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GUIDELINES

Guidelines for the labelling of leucocytes with ^{111}In-oxine

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Abstract We describe here a protocol for labelling autologous white blood cells with ^{111}In-oxine based on previously published consensus papers and guidelines. This protocol includes quality control and safety procedures and is in accordance with current European Union regulations and International Atomic Energy Agency recommendations.

Keywords Guideline · White blood cells · Scintigraphy · ^{111}In-oxine · Infection

Purpose

White blood cells (WBC) labelled with ^{111}In-oxine (^{111}In-8-hydroxyquinoline) have been successfully applied in the field of infection/inflammation scintigraphy for many years, but this radiopharmaceutical has been largely replaced by WBC labelled with ^{99m}Tc-HMPAO. Still, ^{111}In-oxine-labelled WBC are routinely used by several centres. In fact, ^{111}In-oxine-labelled WBC have proved to be superior to WBC labelled with ^{99m}Tc-HMPAO for imaging a number of specific clinical indications. Although the general procedures for labelling of WBC with either ^{111}In-oxine or ^{99m}Tc-HMPAO are similar, there are some important differences between the procedures. Despite substantial overlap with the guidelines for the labelling of WBC with ^{99m}Tc-HMPAO, it was decided to prepare separate guidelines for the labelling of WBC with ^{111}In-oxine, to avoid confusion and misinterpretation.

The aim of this document is to provide information on the preparation and quality control of ^{111}In-oxine WBC that may assist nuclear medicine practitioners, radiopharmacists, technicians and other individuals involved. The corresponding guidelines of the Society of Nuclear Medicine, recommendations of the International Atomic Energy Agency (IAEA), several national guidelines, and the most relevant literature were taken into consideration and partially integrated into this text [1–25]. The present guidelines, therefore, neither arise from a consensus conference nor from evidence-based meta-analysis, but were produced by a panel

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These guidelines summarize the views of the Inflammation/Infection Taskgroup of the EANM and reflects recommendations for which the EANM cannot be held responsible. The recommendations should be taken in the context of good practice of nuclear medicine and do not substitute for national and international legal or regulatory provisions. The guidelines have been reviewed by the EANM Dosimetry Committee and the Radiopharmacy Committee.
The guidelines have been brought to the attention of the National Societies of Nuclear Medicine.

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of experts based on data from peer-reviewed literature, from their own experience, and from knowledge of colleagues from all over the world that was shared at meetings, at congresses and during collaborative scientific work including multicentre studies.

This protocol aims to guide the labelling of WBC in accordance with currently effective European Union regulations. However, the specific rules in the country of interest must also be known and applied to practice, because different European countries have different recommendations or laws regarding the production of extemporaneous radiopharmaceuticals, especially when labelled autologous cells are considered, since they cannot be sterilized after labelling. Therefore, the procedure may have to be adjusted to local needs and the equipment available.

Background information

Scintigraphy with labelled autologous WBC is a widely used method for detecting sites of infection. In the mid 1970s, ^{111}In-oxine was introduced as a labelling agent for WBC scintigraphy. The ^{111}In-oxine solution is supplied in a vial as a ready-to-use radiopharmaceutical. Indium forms an uncharged pseudo-octahedral N_3O_3 complex with three molecules of 8-hydroxyquinoline (oxine). The complex is a nonspecific blood cell labelling agent, as it is neutral and lipid-soluble, which enables it to penetrate through the bilayer cell membrane. Within the cell, indium becomes firmly attached to cytoplasmic components (such as lactoferrin). The liberated 8-hydroxyquinoline is released by the cell. The mechanism of labelling cells with indium ^{111}In-oxine is thought to involve an exchange reaction between the 8-hydroxyquinoline carrier and subcellular components which chelate indium more strongly than 8-hydroxyquinoline. The low stability constant of the ^{111}In-oxine complex, estimated at approximately 10^{10}, supports this theory.

In normal individuals, after injection of labelled leucocytes about 60% of the radioactivity is immediately taken up by the liver, spleen, bone marrow and other tissues. There is only a very short transient hold-up in the lungs. The remainder shows exponential clearance from the circulation with a half-life between 5 and 10 h, resulting in a final uptake of about 20% in the liver, 25% in the spleen, 30% in the bone marrow and 25% in other organs. Clearance of activity derived from labelled leucocytes from liver and spleen is very slow. In addition, there is very low excretion of activity in both the urine and feces.

For WBC scintigraphy, either mixed leucocytes or isolated granulocytes can be used. When mixed leucocytes are labelled with ^{111}In-oxine, about 60–70% of the radioactivity is bound to granulocytes. Labelled mixed leucocytes can display higher blood pool activity, especially in the early images, due to the presence of labelled lymphocytes and residual erythrocytes.

When compared to ^{99m}Tc-HMPAO-labelled WBC, there are some advantages and disadvantages in using ^{111}In-oxine-labelled WBC. The main advantage of ^{111}In-oxine over ^{99m}Tc-HMPAO is the higher labelling efficiency (LE) and less efflux of radioactivity from the labelled WBC. The costs of ^{111}In-oxine-labelled WBC are generally lower than those of HMPAO-labelled WBC, although in some European countries HMPAO is available at low cost as a generic drug. Furthermore, if a bone marrow scan is required at 24 h (usually performed with ^{99m}Tc-nanocolloids of albumin), the use of ^{111}In-oxine-labelled WBC does not interfere with imaging of ^{99m}Tc-nanocolloids, because different energy windows can be used to detect ^{99m}Tc and ^{111}In simultaneously. Finally, ^{111}In-labelled WBC are preferentially indicated for imaging abdominal infections and Inflammatory bowel disease, since there is hardly any intestinal excretion of ^{111}In-oxine.

On the other hand, planar images obtained with ^{111}In-labelled WBC are of substantially lower quality than those obtained with ^{99m}Tc-labelled WBC. SPECT images of ^{111}In-labelled WBC are of very low quality as well, unless the acquisition time is largely increased. In addition, ^{111}In-oxine has to be ordered in advance, whereas ^{99m}Tc is readily available from portable generators. The most important disadvantage, however, is the radiation exposure of labelled cells, critical organs (spleen) and the whole body to ^{111}In-oxine (Table 1), which is substantially higher than that from ^{99m}Tc-HMPAO.

Common indications for ^{111}In-oxine WBC scintigraphy

^{111}In-oxine-labelled WBC scintigraphy may be applied to detect and localize any occult site of infection and to determine the extent of the process in various disorders, including:

- Inflammatory bowel disease
- Intra-abdominal infection
- Osteomyelitis of the appendicular skeleton
- Diabetic foot
- Infected joint and vascular prosthesis
- Lung infections
- Neurological infections
- Fever of unknown origin
- Postoperative abscesses
- Endocarditis
- Infected central venous catheters or other devices

^{111}In-oxine-labelled WBC are particularly useful for the detection of inflammatory sites in the abdomen, where ^{99m}Tc-HMPAO-labelled WBC are less suitable due to high bowel excretion.

Table 1 Radiation dosimetry for ^{111}In-labelled leucocytes

Population	Administered activity (MBq)	Organ receiving the largest radiation dose (Spleen) (mGy/MBq)	Effective dose equivalent (mSv/MBq)
Adults	10–18.5	5.5	0.59
Children (5 years old)	0.15–0.25/kg	17.0	1.8

International Commission on Radiological Protection. Annals of the ICRP, Publication 53, Radiation Dose to Patients from Radiopharmaceuticals. Pergamon, Elsevier Science, London; 1988, pp. 255–256

Precautions

During the labelling procedure, blood and blood components of the patient, who could potentially be infected with pathogens, need to be handled. To prevent contamination of the operator who is performing the labelling, waterproof gloves should be worn throughout the procedure. Special caution should be taken when handling needles.

Since ^{111}In-oxine WBC have to be reinjected into the patient, strict aseptic conditions are required for the labelling procedure. For this purpose, only sterile reagents and disposable plastic-ware should be used and sterile gloves, cap and mask should be worn. Usually, WBC are labelled in a laminar flow cabinet or isolator installed according to local regulations. Recently, certified sterile closed-kit labelling devices have become available that may represent a good approach to WBC labelling with further protection for patient and operator, despite the fact that they have to be used in a sterile cabinet as well.

Simultaneous labelling of WBC from multiple patients is discouraged in order to prevent possible cross-contamination. Labelling of WBC of different patients should be carried out at physically separated locations, unless closed devices are used. At all times correct identification of the patient's blood products should be guaranteed. All syringes, tubes and any material in contact with the patient's blood components should be clearly labelled with the patient's name, bar-code and/or colour code.

During the labelling of WBC with ^{111}In-oxine care should be taken not to damage the leucocytes, as this would result in leakage of the radioactivity from the cells, adhesion of labelled leucocytes to the vascular endothelium (especially in the microvasculature of the lungs) and loss of motility. To avoid degradation of the radiopharmaceutical and radiation damage to labelled cells, ^{111}In-oxine-labelled WBCs should be reinjected as soon as possible, but not later than 1 h after labelling.

Labelling of mixed leucocytes causes radiation damage to the lymphocytes as a result of self-irradiation by internal conversion of electrons and Auger electrons. However, since the lymphocytes are unable to divide after labelling and are eliminated through apoptosis and phagocytosis, the risk of lymphoid malignancies after administration of ^{111}In-oxine-labelled mixed leucocytes is considered to be negligible.

Procedure

A. Isolation of WBCs

A1. Collection of blood Fill a 60-ml syringe with 9 ml of acid-citrate-dextrose anticoagulant solution (ACD; formulation A according to the European Pharmacopoeia, consisting of 0.73 g of anhydrous citric acid, 2.2 g of sodium citrate dihydrate and 2.45 g of dextrose monohydrate in 100 ml of water for injection) and add 51 ml of the patient's blood to this syringe. Use a needle with an inner diameter of at least 20 G to prevent damage to the WBC. Damage is related to shear stress due to high laminar flow in small needles when using large syringes. Blood withdrawal should be slow and smooth in order to prevent the formation of bubbles and foaming. Mix the blood–ACD solution by gently turning the syringe end over end a few times (do not mix by shaking). At least, 2×10^8 leucocytes are required to achieve good LE. In patients with neutropenia ($<2\times10^3$ neutrophils/mm^3), an additional syringe of ACD anticoagulant and blood may be needed. Although the use of smaller volumes of blood (down to as little as 20 ml) has been described in the literature, this is not recommended, because it tends to reduce the LE.

Smaller blood volumes can be drawn from children, depending on feasibility and considering that the activity is determined according to body weight and local regulations. In this case, the use of smaller syringes and needles is advised (use multiple 10-ml syringes containing 1.8 ml of ACD).

A2. Isolation of cell-free plasma Dispense 15 ml of the blood–ACD solution into a Falcon centrifugation tube and centrifuge at 2,000*g* at room temperature for 10 min. Separate the cell-free plasma (CFP) from the pellet. The CFP will be used as the medium for cell resuspension after labelling. Isotonic phosphate-buffered saline, pH 7.4 (PBS), or a 0.9% aqueous solution of sodium chloride (saline) could be used as an alternative to CFP, although CFP is a more physiological medium. There is no scientific evidence that supports preference of one medium over another. CFP should not be used in the labelling step, because indium-chelating plasma proteins such as transferrin cause degradation of the ^{111}In-oxine complex, resulting in a low LE [24].

A3. Isolation of mixed leucocytes First, erythrocytes are allowed to sediment with the aid of 2-hydroxyethyl starch (10% HES, pharmaceutical grade). While several formulations of HES plasma expander are commercially available, it is highly recommended to use high molecular weight HES 200/0.5 or 200/0.6 (mean molecular weight of 200 kDa), since formulations of lower molecular weight HES do not work as well as a sedimentation agents for getting leucocyte-rich plasma (LRP) from blood. Add 4.5 ml of 10% HES to the remaining 45 ml of the blood–ACD mixture. Although a ratio of blood–ACD mixture to HES of 10:1 is recommended, the concentration of HES can be increased up to a ratio of 5:1 for patients with polycythaemia or sickle-cell anaemia. Gently turn the syringe end over end a few times. Place the syringe with the opening up and allow the erythrocytes to sediment. This takes 30 to 45 min. Collect the LRP in a Falcon centrifuge tube. This can be achieved via a long lumbar needle or a butterfly needle of at least 20 G by gently pushing the piston of the syringe up without disturbing the erythrocytes. An alternative way to transfer the LRP is to use a 5-inch Kwill filling tube. Centrifuge the LRP at 150*g* for 5 min. Application of higher centrifugal forces should be avoided, since this would lead to increased platelet contamination. Lower centrifugal forces can be applied if the centrifugation time is adjusted accordingly. (*NB*: To avoid resuspension of the leucocytes, the centrifuge's brakes should be switched off in all centrifugation steps.)

Remove the platelet-rich plasma (PRP) and gently resuspend the mixed leucocyte pellet. As an optional step, the pellet could be washed with saline (or alternatively PBS) to reduce the number of contaminating platelets. For this purpose, gently resuspend the pellet in 3 ml of saline (or alternatively PBS), centrifuge at 150*g* for 5 min and remove the supernatant from the leucocyte pellet. Gently resuspend the mixed leucocytes in 1 ml of saline (or alternatively PBS) and use this cell suspension for labelling (step B).

A4. Isolation of granulocytes (optional) Although labelling of mixed leucocytes (from step A3) is recommended, purified granulocytes can be used instead. Optionally, granulocytes can be isolated from mixed leucocytes by gradient centrifugation. For this purpose, prepare gradient solution A and gradient solution B. Gradient solution A consists of A1.0 ml 9% NaCl, 5.5 ml Percoll (colloidal silica particles coated with polyvinylpyrrolidone; GE Healthcare, Little Chalfont, UK, or Sigma-Aldrich, St Louis, MO) and 3.4 ml water for injection, and gradient solution B consists of 1.0 ml 9% NaCl, 7.0 ml Percoll and 1.9 ml water for injection. Carefully inject with a syringe 4 ml of gradient solution A and subsequently 4 ml of gradient solution B under the mixed leucocyte suspension (i.e. at the bottom of the tube). Take care that the cell suspension and the gradient solutions do not mix. Centrifuge the gradient at 150*g* for 30 min. The granulocytes are now visible as a white layer between the gradient solutions, whereas the mononuclear cells and residual platelets are on the top of the gradient and erythrocytes are in the pellet. Carefully aspirate the granulocyte layer with a plastic Pasteur-type pipette and dispense them into a Falcon tube. Add 10 ml of saline solution (or PBS) and centrifuge at 150 *g* for 10 min. Remove the supernatant and gently resuspend the granulocyte pellet in 1 ml of saline (or PBS). As an easy alternative for Percoll, Lymphoprep has been used [26], but it has not been licensed for patient use and therefore ethical approval is required.

B. Labelling of WBC with ^{111}In-oxine

Aspirate approximately 20 MBq of ^{111}In-oxine into a 1- ml syringe from a ready-to-use radiopharmaceutical vial and add this solution to the mixed leucocyte cell suspension (or purified granulocytes) and incubate for 10 min at room temperature. Usually, the ^{111}In-oxine solution is formulated in a buffer solution by the manufacturer. However, if an ^{111}In-oxine solution is used without buffer, HEPES buffer (about 6 mg/ml final concentration) can be added to ensure a suitable pH for cell labelling. During incubation, gently swirl the cell suspension periodically to prevent sedimentation of the cells. After the incubation is complete, add at least 3 ml (preferably up to 10 ml) of PBS or saline and centrifuge at 150*g* for 5 min. After centrifugation, remove the supernatant containing unbound ^{111}In-oxine and measure the amount of radioactivity in the pellet and in the supernatant to calculate the LE. Gently resuspend the pellet containing the labelled mixed leucocytes in 3–5 ml of CFP. Dispense the patient dose (10–18.5 MBq) from the cell suspension. The ^{111}In-oxine-labelled WBC should be visually inspected and reinjected into the patient as soon as possible, but not later than 1 h after completion of the labelling procedure. The labelled WBC should be injected slowly, preferably using a needle of at least 22 G (0.7 mm diameter) to prevent cell damage due to shear stress (the inner diameter of the needle is only approximately 50-fold larger than the diameter of the WBC). Check the patient's identity prior to administration of the labelled WBC.

C. Quality controls

Several methods for quality control have been described, although only a few of them are used regularly in clinical routine, as many of these tests are time-consuming. For routine clinical use, visual inspection of final product and determination of the LE are usually considered sufficient. Because ^{111}In-oxine is more toxic to the cells than ^{99m}Tc-

HMPAO, periodic tests for cell viability (e.g. microscopic inspection and trypan blue exclusion test) are highly recommended. A retrospective sterility test could be used as additional quality controls, when desired. All these tests should be included when setting up the methodology for its validation, or when a new variation in the method is introduced. Early in-vivo lung uptake and liver-to-spleen activity ratio are the most commonly used in-vivo indices of problems with radiolabelling.

For process validation, operator validation or periodic process control, additional functional tests such as chemotaxis or phagocytosis assays may be included, but this is not required for routine use.

C1. Visual inspection (recommended routinely) Visual inspection of the preparation searching for clumps, clots, fibrin and platelet aggregates should be performed throughout the procedure and in particular after resuspending the pellet of cells after centrifugation. At the end of the procedure, and before collecting the labelled cells in the syringe for administration to patients, the inspection should be performed carefully by gently rotating the vial. In case of aggregates, they should be dissolved by gently shaking or pipetting the sample. If clumps cannot be dissolved, the preparation should not be injected.

C2. Labelling efficiency (recommended routinely) After each production, the LE should be determined by measuring the amount of radioactivity in the supernatant (soluble ^{111}In compounds) and the pellet (cell-associated ^{111}In) of the labelling solution after centrifugation. The LE can be calculated using the formula:

$$LE = \frac{\text{radioactivity in pellet}}{\text{radioactivity in pellet} + \text{radioactivity in supernatant}} \times 100$$

A LE between 50% and 80% is expected. If the LE is <50% further quality controls should be performed, such as microscopic inspection and trypan blue exclusion test for cell viability (see step C4).

C3. Sterility (recommended periodically) For post-release sterility testing, tests should be performed in accordance with the method described in the most recent European Pharmacopoeia. This test is preferably performed by a microbiologist, and may vary from centre to centre according to local needs and experience. The sterility test has to be performed in triplicate for the validation of the procedure and in case of any modification to the procedure, including new personnel and new reagents. The recent availability of media fills allows validation and revalidation of the labelling procedure with sterility control of each single step of the labelling procedure. If sterility tests are not passed, the process needs to be revalidated. A test for contamination of solutions and reagents with pyrogens (Limulus test, LAL test; PBI International, Milan, Italy, or Endosafe-PTS, Charles River Laboratories, L'Arbresle, France) can also be used in addition to sterility tests. The method is described in detail in the current European Pharmacopoeia.

C4. Trypan blue exclusion test, clumping and cell counting (recommended periodically) Add 25 µl of 0.4% trypan blue solution in water to 25 µl of the labelled leucocyte cell suspension (from step B) and gently mix the solution. Put a drop of the blue mixture in a haemocytometer and place the haemocytometer under a phase-contrast microscope at 100-fold magnification. Check the counting chamber for clumps and microaggregates of cells, count the number of cells and count the percentage of blue-stained cells (cells that have been damaged during de labelling process). As a control, repeat the same procedure using unlabelled leucocytes (from step A3). A preparation with a percentage of dead cells (blue-stained cells) of >4% should not be released for injection into the patient, and consequently new tests for validation of the method should be undertaken.

C5. Cell subset recovery test (recommended for initial validation) The test consists of counting the number of different cell subsets present during the separation and labelling procedure to verify that red blood cell and platelet contamination are within an acceptable ranges. After each crucial step (usually after centrifugations and at the end of procedure) collect a drop of resuspended cells and dispense it into a 5-ml vial with 1 ml saline or PBS. Count the cells using a routine cytofluorimeter for haematology or a hemocytometer slide viewed under an optical microscope. Limits of acceptability in the final cell suspension are: erythrocyte/WBC ratio<3 and platelet/WBC ratio<1.

C6. Measurement of cell efflux of ^{111}In (recommended for initial validation) Despite irreversible binding of ^{111}In to nuclear and cytoplasmic proteins, damaged leucocytes may release more radioactivity and at a higher rate than intact cells. Efflux can be measured by preparing three aliquots of labelled leucocytes and incubating them at 37°C. After 1 h, the aliquots are centrifuged at 150 *g* for 10 min and the amounts of radioactivity in the pellet and supernatant are counted separately. A release of <5% (i.e. radiochemical purity >95%) at 1 h is acceptable.

C7. In vivo lung uptake (recommended routinely) Early, temporary lung uptake of labelled leucocytes can be normal. However, lung images acquired at 30 min after injection should show an almost complete clearance of lung activity. Focal spots of radioactivity in the lungs at 30 min or later indicate the presence of radiolabelled clumps of cells in the injection sample. Diffuse lung activity, intense

at 30 min and persisting in late images is an indication of cell damage as a result of the labelling procedure, in particular in patients without any known lung disease.

In general, four different patterns of lung activity can be observed:

1. Rapid transit of cells in the lung with disappearance of radioactivity within 5 min.
2. Delayed lung transit of labelled cells, but with complete clearance within 30 min.
3. Prolonged focal or diffuse retention of lung activity with disappearance within 3 h of injection.
4. Delayed lung transit (as in 2) with increased liver activity greater than spleen activity.

Patterns 1 and 2 are normal. Patterns 3 and 4 indicate cell damage, the examination is nondiagnostic and particular care should be taken with image interpretation. (*NB*: It must be kept in mind that some disease processes can be associated with diffuse lung activity and/or delayed washout of labelled WBC.)

Lung transit is a qualitative test. In case of doubt, a quantitative test of liver-to-spleen ratio can be performed as described below.

C8. In vivo liver-to-spleen ratio (recommended periodically) Normally, at any time point, spleen activity should be higher than liver activity. Tissue activity can be quantified by region of interest analysis and should be normalized to the area of the region of interest. A liver activity the same as or higher than spleen activity indicates cell damage, the scan may be nondiagnostic and particular care should be taken with image interpretation.

Methodological issues requiring further clarification

- The optimal formulation of HES plasma expander and the value of alternatives, such as succinylated gelatin and methyl cellulose.
- The use of PRP instead of CFP, or PBS or saline for centrifugation after the labelling.
- The use of PBS as an alternative for CFP for reconstitution of labelled WBC.
- The use of gradient solution for granulocyte separation.
- Qualification and training of personnel required for WBC labelling.
- Requirements for equipment and infrastructure where WBC labelling is performed.

Closed disposable sterile systems for WBC labelling

The recent availability of a closed disposable sterile system (Leukokit; GE Healthcare, Little Chalfont, UK) for WBC separation and labelling offers an additional advantage for operator protection and for avoiding sample contamination. It is a licensed medical device distributed worldwide that may allow simplification of the required infrastructure, although to date there is no defined legislation for the use of this type of product in a different way from that of open systems. The kit includes a sterile GMP-produced vial of anticoagulant agent (ACD-A), a vial of 10% HES and a vial of PBS for cell washing and resuspension, thus avoiding possible causes of contamination of the labelled product.

Procedure and personnel validation

The WBC labelling process must be simulated for validation of the process prior to starting clinical studies in a specific laboratory. It is recommended that the requirements for the validation procedure are more strict than those for regular quality control. The validation procedure should include control of LE (>60%), sterility test (negative), pyrogenicity (absent), viability of cells (>98%), cell subset recovery test (in final cell suspension erythrocyte/WBC ratio <3) and measurement of "in vitro" cell efflux of ^{111}In within the first hour after labelling (<5%, i.e. radiochemical purity >95%). Sterility tests can be done with media fills or using different culture media. Tests may vary considerably and may include bacterial growth medium (e.g. agar) plates for environmental monitoring and hand-wash plates for hand wash validation.

Procedure and personnel validation should be performed at least three times for each new operator prior to initiation of clinical studies and should be repeated at regular intervals (suggested every 6 months) and after a significant change in the method or reagents.

At the moment, no country has defined by law a qualification, course or course programme for training of personnel. Except for defined local regulations, it is accepted that specifically trained medical doctors, radiopharmacists, pharmacists, chemists, radiochemists, biologists, or technicians perform the labelling of WBC under the supervision and responsibility of the Qualified Person, who is ultimately responsible for quality control and quality assurance. In this context, a training programme accepted worldwide for personnel who will be performing radiolabelling of blood elements is advisable and also suggested by other international organizations such as IAEA and ISORBE.

Briefly, a training course for personnel should include at least:

- General information on radioprotection and use of isotopes
- (Local) rules and recommendations
- Study of available guidelines and pharmacopoeia
- Guidelines for working in aseptic conditions, including the use of a Class IIa safety cabinet

- Information on equipment operation and its maintenance
- Practical skills in labelling cells and blood elements
- Practical skills in performing required in vitro quality controls
- Recommendations for record-keeping

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Disclaimer The European Association of Nuclear Medicine (EANM) has written and approved guidelines to promote the use of nuclear medicine procedures of high quality. The guidelines should not be deemed inclusive of all proper procedures and exclusive of other procedures reasonably directed towards obtaining the same results. The facilities in a specialized practice setting may be different from those in a more general setting. Resources available to care for patients, and legislation and local regulations may vary greatly from one European country or one medical facility to another. For these reasons, these guidelines cannot be rigidly applied.

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