

Guidance for Industry

GAMMA IRRADIATION OF BLOOD AND BLOOD COMPONENTS: A PILOT PROGRAM FOR LICENSING

Additional copies are available from:
Office of Communication, Training and Manufacturers
Assistance (HFM-40)
1401 Rockville Pike, Rockville, MD 20852-1448,
telephone 1-800-835-4709 or 301-827-1800

(Internet) <http://www.fda.gov/cber/guidelines.htm>.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
February 2000**

TABLE OF CONTENTS

NOTE: Page numbering may vary for documents distributed electronically.

I.	PURPOSE.....	1
II.	INTRODUCTION	1
III.	BACKGROUND.....	3
IV.	SPECIFIC CRITERIA	3
	A. IRRADIATION PERFORMED BY THE APPLICANT BLOOD	
	ESTABLISHMENT.....	3
	1. Standard Operating Procedures (SOP).....	3
	a. Equipment and Maintenance	4
	b. Dosage and Time to Deliver Dose	4
	c. Indicators.....	5
	d. Labeling.....	5
	e. Dating Period	5
	2. Quality Assurance (QA).....	6
	a. Process Validation.....	6
	b. Quality Control (QC).....	7
	3. Recordkeeping.....	7
	B. IRRADIATION PERFORMED BY AN OUTSIDE CONTRACTOR	8
	1. Standard Operating Procedure	8
	2. Registration and Regulatory Responsibilities	8
	3. Agreement	9
V.	GLOSSARY	10
VI.	REFERENCES	12

GUIDANCE FOR INDUSTRY¹

GAMMA IRRADIATION OF BLOOD AND BLOOD COMPONENTS:

A PILOT PROGRAM FOR LICENSING

I. PURPOSE

This document provides Food and Drug Administration (FDA) acceptable criteria for the gamma irradiation of blood and blood components for transfusion. FDA believes that the procedures recommended in this document reflect practices currently in use by most manufacturers and represent the prevailing industry standard.

II. INTRODUCTION

Pursuant to section 351 of the Public Health Service Act (42 U.S.C. 262 et seq.) all biological products, including blood and blood components, introduced or delivered for introduction into interstate commerce must be licensed by FDA. Traditionally, manufacturers of blood and blood components have applied for an establishment license and product licenses for Whole Blood, Red Blood Cells, Plasma, Platelets, Cryoprecipitated AHF, Source Plasma and Source Leukocytes. Licenses have been issued by FDA, Center for Biologics Evaluation and Research (CBER), only after a license application review and prelicense inspection determined that the establishment conformed to standards prescribed in the regulations and that the products manufactured by the establishment were manufactured in a manner to assure safety, purity, and potency. Any changes in manufacturing methods or intended use of products have required submission of supplements to each application. More recently, FDA has streamlined the biologics license application process by initiating a process to eliminate the establishment license application (ELA) filing and consolidate the product application into a single biologics license application (BLA) (October 20, 1999, 64 FR 56441). Reporting changes to an approved application have also been modified by the new requirements of 21 CFR 601.12-Changes to an Approved Application (July 24, 1997, 62 FR 39890). However, even with the efficiencies of the BLA and 21 CFR 601.12 revisions, the process of the BLA, supplement preparation, and FDA review, is resource intensive to industry and FDA.

¹ This guidance represents FDA's current thinking on gamma irradiation of blood and blood components intended for transfusion. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

With this in mind, FDA is implementing a pilot program that allows a manufacturer to self-certify conformance to specific criteria as a substitute for CBER review of information submitted in a BLA supplement. FDA has chosen for this pilot, the gamma irradiation of blood and blood components. FDA believes that most manufacturers of gamma irradiated blood and blood components have a positive record of product safety, purity and potency, and a high level of adherence to current Good Manufacturing Practices (cGMP) regulations (21 CFR Parts 606, 210, and 211). This action is part of FDA's continuing effort to achieve the objectives of the President's "Reinventing Government" initiatives, and is intended to reduce unnecessary burdens for industry without diminishing public health protection.

The pilot program allows a manufacturer of gamma irradiated blood components to submit a self-certification statement as a supplement to the approved BLA, together with a written request for and exception from filing a detailed supplement. That is, instead of submitting a BLA supplement with supporting operating procedures and data derived from validation and quality control testing, the manufacturer submits a BLA (Form FDA 356h), a self-certification statement that provides that the manufacturer is in compliance with all applicable FDA regulations (21 CFR Parts 600-680, 210, and 211), and follows the recommendations for gamma irradiated blood and blood components in this guidance document, and a written request to the Director, CBER, for an exception pursuant to 21 CFR 640.120, from the requirement set forth in 21 CFR 601.12(b)(3) to submit a detailed supplement. The applicant should complete page 1 of the Form FDA 356h consistent with the instructions in the guidance document dated May 1999, entitled "Guidance for Industry: For the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Blood and Blood Components Intended for Transfusion or for Further Manufacture and for the Completion of the FDA Form 356h, Application to Market a New Drug, Biologic or an Antibiotic Drug for Human Use" (May 10, 1999, 64 FR 25049). On page 2 of the FDA Form 356h, the applicant should indicate items #2-Labeling and #19-Other (self-certification statement for pilot program) on the checklist and complete the certification/signature section. The self-certification statement should indicate that the manufacturer is ready for inspection. As a further streamlining effort and incentive to participate in the program, FDA will attempt to perform a pre-approval inspection of the manufacturer's manufacturing site(s) within 90 days of receipt of the self-certification statement. The applicant should also forward a written request pursuant to 21 CFR 640.120 for an exception to the requirement set forth in 21 CFR 601.12(b)(3) to file a detailed supplement. The request should reference the applicant's participation in the pilot program.

FDA has determined that there is adequate interest in the pilot program and is implementing the program for approximately one year. At the end of the pilot program, FDA will evaluate the program in terms of product safety, purity, and potency and also in terms of resource efficiency and effectiveness. If the program seems to be efficient and effective without compromising product safety, purity, and potency, FDA intends to allow manufacturers of gamma irradiated blood and blood components to continue to pursue the self-certification alternative. Regardless of the results of the pilot program, manufacturers of gamma irradiated blood and blood components will always be able to submit a detailed BLA supplement and receive a complete review of the application by FDA.

III. BACKGROUND

The reason for irradiating blood and blood components is to prevent graft-versus-host disease (GVHD) by decreasing the number of viable T lymphocytes. 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.

There are reports of GVHD occurring in apparently non-immunocompromised recipients following transfusion of blood donated by family members. (Ref.1-4) GVHD may occur more frequently in cases of family member transfusions than in random donor transfusions because family members are more likely to share the same histocompatibility locus antigen (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's lymphocytes as foreign, and the donor's lymphocytes can survive indefinitely and may react immunologically against the recipient's tissue which express a heterologous haplotype.

Blood and blood components implicated in cases of transfusion associated (TA)-GVHD include: Platelets; Platelets, Pheresis; Granulocytes, Pheresis; Whole Blood; and Red Blood Cells. Methods of producing leukocyte-reduced blood and blood components (including washing, filtration and centrifugation) reduce the number of viable T lymphocytes, but may not decrease the risk of TA-GVHD as effectively as gamma irradiation. (Ref. 5-7)

IV. SPECIFIC CRITERIA

A. IRRADIATION PERFORMED BY THE APPLICANT BLOOD ESTABLISHMENT

When irradiation is performed by a blood establishment in its own facility or in another department of the same facility, i.e., radiation therapy, cGMP as outlined in 21 CFR Parts 606, 210, and 211, must be followed.

1. Standard Operating Procedures (SOP)

SOPs must be developed, approved, implemented and maintained in the following areas (21 CFR 606.100(b) and 211).

a. Equipment and Maintenance

- i. Only those blood irradiators that have been cleared through the 510(k) process (21 U.S.C. 360(k)) by the Center for Devices and Radiological Health, Food and Drug Administration, and properly validated for irradiation of blood and blood components, will be acceptable for this pilot program.
- ii. Manufacturer's instructions should be incorporated into the SOP and must be followed (21 CFR 606.65 and 606.100)
- iii. All equipment used in the production of irradiated blood components should be qualified for such use. Qualification, including installation, operation and performance, should be completed prior to validation and as necessary during the life of the equipment. Qualification should also include measuring the amount of radiation delivered to the product.
- iv. All equipment used in the production of irradiated blood components must be calibrated in accordance with the manufacturer's instructions or comparable procedure (21 CFR 606.60(a)). Calibration of equipment must be performed according to a predetermined and routine schedule as specified in a SOP (21 CFR 606.100(b)(15)).

b. Dosage and Time to Deliver Dose

- i. The dose of irradiation delivered should be 2500 cGy targeted to the central portion of the container and the minimum dose should be 1500 cGy at any other point.
- ii. The time required to deliver the dose should be based on the radiation intensity of the source. The decay of the source should be calculated according to manufacturer's instructions. FDA currently recommends recalibration of the source annually for Cesium-137 and semi-annually for Cobalt-60. The procedure for calculating decay, included in the operator's manual for the irradiator, may be referenced in the SOP.
- iii. The SOP should indicate the maximum number of units of blood or blood components that can be irradiated at one time. This is

a batch and may be dictated by the device manufacturer's procedure and based on the firm's validation data.

- iv. At no time should the total irradiation dose exceed 5000 cGy to any portion of the container.

c. Indicators

An irradiation indicator should be used with each irradiated batch. There should be procedures for the quality control of the indicator system in use which should include, but are not limited to: storage of indicator, verification that the indicator has not been exposed to unacceptable temperatures, and explanation of expected results for each new lot (comparison with the old lot) and corrective action. There must be documentation of such quality control (21 CFR 606.160).

d. Labeling

- i. The immediate container of blood and blood components that has been irradiated should be permanently labeled as irradiated. Applicants must submit labels to CBER for review and approval (21 CFR 606.120(b)(1)).^{2,3}
- ii. Only FDA approved product names and codes shall be used (21 CFR 606.121(c)(1)).

e. Dating Period

- i. The dating period for red blood cell products should not be more than 28 days from the date of irradiation, but should not exceed the dating period of the original product.
- ii. The dating period for platelet and plasma products need not change after irradiation since they are not adversely affected by irradiation.

² Tie-tags and indicators are not appropriate labels for irradiated blood and blood components since the product label, which includes the word "Irradiated," is to be a permanent label attached directly to the product.

³ The special message label, i.e. the purple label referenced in the Uniform Guidelines for the Labeling of Blood and Blood Components 1985, is no longer an appropriate label because the current product labels now must include the word "Irradiated."

2. Quality Assurance (QA)

For the pilot program, the following procedures should be used to validate the irradiation system:

a. Process Validation

- i. Blood component irradiation must be validated (21 CFR 211.100). Validation should include measuring the amount of irradiation absorbed by the product, including all load configurations, using predetermined parameters.
- ii. Validation should be performed on a fully loaded canister to obtain the maximum and minimum dose of irradiation to which the blood and blood components will be subjected.
- iii. Validation is performed using a dosimetry system.

The dosimetry system should provide a dose map. In the scientific literature there are discussions regarding dosimetry systems in current use. (Ref. 8)

The medium for dosimetry should be one that closely resembles blood, e.g., water or some types of acrylic. (Ref. 9)

The dose map should be reviewed and retained in the records.

A test run should be performed three (3) times on load configurations using blood products to verify that the validation parameters are met.

The process should monitor the temperature of the blood products during the irradiation procedure to ensure that the time the blood products spend out of a controlled environment is limited to prevent the warming of the red cell products above 10°C and platelet products above 24°C.

b. Quality Control (QC)

- i. Equipment used in the production of irradiated blood components must have routine quality control testing performed on a scheduled basis (21 CFR 606.140(b)). The QC must, at a minimum, follow the manufacturer's instructions (21 CFR 606.60(a)).

ii. Each day of use

The timer on the irradiator should be compared visually against the back-up timer if available or with a certified stopwatch if there is not a back-up timer, and the results of the comparison should be documented.

If a moving turntable is part of the equipment, a visual check of the turntable should be made to determine that it is rotating. Observations should be documented.

iii. Monthly

If the irradiator in use has a backup timer, the two timers should be checked monthly using a certified National Institute of Standards and Technology (NIST) stop watch. Observations should be documented.

iv. Periodically

Although blood irradiators are considered safe, facilities should periodically check for radiation leakage with a Geiger counter or using a wipe test. (Ref. 7-8)

3. Recordkeeping

Records must be maintained according to 21 CFR 606.160.

- i. Records must document the significant steps in the irradiation of each component including identification number and quality assurance personnel, and these records should be reviewed by

quality assurance.

- ii. The duration of the irradiation procedure must be recorded.
- iii. The dose of irradiation must be indicated for each batch.
- iv. The identity of the person performing the irradiation must be indicated.
- v. The date, time and site of the irradiation must be recorded.

B. IRRADIATION PERFORMED BY AN OUTSIDE CONTRACTOR

1. Standard Operating Procedure

- a. The blood establishment should establish and maintain procedures to ensure that any outside contractor has appropriate SOPs in place and performs manufacturing steps according to the blood establishment's specifications. The blood establishment should also establish and maintain procedures to ensure that the contractor meets the requirements of the regulations.
- b. The SOPs and records of both the blood establishment and the outside contractor should be consistent with Section A of this document.
- c. If irradiation of blood and blood components is performed by an outside contractor, each party must have SOPs specifying those steps performed by the blood establishment as well as those performed by the outside contractor (21 CFR 606.100(b)).

2. Registration and Regulatory Responsibilities

Since the contract facility is performing a manufacturing step, it must be registered with FDA (21 CFR 607.7(a)). The applicant should identify and have evidence of registration of the contractor. All contract facilities are subject to FDA inspection and all applicable cGMP regulations (21 CFR 600.20; 21 CFR Parts 606, 210, and 211).

3. Agreement

There should be a written agreement between the applicant and the outside contractor that outlines the responsibilities of each party to the agreement.

V. GLOSSARY

Applicant: Any legal person or entity who has submitted an application to manufacture a product subject to licensure under section 351 of the Public Health Service Act (42 U.S.C. 262).

Contractor: Any person or entity, not the applicant, who performs part or all of the manufacturing of the licensed product at the request of the applicant. The applicant assures the contractor's compliance with the applicable product and establishment standards. Both the applicant and the contractor are legally responsible for the work performed by the contractor.

Component: That part of a single-donor unit of blood separated by physical or mechanical means (21 CFR 606.3(c)).

CFR: Code of Federal Regulations.

Current Good Manufacturing Practice (cGMP): Methods used in, and the facilities or controls used for, the manufacture, processing, packing, or holding of a drug including, but not limited to, blood products, to assure that such product meets the requirements of the Federal Food, Drug and Cosmetic Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess (See FD&C Act, Sec. 501(a)(2)(B)). cGMP ensures products are consistently manufactured and controlled by quality standards appropriate to their intended use. It encompasses both manufacturing and quality control/quality assurance procedures.

Dose Map: Measures the delivery of radiation within a simulated blood component or over an area in which the blood component is placed.

Dosimetry: A system used for determining absorbed dose, consisting of dosimeters, measurement instruments and their associated reference standards, and procedures for the system's use.

Validation: Establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes.

Qualification: Establishing confidence that process equipment, reagents, and ancillary systems are capable of consistently operating within established limits and tolerances. Process performance qualification is intended to establish confidence that the process is effective and reproducible.

Quality Assurance (QA) Program: An organization's comprehensive system for manufacturing safe, effective, and quality products according to regulatory standards. This program includes preventing, detecting, and correcting deficiencies that may compromise product quality.

Quality Control/Quality Assurance (QC/QA) unit: One or more individuals designated by, and reporting directly to, management with defined authority and responsibility to assure that all quality assurance policies are carried out in the organization.

Quality Control (QC): A component of a QA program that includes the activities and controls used to determine the accuracy and reliability of the establishment's personnel, equipment, reagents, and operations in the manufacturing of blood components including testing and product release.

VI. REFERENCES

1. Juji, T., Takahashi, T. Report for Blood Research Project. Tokyo: 1986.
2. Otsuka, S., Kunieda, K., Mirose, M., et al. Fatal erythroderma (suspected graft-versus-host disease) after cholecystectomy: retrospective analysis. *Transfusion* 1989; 29:544-548.
3. Sakakibara, T., Ida, T., Mannouji, E., et al. Post-transfusion graft-versus-host disease following open heart surgery: Report of six cases. *J Cardiovasc Surg* 1989; 30:687-691.
4. Thaler, M., Shamiss, A., Orgad, S., et al. The role of blood from HLA-homozygous donors in fatal transfusion-associated graft-versus-host disease after open heart surgery. *New Eng J Med* 1989; 321:25-28.
5. Anderson, K.C., Weinstein, H.J. Transfusion associated graft-versus-host-disease. *New Eng J Med* 1990; 323:315-321.
6. Leitman, S.F., Holland, P.V. Irradiation of blood products. *Transfusion* 1985; 25:293-303.
7. Akahoshi, M., Takanashi, M., Masuda, M., et al. A case of transfusion-associated graft-versus-host disease not prevented by white cell-reduction filters. *Transfusion* 1992; 32:169-172.
8. Moroff, G. and Luban, N.L.C. The irradiation of blood and blood components to prevent graft-versus-host disease: technical issues and guidelines. *Transfus Med Rev* Jan 1997; 11(1):15-26.
9. Leitman, S.F. Dose, dosimetry, and quality improvement of irradiated blood products. *Transfusion* 1993; 33(6):447-449.