223 emits alpha, beta, and gamma radiation, as mentioned above, use of a GM survey meter is recommended for contamination testing of workbenches and floors because it allows highly sensitive separate measurement of beta particles and gamma rays. If sites of contamination are detected and the radiopharmaceuticals handled in the environment are known, the contaminating radionuclides can be identified.

Decontamination: If radioactive contamination of workbenches, floors, etc. is discovered, decontamination must be carried out without delay. If the contamination is detected soon after it occurs, immediate decontamination can be performed by applying an absorbent paper towel, etc. and using water, detergent, citric acid, or another chelating reagent. If the contamination caused by this drug cannot be removed sufficiently, it is also effective to wet the contaminated site with a 0.01 M solution of ethylenediaminetetraacetic acid (EDTA) and then wipe it off. Attention must be paid to avoid fissures, pinholes, etc. in the gloves used during decontamination so that secondary contamination of the worker does not occur. If complete decontamination is impracticable, the contaminated site must be covered with water absorptive polyethylene sheets, etc. and the cover must be marked with an oil-based pen to show the extent of contamination, the measured values, and the date of occurrence. Measures to keep persons away from the site, such as setting up barriers, may also help to prevent the spread of contamination.

10.2. Exposure of workers (external and internal exposure)

Based on the Ordinance for Enforcement of the Medical Care Act, Article 30 (18, 27) as well as PFSB Notice No. 188, 2(5) Limits, Items 1-2, and 2(6) Doses, etc., Calculations 1-5, efforts must be made to prevent exposure of medical care professionals (workers) to radiation. While the dosage of radium dichloride can vary from patient to patient, a dosage of 10 MBq* was used to calculate the external exposure dose to workers in relation to working time and distance from the radiation source (Table 5). Ra-223 is part of a decay series, as depicted in Figure 1, with the parent nuclide (Ra-223 itself) and the progeny of the series existing in a state of radioactive equilibrium (secular equilibrium). In the equilibrium state, the radioactivity of each progeny is equal to the radioactivity of the parent nuclide. For calculation of the exposure dose, a constant for each progeny was added to the effective dose rate constant of Ra-223 published in the Isotope Pocket Data Book, 11th Edition, i.e., 0.0454 [µSv × m2 × MBq-1 × h-1] was used for Ra-223 in equilibrium (ref. Table 2).

Table 5: External exposure doses to workers

Step	Effective dose (whole body) Per person			Skin Per person			Dose limit	
	Working time (min.)	Distance (cm)	Exposure dose (mSv)	Working time (min.)	Distance (cm)	Exposure dose (mSv)	Effective dose limit (whole body)	Equivalent dose limit
Preparation	10	50	1.17×10^{-4}	10	1	0.291	Workers 50 mSv/ year 100 mSv/ 5 years Women with the possibility of being pregnant 5 mSv/ 3 months	500 mSv/ year
Admini-stration	5	50	5.83×10^{-4}	5	1	0.146		

Based on “Ministry of Health and Welfare Public notice No. 398, 26 December 2000”[22], internal exposure in a week is calculated as shown below. With reference to the “Practical Manual for Medical Radiation Management”[30], the effective dose, E (mSv/week), is determined using the following formula:

$$E = e \times I$$

where I is the inhaled amount of the medical radionuclide (Bq) in 1 week and

$I = 1.2 \times 10^6 \times C \times t$

1.2×10^6: Volume of air inhaled by an adult in 1 hour (cm^3/h)

C = Concentration of radioactivity in the air in 1 week (Bq/cm^3)

t = Working time / week

$C = A \times$ dispersion rate × days of use in 1 week / ($V \times 10^6 \times 8$ [h] × operation days of the exhaust facility in 1 week)

A = Estimated maximum use in 1 day (Bq).

V = Discharged air indoors (m^3/h), 8 operating hours / day.

For this drug, the following figures apply. A: 3.85 MBq, dispersion rate: 0.001, discharged air indoors: V: 560 (m^3/h) × 8(h), days of use during 1 week: 1 day (days of use for this drug), operation days of the exhaust facility in 1 week: 5days, working time: 10 min. (0.167 h), e (effective dose coefficient if Ra-223 is inhaled): 5.7×10^{-3} (mSv/Bq). Thus, internal exposure (E: effective dose [mSv]) can be calculated as follows:

$C = 3.85 \times 10^6 \times 0.001 \times 1 / (560 \times 10^6 \times 8 \times 5) = 1.72 \times 10^{-7}$ (Bq/cm^3)

$I = 1.2 \times 10^6 \times C \times 0.167 \times 1 = 0.034$ (Bq)

$E = e \times I = 5.7 \times 10^{-3} \times 0.035 = 1.94 \times 10^{-4}$ (mSv)

10.3 Important points for workers

It is essential for workers to understand this manual and the pharmacokinetics of this drug, to sufficiently explain the principles of radiation protection mentioned above to patients and their family members, and to ensure safety management at medical institutions. It is also essential for physicians with expertise to give workers appropriate training and develop a cooperative

framework within medical institutions. If emergency medical measures are necessary, appropriate medical actions have priority over the matters related to compliance with radiation protection detailed above.

In particular, persons engaged in nursing patients must pay special attention to the following points during the initial 1 week after administration (ref. 5.3).

(1) Wear disposable rubber gloves if there is a risk of contact with the patient's urine, feces, or blood or if clothing, etc. soiled by these substances is handled.

(2) Be sure to wash the hands thoroughly using soap after contact with a patient's blood, etc.

(3) Wash clothing, etc. worn by the patient separately from those of other family members, etc. Carefully rinse sheets or underclothes that have been soiled with blood or urine.

11. Disposal of medical radioactive contaminants (Ra-223 contaminated objects)

Objects contaminated by Ra-223 are considered to be "medical radioactive contaminants" as specified in Article 30 (11) of the Ordinance for Enforcement of the Medical Care Act. Medical radioactive contaminants may be stored and disposed of in the "disposal facilities" of medical institutions according to Article 30 (11) of the Ordinance for Enforcement of the Medical Care Act[11-1)]. Handling of contaminated waste can be assigned to JRIA by the facilities.

For handling of diapers, urine bags, and other objects soiled with human excreta, blood, etc., refer to "Handling of Diapers, etc. of Patients Administered Radiopharmaceuticals" (Guidelines for Health Care Providers Performing Nuclear Medicine Practices) and the "Manual for Handling of Diapers, etc. of Patients Administered Radiopharmaceuticals" (Japan Radiological Society, Japanese Society of Radiological Technology, Japanese Society of Nuclear Medicine, Japanese Society of Nuclear Medicine Technology, and Japan Association of Radiological Protection in Medicine).[25)]

Note 11-1: JRIA is assigned as the contract organization to treat contaminated waste, according to Article 30, paragraph 14 (8)-1 of the Ordinance for Enforcement of the Medical Care Act (2001-09-28), which specifies the person receiving the consignment for disposal of materials that have been contaminated by medical radionuclides or radionuclides.

12. References

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Glossary

International Atomic Energy Agency (IAEA):

A UN organization established in 1957 to promote the peaceful use of nuclear energy. It provides assistance to developing countries and implements safeguards to prevent military use of nuclear energy. Based on ICPR concepts, the IAEA prepares standards for radiation protection and safety of radiation sources. Countries all around the world adopt these standards for their corresponding laws and ordinances.

International Commission on Radiological Protection (ICRP):

The International X-Ray Radium Protection Committee (IXRPC) was founded in 1928. It was reorganized in 1950 and received its present name at that time. The ICRP investigates protection concepts, numerical standards, etc. and presents relevant recommendations. Such recommendations are not only normative for laws and ordinances concerning radiation protection in countries worldwide, but also apply to practical radiation management.

National Institute of Standards and Technology (NIST):

The National Institute of Standards and Technology (NIST) is a National Metrological Institute found in 1901. Its mission is to promote U.S. innovation and industrial competitiveness by advancing measurement science, standards, and technology in ways that enhance economic security and improve the quality of life.

Physical half-life ($Tp_{1/2}$):

The time in which radioactivity decreases to half of its initial value. In this manual, “half-life” is used to indicate physical half-life.

Biological half-life ($Tb_{1/2}$):

The time required for removing half of the quantity of a substance from an organism or its components by biological processes.

Alpha particles (α-rays):

One type of radiation. It consists of stable helium (He-4) atoms with an atomic number of 2 and a neutron number of 2, which are emitted with radioactive decay. Alpha particles show a strong ionizing effect over a very short range within substances as they are halted several centimeters from the radiation source even in free air. For this reason, they can be blocked even by paper and the like. Because of the strong ionizing effect, attention has to be paid to internal exposure if an alpha-emitting substance enters the body.

Beta particles (β-rays):

One type of radiation. It consists of high-speed electrons emitted with β-decay. The penetration force is weak so that normally an aluminum sheet several millimeters thick or a plastic sheet of about 1 cm provides sufficient shielding.

Gamma rays (γ-rays):

Electromagnetic radiation that is generated when excited atomic nuclei transition to a more stable state. In general, γ-rays are emitted along with nuclear decay or nuclear reactions and possess a radionuclide-specific, single-band spectral energy. However, there are also radionuclides that emit γ-rays of different energies with a single decay. X-rays are another form of electromagnetic radiation, but γ-rays originate in the atomic nucleus and X-rays are emitted from electrons outside the nucleus. Because γ-rays have a strong penetrating force, lead shielding is generally required.

Dose:

For the purpose of radiation protection, it specifies a quantity that assesses the effect of exposure by a common measure based on the type of radiation and the mode of exposure. The unit of the dose is the Sievert (Sv).

Exposure dose:

In general, the quantity of radiation received by the human body.

External exposure:

Exposure to radiation from outside the body. In the case of external radiation, X-rays, γ-rays, and neutrons have a strong penetrating force and can affect all body tissues, whereas the penetrating force of beta particles is weak and their main impact is on the skin and eyeballs.

Internal exposure:

Radiation received from radioactive substances that have entered the body. There are three ways for such substances to enter the body – by inhalation, by oral intake, and via the skin.

Dose rate:

The quantity of radiation per unit time.

1 cm dose equivalent (rate):

Since the effective dose cannot be measured directly, the International Commission on Radiation Units and Measurement (ICRU) has proposed two quantities for practical measurement of external exposure. These are the ambient dose equivalent H*(d) for monitoring work environments, which always shows higher values than the effective dose under ordinary exposure conditions and thus allows safe evaluation, and the personal dose equivalent Hp(d) that is used for monitoring the dose to personnel. Both are used internationally, including in Japan. In the case of exposure to X-rays or γ-rays, the highest impact exposure dose is not at the body surface, but instead affects the tissues at a certain depth. If the exposure dose at a depth of 1 cm from the body surface is used as the assessment standard, the value will always be higher than the effective dose and is considered to permit exposure management with an adequate safety margin. The International Commission on Radiological Protection (ICRP) has recommended d = 10 mm. Based on this, in Japan, (H*(10)) is called the 1 cm dose equivalent for facilities and (Hp(10)) is the 1 cm dose equivalent for personnel, with both parameters generally being known as 1 cm dose equivalents. Glass badges, survey meters for radiation control, and other instruments are marked to display such values.

70 μm dose equivalent:

For weakly penetrating radiation, the dose equivalent to tissue 70 μm from the body surface (d = 0.07 mm) is applied as the dose equivalent of the skin (the radiation dose taking biological effects into consideration). The 70 μm dose equivalent for facilities and the 70 μm dose equivalent for personnel are both generally known as 70 μm dose equivalents. Exposure quantities for personnel are assessed by using glass badges and personal dosimeters.

Effective dose rate constant:

This is a constant for determining the effective dose per hour at a distance of 1 m from an unshielded point source with radioactivity of 1 MBq ($\mu Sv \times m^2 \times MBq^{-1} \times h^{-1}$).

Dose limit:

This is the effective dose or equivalent dose to individuals that must not be exceeded from the viewpoint of radiation protection. The dose limits in the existing laws and ordinances were established on the basis of ICRP recommendations (1990). The effective dose limit for workers is 50 mSv per year and 100 mSv over 5 years. The dose limit for the general

public is 1 mSv per year. These dose limit values represent the sum total of external and internal exposure, but do not include exposure due to natural radiation and medical practice.

Equivalent dose:

The following formula is used to calculate the equivalent dose (H_T) to a tissue or an internal organ:

$$H_T = \sum_R w_R D_{T,R}$$

where $D_{T,R}$ is the average absorbed dose received by the tissue or internal organ (T) from radiation R, and w_R is the radiation weighting factor. If there are more than one radiation type, the summation of each radiation will be the equivalent dose (H_T). Generally, the Sievert (Sv) is used as the unit for the equivalent dose.

Effective dose:

The following formula is used to calculate the tissue-weighted total of the equivalent doses to all specified tissues and internal organs of the human body:

$$E = \sum_T w_T H_T = \sum_T w_T \sum_R w_R D_{T,R}$$

where w_R $D_{T,R}$ or H_T is the equivalent dose (T) to the tissue or internal organ, and w_T is the tissue weighting factor. Generally, the sievert (Sv) is used as the unit for the effective dose.

Dispersion rate:

This a factor used in calculating the concentration of a radionuclide in discharged air or in room air.

Gas – using a gas trap	10^{-1}
without a gas trap	1
Liquids or solids	10^{-3}

Notice No. 188 of the Pharmaceutical and Food Safety Bureau, 12 March 2001

Occupancy factor:

The ratio of the estimated dose actually received from a patient by a third party to the cumulative dose that would be received after remaining for an infinite time (until complete radionuclide decay) at 1 m from the point source (patient) of the radionuclide.
(Report No. 70 from the Safety Division (SD), PMSB, MHLW, dated 30 June 1998, as amended by the Notification of the Director of the Guidance Division, Health Policy Bureau (HPB), Report No. 1108, part 2 of the Guidance of Medical Service Division Health Policy Bureau, 8 November 2010)

Medical radioactive contaminants:

"Medical radionuclides, medical radionuclides for positron emission tomography, or matter contaminated by radionuclides" as stipulated in the Ordinance for Enforcement of the Medical Care Act.

Bayer Yakuhin, Ltd., provided the draft translation of the manual, their internal-use material, as a courtesy. Radionuclide Therapy Expert Committee of Medical Science and Pharmaceutical Committee of Japan Radioisotope Association reviewed and finalized.