

Gamma Irradiation of Blood Products (7/22/93)

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To: All Registered Blood Establishments

From: Acting Director, Office of Blood Research and Review

Subject: Recommendations Regarding License Amendments and  
Procedures for Gamma Irradiation of Blood Products

This memorandum transmits recommendations regarding license amendments and procedures pertinent to irradiated blood and blood products. Irradiation of these products is a practice which has developed over many years to reduce the risk of transfusion--associated graft-versus-host disease in recipients at this complication. Since labeling of blood and blood products as irradiated pertains to safety and intended use, irradiated and non-irradiated products are considered different products by the Center for Biologics Evaluation and Research. Recommendations are provided here regarding manufacturing and quality control procedures, labeling and other aspects of production and use of irradiated blood and blood products. When the products are intended for interstate shipment, license amendments are required, as described in the recommendations.

/s/

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RECOMMENDATIONS REGARDING LICENSE AMENDMENTS AND PROCEDURES  
FOR GAMMA IRRADIATION OF BLOOD PRODUCTS

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I. INTRODUCTION

Graft-versus-host disease (GVHD) is a common complication after bone marrow transplantation. GVHD has also been reported after transfusion in immunocompromised hosts, though such reports have been uncommon. 1,2 More recently, cases of transfusion-associated GVHD in immunocompetent patients have been reported when both donor and recipient share genes for HLA determinants, a situation most likely to occur when family members serve as donors. 3,4 While irradiation of blood components intended for immunocompromised patients has been used for over 30 years, more recently, irradiation of directed blood donations from first degree family members (parents, children, siblings) was recommended by the American Association of Blood Banks (AABB) to reduce the risk of graft versus host disease (GVHD) and, effective 1 May 1993, the AABB's recommendation was extended to blood derived from all donors who are genetically related to the recipient. 5 This memorandum provides information on preparing blood products irradiated with gamma or ionizing radiation. Conclusive data are not available regarding all potential effects of radiation on blood cells. This memorandum describes quality control applicable to the manufacture of irradiated blood products and procedures applicable to licensure of such products, including quality control, stability and labeling. The uncertainties which exist regarding product quality are addressed in discussion of labeling procedures

II. BACKGROUND

A. TRANSFUSION-ASSOCIATED GVHD.

GVHD occurs when viable T lymphocytes in transfused blood or blood components engraft, multiply, and react against the tissues of the recipient. GVHD may be seen when blood components are transfused to immunocompromised recipients, such as bone marrow transplant patients, patients with malignancies receiving aggressive chemotherapy and persons with congenital immune deficiency syndromes. Luban and Sacher have suggested that several factors affect the incidence of transfusion-associated GVHD: 1) Histocompatibility factors and lymphocyte subsets; 2) Type

of blood component, dosage of immunocompetent cells per transfusion and rate of infusion; 3) Underlying medical condition; 4) Type of immunosuppressive therapy or chemotherapy; 5) Age of patient; and 6) Microbial factors.  
6

There are recent reports of GVHD occurring in apparently non-immunocompromised recipients following transfusion of blood donated by family members, 7-10 and the probability of such occurrences has been estimated using accepted genetic principles. 4,11,12 While the true incidence of transfusion-associated GVHD is not known, estimates of frequency are available from theoretical calculations, from limited studies in selected populations outside the U.S., and from survey data:

. 1990 AABB Questionnaire of 1,999 hospitals showed 12 cases of transfusion-associated GVHD among 14,296,314 blood components administered, of which 570,859 had been irradiated. 13

. A retrospective study of 63,257 patients who had undergone cardiac surgery in Japan yielded 96 cases of GVHD attributed to transfusion (incidence = 1 case/659 transfusions). 7

. There is consensus that transfusion of blood from HLA homozygotes to HLA heterozygotes with a shared haplotype constitutes a situation that is high risk for occurrence of transfusion-associated GVHD. Calculations of the frequency of this occurrence in the U.S. vary from 1/500 14 to 1/7174. 11 These numbers vary due to differences in the databases used for calculation and in the definitions of HLA compatibility.

. There are additional reports describing methods for calculating risk estimates among relatives, e.g., if donor and recipient are related as grandparent, uncle or aunt, the risk is one-half that which would pertain if donor and recipient were parent and child. 4,12

In cases of family member transfusions, GVHD may occur more frequently than in random donor transfusions because family members are more likely to share the same HLA haplotypes than people in the population at large. In many of these cases, it was found that the donors were HLA homozygous for one of the recipient's haplotypes. In such situations, the recipient's lymphocytes do not recognize HLA antigens on the donor lymphocytes as foreign, and the donor lymphocytes can survive indefinitely and may react immunologically against the recipient's tissues. Immunocompromised patients who are suitable candidates for receiving irradiated blood products have been categorized in the

scientific literature according to risk status. 15-22 AABB now recommends the irradiation of directed donations from all family member donors to immunocompetent recipients. 5

Platelets; Platelets, Pheresis; Granulocytes, Pheresis; Whole Blood; and Red Blood Cells contain 100,000 or more lymphocytes per unit and have been implicated in cases of GVHD. Red Blood Cells, Deglycerolized may contain small numbers of residual T lymphocytes, but no case reports of GVHD associated with this product have been published. 23 There are sufficient lymphocytes in single donor plasma to initiate GVHD in immunocompromised patients and GVHD possibly related to fresh frozen plasma has been reported in an infant with congenital immunodeficiency. 24 Cryoprecipitated AHF has not been reported to be associated with GVHD. Methods of producing leukocyte-reduced whole blood and components (including washing, filtration, and centrifugation) reduce the number of viable T lymphocytes, but may not decrease the risk of GVHD as effectively as irradiation. 1,25,26 White cell filters have not been effective to date, but their use continues under investigation.

#### B. IRRADIATION OF BLOOD PRODUCTS TO PREVENT GVHD.

Gamma irradiation of blood products has been in routine use in conjunction with bone marrow transplantation for approximately twenty years. The evidence in support of gamma irradiation of blood products for transfusion in prevention of GVHD is:

1. Gamma irradiation can abrogate the ability of lymphocytes to proliferate in vitro. 1500 cGy of gamma radiation reduce lymphocyte response to mitogens by 90%, 27 while 5000 cGy result in a 98% decrease in mitogen stimulation. 28 Published studies indicate that doses of 1500 to 2000 cGy reduce mitogen-responsive lymphocytes by 5 to 6 orders of magnitude. 19 Similar effects have been reported using 1500 to 2500 cGy. 25
2. Various studies have shown that the incidence of GVHD can be reduced if lymphocytes are physically or immunologically removed from donor bone marrow.
3. Limited studies 2 support the contention that gamma irradiation of blood products may prevent transfusion-associated GVHD.
4. Clinical observation over approximately 30 years during which transfusion of irradiated blood has been practiced has resulted in only 2 case reports of GVHD in recipients of irradiated blood products, and these

cases involved use of a suboptimal dose of irradiation. 19,29

C. EFFECTS OF GAMMA IRRADIATION ON PRODUCT QUALITY AND STABILITY.

1. Damage to cellular products. Gamma irradiation has been shown to affect red cells 28,30,31 so that use of the component should be modified.

a. RED BLOOD CELLS

i. The 24 hour recovery of irradiated red blood cells, after storage, is decreased compared to controls. Published data from several laboratories show that red blood cells irradiated within 24 hours of collection maintain satisfactory viability up to 28 days, while cells stored for 42 days had unsatisfactory viability (for cells irradiated on the day of collection and stored for 42 days, the 24 hour autologous recovery is  $68.5 \pm 8.1\%$  vs  $78.4 \pm 7.1\%$  for non-irradiated controls).<sup>30</sup>

Other data have been interpreted to suggest that red cells irradiated within 24 hours of collection can be stored satisfactorily for up to 35 days and that red cells irradiated as late as 14 days after collection may be satisfactorily stored for an additional 28 days (G. Moroff, personal communication).

ii. Units of red blood cells which have been irradiated have been shown to contain approximately twice as much extracellular potassium after equivalent periods of storage as non-irradiated controls. 31-33 The data show that irradiation of red blood cells may increase the rate of potassium ion leakage upon storage. Therefore, a high plasma potassium level may result if a significant portion of the total blood volume is replaced with irradiated red cell components .

iii. Red blood cells which have been irradiated have been shown to contain more cell-free hemoglobin (approximately

50% increase) than control cells after equivalent periods of storage. 31,33

b. PLATELETS

Significant changes in cell function have not been demonstrated in platelet products and changes in storage are not required for platelets irradiated on the day of collection. 34-35 Platelets irradiated at times up to 5 days after collection showed no post-irradiation change in function. 36,37

2. Theoretical risks associated with use of irradiated blood Products.

a. POTENTIAL FOR MALIGNANT TRANSFORMATION OF IRRADIATED NUCLEATED CELLS CAPABLE OF SURVIVAL IN THE RECIPIENT. Radiation of nucleated cells may result in malignant transformation. Quantitative risk assessment of this phenomenon occurring in irradiated blood has not been performed, but there is evidence that this theoretical risk is extremely remote. First, there are no reports of non-autologous malignancy in recipients of irradiated blood.

Second, studies with murine cells indicate that the amount of radiation used for blood components is much more likely to cause complete cell death than a single transformation event. It is also known that murine cells are much more susceptible to radiation-induced transformation than human cells. Thus, although existing data are insufficient to prove that there is no risk of transformation, there are no data to substantiate such a risk, and the data that are available indicate a very low risk. 38-40

b. ACTIVATION OF LATENT VIRUSES

Gamma irradiation has been shown to disrupt the latency of viruses which are potential contaminants of blood products. Despite the theoretical risks of viral activation, no reports of adverse events reflecting such occurrences have been published or received by FDA, and it is likely that the amount of radiation routinely used substantially exceeds amounts associated with this risk.

III. LICENSE AMENDMENTS FOR IRRADIATION OF BLOOD AND BLOOD PRODUCTS

Facilities irradiating blood products to be shipped in interstate commerce should submit applications for amendments to those license affected. The amendments should be submitted in duplicate with the appropriate product license application for and include the following:

A. STANDARD OPERATING PROCEDURES (SOPs).

The SOPs for irradiation of Whole Blood and blood components should describe:

- i. the irradiator;
- ii. the dose delivered to the center of the container, corrected for air - liquid differences 41 (including dosage validation data);
- iii. the strength of the source;
- iv. the length of time required to deliver the irradiation; and
- v. how monitoring will be performed to determine that the intended dose is actually delivered (see III.C).

B. IRRADIATION BY CONTRACTOR.

If product irradiation is to be performed in a different facility (e.g., a hospital radiation therapy department), the terms of the agreement with such facility should be included. Establishments performing the irradiation are participating in the manufacture of a product and should register with the FDA in accord with 21 CFR 607.

The terms of the agreement should specify that the operations are under the control of the blood establishment with respect to the procedures for irradiation of blood products, including the activities specified above, and for review of training and audit by the blood establishment. The documentation should allow FDA to determine that the contractor performing the irradiation is operating effectively as part of the licensed establishment.

C. RADIATION DOSAGES AND VALIDATION.

Cesium-137 is the most commonly used source for irradiation of blood and blood components; use of Cobalt-60 or a linear accelerator may also be acceptable.<sup>1,15,25,28,42,43</sup> The dose of irradiation delivered should be 2500 cGy targeted to the central portion of the container and 1500 cGy should be the minimum dose at any other point. It should be recognized that the irradiation delivered to the instrument canister (as identified by isodose curves supplied by the

manufacturer) may differ from the actual dose delivered to the blood bag or container (as quantified by thermoluminescence dosimeter (TLD) chips or other direct method of measurement). Validation studies should be performed to establish the performance of the irradiator within these limits, and maintenance procedures established to ensure satisfactory ongoing performance.<sup>6,15,44</sup> Validation should be done annually and after mechanical repairs, especially those involving the sample-handling apparatus (e.g., the turntable). Use of indicator devices, which signal exposure of the blood product container to radiation, is encouraged.

D. REMOVAL OF PLASMA PRIOR TO RELEASE.

Elevated potassium levels have been reported in irradiated red blood cell products.<sup>31,33</sup> Removal of residual plasma may reduce the risks associated with high plasma potassium. If this practice is used in manufacture of irradiated blood products, it should be described in the amendment.

E. LABELING.

1. Irradiated blood product containers should be permanently labeled as irradiated. Removable tie-tags are not acceptable for this purpose.
2. The license number should not appear on the container label unless the blood establishment is licensed by FDA for preparation of the irradiated blood product.
3. The circular of information should be modified to include a discussion of appropriate indications for irradiated blood products and appropriate warnings based on the known safety concerns, namely:

Irradiated blood products are indicated for use in patients at risk of transfusion-associated GVHD.

Caution should be used when administering irradiated red cell products to patients at risk for hyperkalemia, if supernatant plasma has not been removed from the product just prior to transfusion.

4. The dating period for red blood cell products (Red Blood Cells, Whole Blood) should be not more than 28 days from the date of irradiation, but otherwise not more than the dating period of the non-irradiated product.
5. The dating period for Platelets and Platelets, Pheresis should be in accord with established

regulations and guidelines, regardless of the day of irradiation.34-37

6. Approved product names and drug codes will be provided by FDA at the time of application for licensure.

#### IV. RECORDS

Records must be maintained according to 21 CFR 606.160, to document the following significant steps in the irradiation of each product:

A. The radiation source: Identify the strength of the source, duration and level/dose (number of cGy) of irradiation, and identity of operator, and the date and time of irradiation.

B. Total irradiation: If a product is irradiated more than once, the documentation should clearly indicate the steps taken; individual irradiation doses should be cross-referenced and the total (additive) irradiation dose recorded.

C. Site of irradiation: If the irradiating facility is different from the collecting facility, the records should include information regarding this irradiating facility.

D. Quality control of the irradiating device: Quality Control should include calibration and documentation of the procedures discussed in the SOP section of this memorandum or equivalent procedures.

E. Personnel training: Training should include safety procedures, and radiation monitoring.

V. When a fatality due to transfusion-related GVHD has been confirmed, the FDA must be notified as soon as possible by telephone with a written report of the investigation to follow within seven days after the fatality [21 CFR 606.170 (b)]. Direct such notifications to the:

Director  
Office of Compliance, HFM-600  
Center for Biologics Evaluation and Research  
1401 Rockville Pike, Suite 200N  
Rockville, MD 20852-1448  
Telephone: 301-594-1191

Fatal GVHD in bone marrow transplant recipients who received Whole Blood or blood components during the post-transplantation period need not be reported if the fatality was caused by the marrow graft.

## VI. INFORMATION SOURCES

Technical questions, information and comments may be directed to the:

Division of Blood Collection and Processing, HFM-350  
1401 Rockville Pike, Suite 200N  
Bethesda, MD 20852-1448  
Phone: (301) 594-6700 FAX: (301) 594-6431

Questions, information and comments concerning labeling or shipment may be directed to the:

Division of Blood Establishment and  
Product Applications, HFM-370  
1401 Rockville Pike, Suite 200N  
Bethesda, MD 20852-1448  
Phone: (301) 594-2012 FAX: (301) 594-1973

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