

The Irradiation of Blood and Blood Components to Prevent Graft-Versus-Host Disease: Technical Issues and Guidelines

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IRRADIATION of whole blood and cellular components is currently the only accepted methodology to prevent transfusion-associated graft-versus-host disease (TA-GVHD). TA-GVHD occurs when viable donor T-lymphocytes proliferate and engraft in susceptible individuals after transfusion. TA-GVHD results in significant morbidity and mortality in approximately 80% to 90% of individuals so affected.¹ Patients who may be susceptible to TA-GVHD have been described in a number of recent reviews to which the reader is referred.²⁻¹² Although there is general agreement about most categories of patients who should receive irradiated blood components, there is a lack of consensus regarding others. This reflects the relative rarity of documented cases of GVHD. Some reports stratify the need for irradiation using such terms as "clearly indicated" or "probably indicated."¹¹

Irradiation of cellular components with ionizing radiation results in the inactivation of T lymphocytes. Ionizing radiation readily penetrates nucleated cells and damages nuclear DNA either directly or by generating ions and free radicals that have biological actions. The damage to T lymphocyte DNA prevents postinfusion proliferation that abrogates the potential for GVHD.¹³

Two types of ionizing radiation, γ rays and x-rays, inactivate T lymphocytes. Both can be used to irradiate blood and blood components. At a given absorbed dose, both γ and x-rays are equivalent in their ability to inactivate T lymphocytes. Gamma rays originate from within the atomic nucleus of cesium 137 (¹³⁷Cs) or cobalt 60 (⁶⁰Co). Free-standing blood bank irradiators are the predominant instruments used for blood and blood component irradiation. They use one of these two isotopes as the irradiation source. X-rays are generated from the interaction of electrons and a metallic surface. Linear accelerators that generate X-rays for patient therapy (teletherapy) may also serve as an irradiation source for irradiating blood and blood components.

Although blood and blood components have been irradiated since the 1970s, limited attention has been given to technical aspects of this practice.

This report reviews these issues, emphasizing the specific practices that are now being used. The following items are addressed:

1. Instrumentation that can be used to treat blood components.
2. Current consensus about which components should be irradiated.
3. The data that provides the basis for the storage periods for red cells and platelets after irradiation.
4. The data supporting the dose of irradiation currently being used.
5. Other measurements that should be performed as part of a quality assurance program.

INSTRUMENTATION FOR IRRADIATION

The basic operating principles and configurations of a free-standing irradiator with either a cesium (¹³⁷Cs) source or a linear accelerator are shown schematically in Figure 1. With a free-standing ¹³⁷Cs irradiator, the blood components are contained within a metal canister that is positioned on a rotating turntable. Continuous rotation allows for the γ rays, originating from one to four closely positioned pencil sources, to penetrate all portions of the blood component. The number of sources and their placement depend on the instrument and model. The speed of rotation of the turntable also depends on the make or model of the instrument. A lead shield encloses the irradiation chamber. Free-standing irradiators employing ⁶⁰Co as the source of γ rays are comparable except that the canister containing the blood component does not rotate during the irradiation process; rather, tubes of ⁶⁰Co are placed in a circular array around the entire

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A. FREE-STANDING IRRADIATOR (Cesium-137 source) **B. LINEAR ACCELERATOR**

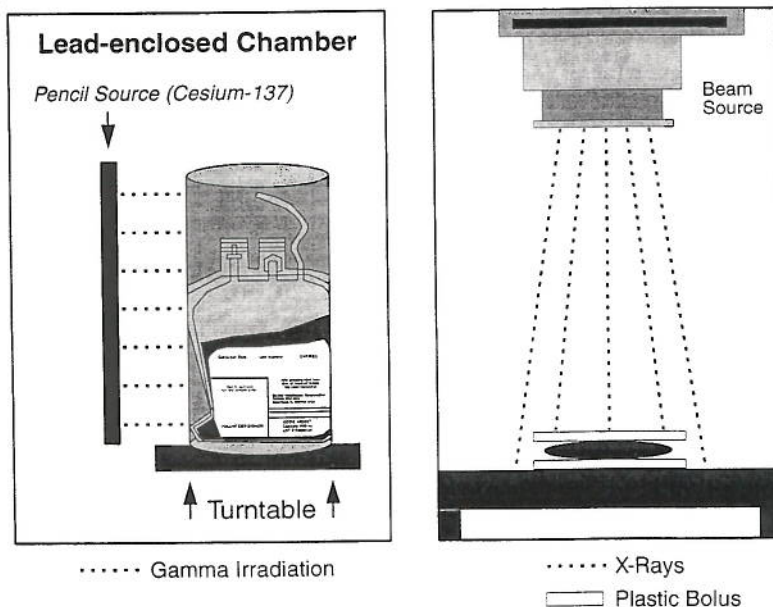


Fig 1. Diagrams of the type of instrumentation being used for blood irradiation. (A) Configuration of a free-standing γ irradiator using a Cesium 137 source. (B) Configuration of a linear accelerator.

canister within the lead chamber. When free-standing irradiators are used, the γ rays are attenuated as they pass through air and blood but at different rates.¹⁴ The magnitude of attenuation is greater with ^{137}Cs than with ^{60}Co .

Linear accelerators generate a beam of X-rays over a field of given dimension. Routinely, the field is projected on a table-top structure. The blood component is placed (flat) between two sheets of biocompatible plastic several centimeters thick. The plastic on the top of the blood component (ie, nearer to the radiation source) generates electronic equilibrium of the secondary electrons at the point where they pass through the component container. The plastic sheet on the bottom of the blood component provides for irradiation back-scattering that helps to ensure the homogenous delivery of the x-rays. The blood component is usually left stationary when the entire x-ray dose is being delivered. Alternatively it may be flipped over when one half of the dose has been delivered; this process involves turning off and restarting the linear accelerator during the irradiation procedure. Although it seems as if the practice of flipping is not required, further data are needed.

COMPONENTS TO BE IRRADIATED

For patients at risk for GVHD, all components that might contain viable T lymphocytes should be

irradiated. These include units of whole blood and cellular components (red cells, platelets, granulocytes), whether prepared from whole blood or by apheresis.

All types of red cells should be irradiated, whether they are suspended in citrated plasma or in an additive solution. There are recent data supporting the retention of the quality of irradiated red cells after freezing and thawing.^{15,16} If frozen-thawed units are intended for GVHD-susceptible individuals and have not been previously irradiated, they should be irradiated because it is known that such components contain viable T lymphocytes.¹⁷

Filtered red cell products should also be irradiated. Extensive leukoreduction through filtration may decrease the potential for GVHD and serve as an alternative to irradiation in the future when questions about the minimum level of viable T lymphocytes that can lead to GVHD are resolved. There are reports of TA-GVHD in patients who received leukodepleted (filtered) red cells; however, the extent of leukoreduction of the components was not uniformly quantified in such reports.¹⁸⁻²⁰ In addition, investigators have suggested that the number of T lymphocytes present in a product that causes GVHD may depend on the extent of patient immunocompetence at the time of transfusion. It is likely that the greater the degree of

immunosuppression, the fewer the viable T lymphocytes that will be required to produce GVHD in susceptible patients.⁴ In a recent review, it was suggested that cytotoxic T lymphocytes, or interleukin-2-secreting precursors of helper T lymphocytes, may be more predictive of GVHD than the number of proliferating T cells alone. Accordingly, this suggests that until further data are available to confirm adequate removal of these T-cell subtypes by leukoreduction, irradiation should be used for blood products destined for patients at risk for GVHD.²¹

Irradiated red cells undergo an enhanced efflux of potassium during storage at 1° to 6°C.^{22,23} Comparable levels of potassium leakage occur with or without prestorage leukoreduction.²⁴ Washing units of red cells before transfusion to reduce the supernatant potassium load does not seem to be warranted for most red cell transfusions because postinfusion dilution prevents the increase in plasma potassium.²⁵ On the other hand, when irradiated red cells are used for neonatal exchange transfusion or the equivalent of a whole blood exchange is anticipated, red cell washing should be considered to prevent the possible adverse effects caused by hyperkalemia associated with irradiation and storage.²⁶

Blood components given to recipients, whether immunocompromised or immunocompetent, that contain lymphocytes that are homozygous for an HLA haplotype that is shared with the recipient, pose a specific risk for TA-GVHD. This circumstance occurs when first and second degree relatives serve as directed donors⁸⁻¹¹ and when HLA-matched platelet components donated by related or unrelated individuals are being transfused.^{27,28} Irradiation of blood components has been recommended in these situations.

Platelet components that have low levels of leukocytes because of the apheresis process and/or leukofiltration should also be irradiated if intended for transfusion to susceptible patients. This is because the minimum number of T lymphocytes that induces TA-GVHD has not yet been delineated.

Fresh frozen plasma does not need to be irradiated routinely because it is generally accepted that the freezing and thawing processes destroy the T lymphocytes that are present in such plasma. During the past 2 years, there have been two brief articles suggesting that immunocompetent progeni-

tor cells may be present in frozen-thawed plasma; the authors therefore suggested that frozen-thawed plasma may need to be irradiated.^{29,30} Further studies are needed to validate these findings and to assess whether the number of immunocompetent cells, that may be present in thawed fresh frozen plasma, is sufficient to induce GVHD. In rare instances, when nonfrozen plasma (termed *fresh plasma*) is transfused, it should be irradiated because of the presence of a sizable number of viable lymphocytes, approximately 1×10^7 cells in a component prepared from a unit of whole blood.

STORAGE OF RED CELLS AND PLATELETS AFTER IRRADIATION

Red Cells

The *in vivo* viability of irradiated red cells, evaluated as the 24-hour recovery, is reduced during storage when compared with nonirradiated red cells.²⁹⁻³³ This has raised questions concerning the maximum storage time for red cells after irradiation. Davey et al³¹ found that with 3000 cGy on day 0, the mean (\pm SD) 24-hour recovery for ADSOL-preserved red cells after 42 days of storage was $68.5 \pm 8.1\%$ compared with $78.4 \pm 7.1\%$ for control, nontreated red cells. Subsequent studies employed total storage periods of between 21 and 35 days after day 0 or day 1 irradiation. After storage for 35 days, the mean (\pm SD) 24-hour recovery for irradiated (3000 cGy) and control ADSOL red cells was $78.0 \pm 6.8\%$ and $81.8 \pm 4.4\%$, respectively.³² In studies with a 28-day storage period, the values for irradiated (2500 cGy) and control ADSOL red cells were $78.6 \pm 5.9\%$ and $84.2 \pm 5.1\%$, respectively.³³ With Nutricel-preserved red cells treated with 2000 cGy on day 1, mean 24-hour recovery for control and irradiated red cells were 85.0% and 80.7% after 28 days of storage and 90.4% and 82.7% after 21 days of storage.³⁴ Red cells irradiated on day 14 and stored for an additional 14 to 28 days also showed a limited reduction of 24-hour red cell recovery. With irradiation on day 14 and a total storage period of 28 days, the mean (\pm SD) 24-hour recovery for irradiated (2500 cGy) and control ADSOL-red cells was determined to be $82.3 \pm 5.6\%$ and $85.2 \pm 2.3\%$, respectively. When the storage period after irradiation (2500 cGy) was 28 days (total storage time of 42 days), the mean values for irradiated and

control red cells were $69.5 \pm 8.6\%$ and $76.3 \pm 7.0\%$, respectively.³⁵

There are also data indicating that the long-term survival of red cells is minimally influenced by radiation. In addition, *in vitro* red cell properties such as adenosine triphosphate (ATP) levels and the amount of hemolysis are altered to only a small extent relative to control values with extended storage after irradiation.³⁵ However, potassium leakage from the red cells during storage is substantially enhanced by irradiation.³¹⁻³⁵ The mechanism for this effect has not been elucidated. There does not seem to be an association between irradiation-induced changes in red-cell viability and potassium leakage, as was once thought.

In the United States, the Food and Drug Administration (FDA) guidelines call for a 28-day maximum storage period for red cells after irradiation, irrespective of the day of storage on which the treatment was performed, with the proviso that the total storage time cannot exceed that for nonirradiated red cells.

Platelets

In contrast to red cells, the storage period at 20°-24°C for irradiated platelet components does not need to be modified. Both *in vitro* and *in vivo* platelet properties are not influenced to any extent by irradiation. Many studies have confirmed that platelet properties are retained immediately after irradiation and at the conclusion of a 5-day storage period, whether irradiation is performed pre-storage or mid-storage.³⁶⁻⁴² One recent report indicated some differences in selected *in vitro* parameters between irradiated and control platelets after storage.⁴³

DOSE OF RADIATION

Until recently, there were no standards pertaining to the dose of radiation that should be used. A 1989 survey indicated that a range of irradiation dose levels between 1500 cGy and 5000 cGy (1 rad = 1 cGy) were being used, with the majority of facilities employing 1500 cGy.⁴⁴ These reported irradiation values were for the most part estimates and retrospective calculations because most facilities were not performing any type of dosimetry measurement. Furthermore, such values may be different from current values determined through dose mapping, because until recently there was no standardized way of calculating or reporting

irradiation dose. The selection of 1500 cGy as the target irradiation dose was based on studies in the 1970s that showed that 500 cGy abrogated the mixed lymphocyte response of isolated lymphocytes.^{45,46} Recent studies with a more sensitive limiting dilution assay (LDA) indicated that 2500 cGy (measured at the internal midplane of a component) is the most appropriate dose.^{47,48} In these experiments, red cell and platelet components were irradiated in plastic containers with increasing doses of radiation. After each dose, samples were removed and the clonogenic proliferation of T lymphocytes was measured in a limiting dilution culture system. With red cell units, 500 cGy had a minimal influence, whereas 1500 cGy inactivated T lymphocyte proliferation by approximately 4 logs; however, some growth was still observed in each experiment. Increasing the dose to 2000 cGy resulted in no T-lymphocyte proliferation in all but one experiment. No growth was observed after 2500 cGy.⁴⁷ In a subsequent study that used plateletapheresis components with sufficient T lymphocytes to perform the LDA, the influence of 1500 cGy and 2500 cGy was evaluated.⁴⁸ With 1500 cGy, substantial inactivation was measured; however, some growth was still observed in all experiments. As noted with the red cell experiments, 2500 cGy resulted in complete abrogation of clonogenic T-lymphocyte proliferation. Another recent study that used more traditional assay methods to assess T-lymphocyte inactivation recommended that an irradiation dose of 2800 to 3000 cGy.⁴⁹ The FDA has recommended that the irradiation process should deliver 2500 cGy to the internal midplane of a free-standing irradiation instrument canister, with a minimum of 1500 cGy at any other point within the canister. (See the section on quality assurance measures dealing with dose mapping.)⁵⁰

QUALITY ASSURANCE MEASURES

One must document that the instrument being used for irradiation is operating appropriately and confirm that blood components had been irradiated. To assure that the irradiation process is being conducted correctly, specific procedures are recommended for free-standing irradiators and linear accelerators, which are summarized in Tables 1 and 2. The procedures to be used with free-standing irradiators are an update to the guidelines provided several years ago by Anderson.⁵¹ Included are current recommendations from the FDA.

Table 1. Recommended Quality Assurance Measures to be Used with Free-Standing Gamma Irradiators

Measure	Time Interval
Dose mapping	Annually: ^{137}Cs Semiannually: ^{60}Co
Adjustment of irradiation time to correct for isotopic decay	Annually: ^{137}Cs Quarterly: ^{60}Co
Assuring no radiation leakage (Geiger counter, film badges, wipe tests)	Periodically
Timer accuracy	Quarterly
Turntable operation (^{137}Cs)	Daily
Preventive maintenance	Annually
Qualitative indicator label	Each component

Dose mapping measures the delivery of radiation within a simulated blood component or over an area in which a blood component is placed. This applies to an irradiation field when a linear accelerator is used or to the canister of a free-standing irradiator. Dose mapping is the primary means of ensuring that the irradiation process is being conducted correctly. It documents that the intended dose of irradiation is being delivered at a specific location (such as the central midplane of a canister), and it describes how the delivered irradiation dose varies within a simulated component or over a given area. This allows conclusions to be drawn about the maximum and minimum doses being delivered. Dose mapping should be performed with sensitive dosimetry techniques. A number of commercially available systems have been developed in recent years. Other quality assurance measures that need to be done include the routine confirmation that the turntable is operating correctly (for ^{137}Cs irradiators), measurements to ensure that the timing device is accurate, and the periodic lengthening of the irradiation time to correct for source decay. With linear accelerators, it is necessary to measure the characteristics of the x-ray beam to ensure consistency of delivery.

Confirming that a blood component has, in actuality, been irradiated is also an important part of a quality assurance program. At least one

commercial firm has developed an indicator label for this purpose.

DOSE MAPPING WITH FREE-STANDING IRRADIATORS

For free-standing irradiators, a dose-mapping procedure will measure the delivered dose throughout the circular canister in which the blood component is placed. To establish a two-dimensional map, a dosimetry system is placed in a canister that is completely filled with a blood/tissue-compatible phantom composed of water or an appropriate plastic such as polystyrene.^{52,53} The dosimetry material is placed within the phantom in a predetermined way. This approach provides data that describe the minimum levels of irradiation that would be absorbed by a blood component placed in the canister and recognizes that maximum attenuation will occur when the canister is completely filled with a blood-compatible material. Relevantly, it was shown recently that the absorbed dose at the central midplane of a canister (ie, at the center point) decreased by approximately 25% (from 3100 to 2500 cGy) in a ^{137}Cs irradiator (JL Shepherd and Associates, San Francisco, CA) when the loading of the canister was changed from 0% (air) to 100% (with blood components).⁵⁴ An irradiation-sensitive film dosimetry system (International Specialty Products) that will be described later in this report was used for this purpose. A linear relationship was observed between the amount of fill and the measured central dose. With 1 and 2 units of blood components, the central dose relative to air was 0.98 and 0.93. The minimum and maximum levels were influenced in the same manner as the central dose on decreasing the proportion of the canister that contained air.

Other studies have shown that the extent of variability in the dose delivered to the interior of simulated blood units (water or saline in plastic blood storage containers) depended on the model of the ^{137}Cs free-standing irradiator.^{55,56} An immobilized grid of thermoluminescent dosimeters in a plastic sheet were placed within the simulated blood units to measure dose delivery. See the section on dosimetry systems in use. It was also shown that a spacer into the bottom of the canister increases the minimum level of radiation within the simulated blood units as expected from the results of full-canister dose mapping involving a phantom.⁵⁶ The extent of variability with ^{137}Cs irradiation

Table 2. Recommended Quality Assurance Measures to Be Used with Linear Accelerators

Measure	Time Interval
Dose mapping	Quarterly
Consistency of x-ray beam quality	Quarterly
Consistency in size of irradiation field	Periodically
Qualitative indicator label	Each component

tions is influenced by a number of factors, including the number of sources, turntable speed, and the presence of a spacer at the bottom of the canister. These studies underscore the need for consistency in loading the canister.

Attenuation of the irradiation dose delivered is a function of physical density, electronic density, and atomic number with three major processes: photoelectric, Compton, and pair production. In practical terms, attenuation is caused when the irradiation enters a liquid, such as water or blood. The extent of attenuation depends on a number of factors, including the dimensions of the canister. In a fully filled canister, as is used for dose mapping, the attenuation will increase as the irradiation transverses to the center point. The dose map that is generated describes the dose distribution. As depicted in the theoretical dose map shown in Figure 2, the edges of the canister are exposed to a greater dose of irradiation compared with the center line because the attenuation is less in the periphery. The attenuation with ^{60}Co is less than that seen with ^{137}Cs .

When an irradiator is purchased, the distributor will provide a central dose level that is determined

in a blood-compatible environment. In the 1970s and 1980s manufacturers provided a central dose that was determined in air, resulting in the use of timer settings that provided for a dose level that was somewhat less than what was expected. Subsequent to the issuing of the FDA guidelines in July 1993⁵⁰ and the use of dose mapping, it has been necessary to readjust irradiation times with some instruments because the attenuation effect had not been considered previously.

A theoretical two-dimensional dose map describing the irradiation dose distribution through a fully filled canister of a free-standing ^{137}Cs irradiator is shown in Figure 2. To obtain this dose map, dosimeters would have been positioned in the central axis and the edge of circular canister from the top to the bottom of the canister. The y dimension of the map depicts the top to bottom axis of the canister, whereas the x dimension depicts the cross-sectional axis. For the theoretical situation described in Figure 2, the central midplane dose is 2560 cGy, slightly above the minimum standard of 2500 cGy, and the minimum dose is 1750 cGy. In this irradiation dose map, the minimum dose is at

Top	2400	2000	2450
Center	2700	2340	2730
	2950	2560	2980
Bottom	2810	2400	2780
	2380	1750	2420
	Edge	Midplane	Edge

Fig 2. Representation of the presumed dose of radiation absorbed from a Cesium ^{137}Cs source at specific locations in a fully filled circular canister. The dose levels listed were chosen to illustrate the concepts addressed in the text. Instrument differences, including the number of sources, the arrangement of the sources, and dimensions of the canister can influence the amount of radiation delivered through a canister.

the central bottom of the canister, a common finding in actual practice.

The dose map can also be used to assess whether the turntable of a ^{137}Cs irradiator is rotating in an appropriate manner. The occurrence of comparable readings at the two edges of the two-dimensional map, as depicted in the theoretical dose map, indicates that the canister is rotating evenly in front of the ^{137}Cs source. If the turntable were not rotating, the dose levels at the edge of the map closest to the source would be much higher than that found on the opposite edge, ie, the side located distant to the source.

According to the 1993 recommendations from the FDA, dose mapping should be performed routinely on an annual basis and after a major repair, especially one involving the sample handling apparatus such as the turntable.

Dosimetry Systems In Use

The delivered irradiation dose can be measured by a variety of dosimetry systems. In recent years, several commercial interests have developed complete systems for use with free-standing irradiators; each system consists of a phantom that fills the canister and a sensitive dosimetry system. Three main types of dosimetry measurement systems are available (Table 3). These dosimeters are referred to as routine dosimeters. They are calibrated against standard systems, usually at national reference laboratories such as the National Institute of Standards and Technology in the United States. The routine dosimeter measurement systems were initially developed for use with ^{137}Cs irradiators because this is the predominant irradiation source for blood. More recently, they have been developed also for use with ^{60}Co irradiators.

Thermoluminescent dosimeters (TLD chips) are one type of routine dosimeter. TLD chips are small plastic chips with millimeter dimensions having a crystal lattice that absorbs ionizing radiation. Specialized equipment is used to release and measure the energy absorbed by the TLD chip at the time of the test irradiation. In one commercially available

system, chips are placed at nine different locations within a polystyrene phantom that fits into the canister of the IBL 437C irradiator (CIS US, Inc, Bedford, MA). The timer setting used routinely for an instrument is used in the test procedure.

There are two systems that use radiochromic film. On exposure to irradiation, the film darkens, resulting in an increase in optical density. The optical density, determined at various locations on the film, is linearly proportional to the absorbed irradiation dose. Standard films that are irradiated at a given dose level with a calibrated source at a national reference laboratory provide the means to assess the absolute level of absorbed irradiation. This type of dosimeter is basically an x-ray film comparable with that used in clinical practice. With this device, the map that is developed identifies the absorbed irradiation dose that is measured at a large number of locations. In one system, a film contained in a thin water-tight casement is placed into the canister (International Specialty Products, Wayne, NJ). This approach is being used with a variety of irradiators. The canister is filled completely with water before the irradiation procedure. This system provides a direct readout of the dose that is delivered throughout the canister. The timer setting used routinely is employed for the test procedure. In a second system, a film having different radiation sensitive characteristics is embedded between two halves of a circular-fitting polystyrene plastic phantom (Nordion International, Kanata, Ontario). Irradiation of specialized films is performed with a number of timer settings, each being larger than that used routinely. The map produced is normalized for a central midplane dose of 2500 cGy. The time to produce the 2500 cGy will have been predetermined with a different dosimeter system, the Fricke system, in which absorbed radiation causes a change in the state of a iron salt that can be assessed spectrophotometrically.

Another approach to irradiation dose mapping employs a solid-state electronic dosimeter that is technically referred to as a *metal-oxide silicon field effect transistor* (MOSFET). A board contains a number of small transistors in an arrangement that provides data for a dose map. This board is placed between two halves of a circular polystyrene phantom that fits into the canister. This dosimeter absorbs and stores the radiation dose imparted to it electronically. The radiation causes the formation of holes in the metal-oxide layer that becomes

Table 3. Dosimeters in Routine Use

Type	Measurement
Thermoluminescent (TLD) chips	Emission of light
Radiochromic film	Optical density
Electronic sensors*	Voltage

*Metal-oxide field effect transistors (MOSFET).

trapped within the transistor. The magnitude of the holes is evaluated by measuring the voltage across the transistor with a voltmeter. The voltages measured are converted to absorbed dose.

With each dosimetry system, measurements are used to express the absorbed irradiation dose of Grays (or centiGrays). All dosimetry measurements are associated with a degree of uncertainty or possible error. The magnitude of the uncertainty depends on the kind of dosimeter used. For most dosimeters, the level is $\pm 5\%$ of the measured value. For a central absorbed dose level of 2560 cGy (see theoretical dose map in Fig 2) the value could be as high as 2788 cGy or as low as 2432 cGy. Correspondingly, a measured value of 2400 cGy could be as high as 2520 cGy or as low as 2380 cGy. Because the measured value could in actuality meet the 2500 cGy standard, it is appropriate to accept a value of 2400 cGy as meeting the current standard. The same approach should be used when evaluating the minimum value on a dose map. Albeit arbitrary and cautious, the actual minimum on an irradiation dose map should not be below 1500 cGy.

OTHER MEASURES WITH FREE-STANDING IRRADIATORS

Correction for Isotopic Decay

It is important periodically to lengthen the time of irradiation to correct for decay of the isotopic source that emits the gamma irradiation. Until recently, this was the only major quality assurance measure that was performed routinely.

With the half-life for ^{137}Cs being 30 years, annual lengthening of the timer setting is appropriate. On the other hand, with the half-life of ^{60}Co being only 5 years, the time of irradiation should be increased on a quarterly basis. The additional seconds of irradiation that are needed can be calculated using formulae that can be found in any physics text. Alternatively, distributors of irradiators provide a chart that specifies the appropriate setting as a function of calendar time.

Turntable Rotation

For ^{137}Cs irradiators, it is essential that the turntable operates at a constant speed in a circular pattern to ensure that each part of a blood component is exposed equally to the source. Daily verifi-

cation of turntable rotation is an appropriate quality assurance measure. With some free-standing irradiator models rotation of the turntable can be observed before the door of the compartment in which the canister is positioned is closed. In other models, this can be done only indirectly by ensuring that an indicator light is operating appropriately.

With some older models, there have been occasional reports that the turntable failed to rotate because of mechanical problems. Such problems should not be encountered with the newer models because of changes in the turntable mechanisms. In any event, daily verification of turntable rotation is a prudent quality assurance measure.

Assessing Radioactivity Leakage

Irradiators are constructed so that the isotopic sources are contained in a chamber heavily lined with a protective lead shield to prevent leakage of radioactivity. Accordingly, gamma irradiators are considered to be very safe instruments. Although there have been no reports of source leakage of radioactivity, periodic measurements are warranted to ensure that this is the case. Attaching a film badge to the outside of the irradiator, using a Geiger counter periodically, and performing a wipe test of the inside of the chamber where the canister is positioned at least semiannually are measures that are being used.

DOSE MAPPING WITH LINEAR ACCELERATORS

Linear accelerators that are used therapeutically to provide radiation therapy are carefully monitored to ensure appropriateness of dose to an irradiation field. When blood components are treated with x-rays, the instrument settings are very different than those used to treat oncology patients. Hence, additional periodic quality control measures, primarily to assess the dose delivered to blood components, are needed to ensure that linear accelerators are being operated appropriately when used for blood irradiation.

Currently, there are no commercially available systems for assessing the dose delivered throughout the area of an irradiation field in which blood components are placed for treatment with x-rays. An ideal dosimeter for this purpose would be made of a tissue-compatible plastic phantom, containing

appropriate dosimeter material and a covering that could be placed at the appropriate distance from the source. An alternative approach might involve the use of a blood bag filled with water (simulating a blood unit) containing TLD chips, as described earlier. In comparative studies using such simulated blood units, it was determined that radiation delivery was more uniform with linear accelerators than with ^{137}Cs free-standing irradiators.⁵⁵ This reflects the relative homogeneity of x-ray beams.

In the absence of an available system modified for the irradiation of blood bags, the dose delivered throughout an irradiation field should be mapped with the dosimetric measuring system known as an *ionization chamber*. The ionization chamber is used to calibrate linear accelerators for patient use. In addition, on a yearly basis, dose mapping should be performed using a tissue-compatible phantom.

In view of the widely divergent conditions that are used during the operation of linear accelerators, other parameters pertaining to the x-ray beam should be evaluated on at least a quarterly basis to provide assurance that the instrument is being used appropriately for the irradiation of blood components. The goal is to ensure that the instrument is being set in a consistent fashion. When setting a linear accelerator for blood component irradiation, the following should be measured: (1) the distance between the x-ray source and the position where the blood components are to be placed; (2) consistency in the strength of the x-ray beam; and (3) the intensity of the x-ray beam. The distance between the source and position on the table where blood components will be placed (referred to as the *target*) can be evaluated easily with a calibrated measuring device. This is a simple task that can be performed on a routine basis. The consistency of beam output can be evaluated by measuring the beam current. Beam intensity can be evaluated by measuring the ionization current in a monitoring ionization chamber array that can be expressed in terms of the number of photons delivered per square centimeter. These parameters should be assessed routinely as part of quality control programs used by radiation physicists. A code of practice was published in 1994 by the Radiation Therapy Committee of the American Association of Physicists in Medicine for the quality control of radiotherapy accelerators.^{57,58} The described prac-

tices are used routinely by radiation physicists. It would be prudent to ensure that an institution using a linear accelerator for blood irradiation follow these quality assurance guidelines and recommendations.

CONFIRMING THAT IRRADIATION OCCURRED

It is important to have positive confirmation that the irradiation process has taken place. This is to identify whether an operator fails to initiate the electronically controlled irradiation process or when the irradiation process is not performed because of instrumentation malfunction. A radiation-sensitive indicator label has been developed specifically for this purpose by International Speciality Products, Wayne, NJ. The label containing a radiation-sensitive film strip is placed on the external surface of the blood component. Irradiation causes distinct visually observable changes: The appearance changes from clear red to opaque with obliteration of the word "NOT." When the label is placed on a blood component, there is a visual record that the irradiation process took place. The reliability of this type of indicator was documented recently in a multisite study.⁵⁹

Two versions of the indicator label have been manufactured. The difference is the range of radiation needed to cause a change in the radiation-sensitive film. The ratings for these indicators are 1500 cGy or 2500 cGy. The ratings serve as an approximate guideline for the amount of absorbed radiation that will be needed to completely change the window from reddish to opaque with complete obliteration of the word "NOT." Because the indicator labels are designed for and are used to confirm that the irradiation process has occurred, we have concluded that the 1500 cGy label is the most appropriate tool to perform this quality control measure. This is based on the routinely observed pattern of dose distribution to a blood component in a canister of a free-standing irradiator. Despite a targeted central dose of 2500 cGy, there will be spots at which the dose will be less. If the theoretical dose map presented in Figure 2 is used as an example, there will be a spot that will receive only 1800 cGy. If the 2500 cGy-rated label were to be located on the external surface of a component, there may be minimal changes in the appearance of the radiation-sensitive film window.

This would result in a judgment that the blood component was not irradiated, when in actuality it was treated satisfactorily.

SUMMARY

In recent years, there have been several advances in blood irradiation practice. These include a better definition of the most appropriate dose level that should be used when irradiating blood components. Commercial innovation has provided the tools for a quality assurance program to assess the dose that is delivered throughout the canister in a free-standing irradiator, and, through the use of radiation-sensitive indicator labels, to confirm that the irradiation process has taken place. With the apparent increased use of linear-accelerators to irradiate blood components, appropriate quality assurance measures need to be developed. The maximum storage period for irradiated red cells should be shorter than for nonirradiated red cells if the treatment is performed early during the storage period because irradiation reduces the *in vivo* 24-hour red cell recovery parameter. The storage period for irradiated platelets does not need to be modified. Some questions are being raised regarding whether fresh-frozen plasma should be irradiated to inactivate a small number of immunocompetent progenitor cells that may be present.

Table 4 summarizes the practices that should be followed in connection with the technical issues

Table 4. Summary of Guidelines for Irradiating Blood Components

Dose
2500 cGy to the central midplane of a canister (free-standing irradiator) or to the center of an irradiation field (linear accelerator) with a minimum of 1500 cGy elsewhere.
Dose mapping (Free-standing irradiators)
Routinely, once a year (^{137}Cs) or twice a year (^{60}Co) and after major repairs; the irradiation procedure should be tested using a fully filled canister (water/plastic) with a dosimetry system to map the distribution of the absorbed dose.
Dose mapping (Linear accelerators)
Guidelines are less clear; yearly dose mapping with an ionization chamber and a water phantom. More frequent evaluation of instrument conditions to ensure consistency of x-rays.
Correction for radioisotopic decay
With ^{137}Cs as the source, annually.
With ^{60}Co as the source, quarterly.
Turntable rotation (Free-standing ^{137}Cs irradiators)
Daily verification.
Storage time for red cells after irradiation
For up to 28 days; total storage time cannot exceed maximum storage time for unirradiated red cells.
Storage time for platelets after irradiation
No change due to the irradiation.

that have been addressed in this article. These guidelines follow the recommendations issued in July 1993 by the FDA in the United States. This article and Tables 1 and 2 contain additional guidelines.

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