referred to in Boeing Alert Requirements Bulletin B787–81205–SB270055–00 RB, Issue 002, dated November 25, 2024.

(m) Terminating Action

Accomplishing the actions required by paragraph (l) of this AD terminates the requirements of paragraphs (g), (i), and (j) of this AD for that airplane. After all affected airplanes in an operator's fleet have complied with paragraph (l) of this AD, the AFM revision required by paragraph (i) of this AD may be removed and the maintenance or inspection program revision required by paragraph (j) of this AD may be removed.

(n) Exceptions to Requirements Bulletin Specifications

Where the Compliance Time column of the tables in the ''Compliance'' paragraph of Boeing Alert Requirements Bulletin B787–81205–SB270055–00 RB, Issue 002, dated November 25, 2024, refers to the Issue 001 date of Requirements Bulletin B787–81205–SB270055–00 RB, this AD requires using the effective date of this AD.

(o) Credit for Previous Actions

This paragraph provides credit for the actions specified in paragraph (l) of this AD, if those actions were performed before the effective date of this AD using Boeing Alert Requirements Bulletin B787–81205–SB270055–00 RB, Issue 001, dated December 12, 2023.

(p) Alternative Methods of Compliance (AMOCs)

(1) The Manager, AIR–520, Continued Operational Safety Branch, FAA, has the authority to approve AMOCs for this AD, if requested using the procedures found in 14 CFR 39.19. In accordance with 14 CFR 39.19, send your request to your principal inspector or responsible Flight Standards Office, as appropriate. If sending information directly to the manager of the Continued Operational Safety Branch, send it to the attention of the person identified in paragraph (q)(1) of this AD. Information may be emailed to: *AMOC@faa.gov.* Before using any approved AMOC, notify your appropriate principal inspector, or lacking a principal inspector, the manager of the responsible Flight Standards Office.

(2) An AMOC that provides an acceptable level of safety may be used for any repair, modification, or alteration required by this AD if it is approved by The Boeing Company Organization Designation Authorization (ODA) that has been authorized by the Manager, AIR–520, Continued Operational Safety Branch, FAA, to make those findings. To be approved, the repair method, modification deviation, or alteration deviation must meet the certification basis of the airplane, and the approval must specifically refer to this AD.

(3) AMOCs approved for AD 2019–20–07 are approved as AMOCs for the corresponding provisions of paragraphs (g), (i), and (j) of this AD.

(q) Additional Information

(1) For more information about this AD, contact Emanuel Chaves Torres, Aviation Safety Engineer, FAA, 2200 South 216th St., Des Moines, WA 98198; phone: 562–627–5350; email: *emanuel.chaves.torres@faa.gov.*

(2) Material identified in this AD that is not incorporated by reference is available at the address specified in paragraph (r)(5) of this AD.

(r) Material Incorporated by Reference

(1) The Director of the Federal Register approved the incorporation by reference (IBR) of the material listed in this paragraph under 5 U.S.C. 552(a) and 1 CFR part 51.

(2) You must use this material as applicable to do the actions required by this AD, unless this AD specifies otherwise.

(3) The following material was approved for IBR on [DATE 35 DAYS AFTER PUBLICATION OF THE FINAL RULE].

(i) Boeing Alert Requirements Bulletin B787–81205–SB270055–00 RB, Issue 002, dated November 25, 2024.

(ii) [Reserved]

(4) The following material was approved for IBR on October 11, 2019 (84 FR 54765, October 11, 2019).

(i) Boeing Alert Requirements Bulletin B787–81205–SB270051–00 RB, Issue 001, dated July 5, 2019.

(ii) [Reserved]

(5) For Boeing material identified in this AD, contact Boeing Commercial Airplanes, Attention: Contractual & Data Services (C&DS), 2600 Westminster Blvd., MC 110–SK57, Seal Beach, CA 90740–5600; telephone 562–797–1717; website *myboeingfleet.com.*

(6) You may view this material at the FAA, Airworthiness Products Section, Operational Safety Branch, 2200 South 216th St., Des Moines, WA. For information on the availability of this material at the FAA, call 206–231–3195.

(7) You may view this material at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, visit *www.archives.gov/federal-register/cfr/ibr-locations* or email *fr.inspection@nara.gov.*

Issued on March 12, 2026.

Lona C. Saccomando,

Acting Deputy Director, Integrated Certificate Management Division, Aircraft Certification Service.

[FR Doc. 2026–05327 Filed 3–17–26; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 892

[Docket No. FDA–2025–N–5996]

RIN 0910–AI93

Medical Devices; Radiology Devices; Classification of Blood Irradiators

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to classify blood irradiator devices (product code MOT), unclassified preamendments devices, as follows: blood irradiator devices intended to prevent transfusion-associated graft-versus-host disease into class II (special controls) with premarket notification and blood irradiator devices intended to prevent metastasis into class III (premarket approval) to provide a reasonable assurance of safety and effectiveness of these devices. Elsewhere in this issue of the **Federal Register**, FDA is issuing a proposed order proposing to require the filing of a premarket approval application for blood irradiator devices intended to prevent metastasis.

DATES: Either electronic or written comments on the proposed rule must be submitted by May 18, 2026.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. The *https://www.regulations.gov* electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of May 18, 2026. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are received on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal: https://www.regulations.gov.* Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to *https://www.regulations.gov* will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on *https://www.regulations.gov.*
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see ''Written/Paper Submissions'' and ''Instructions'').

Written/Paper Submissions

Submit written/paper submissions as follows:

- *Mail/Hand Delivery/Courier (for written/paper submissions):* Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in ''Instructions.''

Instructions: All submissions received must include the Docket No. FDA–2025–N–5996 for ''Medical Devices; Radiology Devices; Classification of Blood Irradiators.'' Received comments, those filed in a timely manner (see **ADDRESSES**), will be placed in the docket and, except for those submitted as ''Confidential Submissions,'' publicly viewable at *https://www.regulations.gov* or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240–402–7500.

- Confidential Submissions—To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states ''THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.'' The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on *https://www.regulations.gov.* Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as ''confidential.'' Any information marked as ''confidential'' will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: *http://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf.*

Docket: For access to the docket to read background documents, the plain language summary of the proposed rule of not more than 100 words as required by the ''Providing Accountability Through Transparency Act,'' or the electronic and written/paper comments received, go to *https://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the ''Search'' box and follow the prompts, and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240–402–7500.

FOR FURTHER INFORMATION CONTACT: Julie Sullivan, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 3658, Silver Spring, MD 20993–0002, 240–402–4973, *Julie.Sullivan@fda.hhs.gov.*

SUPPLEMENTARY INFORMATION:

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I. Executive Summary

A. Purpose of the Proposed Rule

FDA (Agency or we) is proposing to classify blood irradiator devices, which are unclassified, preamendments devices, into two classes based on intended use. FDA proposes to classify blood irradiator devices intended to irradiate blood and blood products to prevent transfusion-associated graft-versus-host disease (blood irradiators intended to prevent TA–GVHD), including those intended to inactivate leukocytes and/or lymphocytes to prevent TA–GVHD, into class II (special controls). Under this proposed rule, blood irradiators intended to prevent TA–GVHD would be subject to premarket notification to provide a reasonable assurance of safety and effectiveness of these devices. FDA proposes to classify blood irradiator devices intended to irradiate intraoperatively salvaged blood of cancer patients undergoing surgery to prevent metastasis (blood irradiators intended to prevent metastasis) into class III (premarket approval). A blood irradiator is a prescription device used to deliver a controlled radiation dose to blood or blood products. Blood and blood products in containers, such as blood bags, are placed inside a canister(s) that is loaded into the exposure chamber for irradiation. The radiation dose from blood irradiators intended to prevent TA–GVHD is intended to inactivate viable leukocytes, including lymphocytes, prior to transfusion to prevent TA–GVHD. While TA–GVHD is a rare complication of transfusion, in patients who develop TA–GVHD, it is fatal in the majority of affected patients. The radiation dose from blood irradiators intended to prevent metastasis is intended to result in damage of tumor cells. Blood irradiators within the scope of this proposed rule include an x-ray tube or a radionuclide sealed radiation source (*e.g.,* Cobalt-60 or Cesium-137). FDA currently regulates these unclassified devices as devices that require premarket notification (510(k)), with product code MOT.[1] FDA intends to create a separate product code for blood irradiators intended to prevent metastasis upon finalization of this classification action.[2]

FDA initiated the classification of blood irradiators by consulting the Radiological Devices Advisory Panel at a meeting held on April 12, 2012 (2012 Panel) (Ref. 1). The 2012 Panel recommended that blood irradiators intended to prevent TA–GVHD be classified into class II, because the 2012 Panel believed that general and special controls would provide reasonable

[1] FDA uses product codes to help categorize and assure consistent regulation of medical devices. A product code consists of three characters that are assigned at the time a product code is generated and is unique to a product type. The three characters carry no other significance and are not an abbreviation.

[2] See ''Medical Device Classification Product Codes—Guidance for Industry and FDA Staff,'' available at: *https://www.fda.gov/regulatory-information/search-fda-guidance-documents/medical-device-classification-product-codes-guidance-industry-and-food-and-drug-administration-staff.*

assurance of the safety and effectiveness of these devices. The materials considered by the 2012 Panel noted that one device had been cleared at the time for the prevention of metastasis, but the 2012 Panel did not issue a recommendation as to the classification of blood irradiators intended to prevent metastasis.

FDA initiated the classification of blood irradiators intended to prevent metastasis by consulting the Radiological Devices Advisory Panel at a meeting held on November 7, 2023 (2023 Panel) (Ref. 2). The 2023 Panel recommended that blood irradiators intended to prevent metastasis be classified into class III. The 2023 Panel consensus was that insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of safety and effectiveness of these devices, and blood irradiators intended to prevent metastasis present a potential unreasonable risk of illness or injury.

FDA conducted its own analyses of information from the 2012 and 2023 Panels (Refs. 1 and 2), including risks identified in the Center for Biologics Evaluation and Research (CBER) July 1993 memorandum ''Recommendations Regarding License Amendments and Procedures for Gamma Irradiation of Blood Products'' (CBER Memorandum) (Ref. 3); postmarket data regarding blood irradiators with product code MOT; adverse event reports in FDA's Manufacturer and User Facility Device Experience (MAUDE) database and Medical Device Report (MDR) database; information in CDRH's Medical Device Recalls database, and published scientific literature, as further described below. Based upon the analyses, FDA agrees with the recommendations of the 2012 Panel and the 2023 Panel. As such, FDA is proposing a split classification for blood irradiators.

FDA is proposing to classify blood irradiators intended to prevent TA–GVHD, including those intended to inactivate leukocytes and/or lymphocytes to prevent TA–GVHD, into class II (special controls). FDA is proposing this action based on the determination that general controls alone are not sufficient to provide reasonable assurance of the safety and effectiveness of blood irradiators intended to prevent TA–GVHD, and there is sufficient information to establish special controls, in combination with general controls, to provide such assurance. Under this proposal, premarket notification for blood irradiators intended to prevent TA–GVHD would be required.

Additionally, manufacturers may wish to use predetermined change control plans (PCCPs) as a way to implement future modifications to their devices without needing to submit a new 510(k) for each significant change or modification [3] while continuing to provide a reasonable assurance of device safety and effectiveness.[4] FDA reviews a PCCP as part of a marketing submission for a device to ensure the continued safety and effectiveness of the device without necessitating additional marketing submissions for implementing each modification described in the PCCP.

FDA is proposing to classify blood irradiators intended to prevent metastasis into class III (premarket approval). FDA is proposing this classification as FDA believes that insufficient information exists to determine that general controls and special controls would provide reasonable assurance of safety and effectiveness for blood irradiators intended to prevent metastasis, and that these devices present a potential unreasonable risk of illness or injury. FDA is also proposing, by proposed order published elsewhere in this issue of the **Federal Register**, to require the filing of a premarket approval application (PMA) for blood irradiators intended to prevent metastasis.

B. Summary of the Major Provisions of the Proposed Rule

This rule proposes to classify unclassified, preamendments blood irradiators: blood irradiators intended to prevent TA–GVHD, including those intended to inactivate leukocytes and/or lymphocytes to prevent TA–GVHD, and blood irradiators intended to prevent metastasis. The proposed rule, if finalized, would establish the identification and classification for these blood irradiator devices. The proposed classification action proposes to classify blood irradiators intended to prevent TA–GVHD into class II as well as establish the special controls necessary to provide reasonable assurance of the safety and effectiveness of these devices. Under this proposed rule, premarket notification would be required for blood irradiators intended to prevent TA–GVHD. The proposed classification action proposes to classify blood irradiators intended to prevent metastasis into class III and require filing of a PMA. These proposed classification regulations, if finalized, would identify these blood irradiator devices as intended for prescription use.

C. Legal Authority

The Agency is proposing this classification under the authority of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 301 *et seq.*). Specifically, the relevant authority related to the proposed classification includes section 513(a) through (d) of the FD&C Act (21 U.S.C. 360c(a) through (d)), regarding device classes, classification, and panels and section 515 (21 U.S.C. 360e) regarding PMAs; and section 701(a) of the FD&C Act (21 U.S.C. 371(a)).

D. Costs and Benefits

The proposed rule, if finalized, would classify blood irradiators (unclassified, preamendments devices) into two classes based on intended use. It would classify blood irradiators intended to prevent TA–GVHD into class II (special controls) and blood irradiators intended to prevent metastasis into class III (premarket approval). Separately, FDA also is issuing a proposed order requiring the filing of a PMA for blood irradiators intended to prevent metastasis. Quantified benefits of the proposed rule, if finalized, would consist of cost savings to industry and FDA from a reduction in the quantity and time burden of informal inquiries related to blood irradiators intended to prevent TA–GVHD. We also estimate cost savings to industry and FDA from a reduction in the number of 510(k) submissions necessitating requests for additional information from FDA before and during review. Industry and FDA could incur costs associated with premarket approval applications for current and future blood irradiators intended to prevent metastasis. We additionally quantify one-time costs to industry to read and understand the proposed rule and the proposed order requiring the filing of a PMA, as well as one-time costs to industry to revise labeling. We estimate that the annualized benefits over 10 years would range from $84 to $180,268 at a 7 percent discount rate, with a primary

[3] For the purpose of this proposed rule reference to ''modification'' means a significant change or modification that would generally require a new premarket notification under 21 CFR 807.81(a)(3).

[4] Section 3308 of the Food and Drug Omnibus Reform Act of 2022, Title III of Division FF of the Consolidated Appropriations Act, 2023, Public Law 117–328 (''FDORA''), enacted on December 29, 2022, added section 515C ''Predetermined Change Control Plans for Devices'' to the Federal Food, Drug, and Cosmetic Act (FD&C Act). Section 515C has provisions regarding predetermined change control plans (PCCPs) for devices requiring premarket approval or premarket notification. Under section 515C, supplemental applications (section 515C(a)) and new premarket notifications (section 515C(b)) are not required for a change to a device that would otherwise require a premarket approval supplement or new premarket notification if the change is consistent with a PCCP approved or cleared by FDA.

estimate of $90,176, and from $86 to $184,271 at a 3 percent discount rate, with a primary estimate of $92,178. The annualized costs would range from $0.68 million to $1.51 million at a 7 percent discount rate, with a primary estimate of $1.07 million, and from $0.66 million to $1.53 million at a 3 percent discount rate, with a primary estimate of $1.07 million.

II. Table of Abbreviations/Commonly Used Acronyms in This Document

Abbreviation/acronym	What it means
510(k)	Premarket Notification.
ARO	Accidental Radiation Occurrence.
CBER	Center for Biologics Evaluation and Research.
CDRH	Center for Devices and Radiological Health.
CFR	Code of Federal Regulations.
FDA	Food and Drug Administration.
FD&C Act	Federal Food, Drug, and Cosmetic Act.
Gy	Gray.
MAUDE	Manufacturer and User Facility Device Experience database.
MDR	Medical Device Report.
NRC	Nuclear Regulatory Commission.
PCCP	Pre-Determined Change Control Plan.
PMA	Premarket Approval Application.
Ref.	Reference.
TA–GVHD	Transfusion-Associated Graft-Versus-Host Disease.
U.S.C.	United States Code.

III. Background

A. Need for the Regulation

After the enactment of the 1976 Medical Device Amendments, FDA undertook an effort to identify and classify all preamendments devices in accordance with section 513(d) of the FD&C Act (21 U.S.C. 360c(d)). Section 513(b) of the FD&C Act (21 U.S.C. 360c(b)) requires FDA to classify all preamendments devices into class I, II, or III. Currently, blood irradiators, product code MOT, are unclassified devices subject to premarket notification (510(k)) under section 510(k) of the FD&C Act (21 U.S.C. 360(k)). Marketing of a new device within an unclassified device type requires FDA clearance of a 510(k). As described below, available records indicate FDA granted the first clearance of a blood irradiator intended to prevent TA–GVHD (K837346) in 1983 based on documentation that demonstrated that these devices are substantially equivalent to device(s) of the same type that were in commercial distribution prior to passage of the Medical Device Amendments on May 28, 1976. On May 26, 2005, FDA cleared the Raycell X-ray Blood Irradiator device (K051065). The Raycell X-ray Blood Irradiator is the first device to include, in addition to an intended use for the prevention of TA–GVHD, a second intended use for the prevention of metastasis.[5] To date, FDA has cleared a total of 16 devices under product code MOT. Two of the devices are cleared with dual intended uses to prevent TA–GVHD and to prevent metastasis.

FDA agrees with the 2012 Panel that general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness of blood irradiators intended to prevent TA–GVHD, and sufficient information exists to establish special controls to adequately mitigate the risks to health and provide reasonable assurance of safety and effectiveness of this device. FDA is proposing to classify blood irradiators intended to prevent TA–GVHD into class II. FDA agrees with the 2023 Panel that insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of safety and effectiveness for blood irradiators intended to prevent metastasis, and that the device presents a potential unreasonable risk of illness or injury. FDA is proposing to classify blood irradiators intended to prevent metastasis into class III.

B. FDA's Current Regulatory Framework

The FD&C Act (21 U.S.C. 301 *et seq.*), as amended by the Medical Device Amendments of 1976 (1976 amendments) (Pub. L. 94–295), established a comprehensive system for the regulation of medical devices intended for human use. Section 513 of the FD&C Act (21 U.S.C. 360c) established three classes of devices, reflecting the regulatory controls needed to provide reasonable assurance of their safety and effectiveness: class I (general controls), class II (special controls), and class III (premarket approval).

Section 513(a)(1) of the FD&C Act (21 U.S.C. 360c(a)(1)) defines the three classes of devices. Class I devices are those devices for which the general controls of the FD&C Act (controls authorized by or under sections 501, 502, 510, 516, 518, 519, or 520 of the FD&C Act (21 U.S.C. 351, 352, 360, 360f, 360h, 360i, or 360j) or any combination of such sections) are sufficient to provide reasonable assurance of safety and effectiveness; or those devices for which insufficient information exists to determine that general controls are sufficient to provide reasonable assurance of safety and effectiveness or to establish special controls to provide such assurance, but because the devices are not purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, and do not present a potential unreasonable risk of illness or injury, are to be regulated by general controls (section 513(a)(1)(A) of the FD&C Act.

Class II devices are those devices for which general controls by themselves are insufficient to provide reasonable assurance of safety and effectiveness, but for which there is sufficient information to establish special controls to provide such assurance, including the promulgation of performance standards, postmarket surveillance, patient registries, development and dissemination of guidelines, recommendations, and other appropriate actions the Agency deems necessary to provide such assurance (section 513(a)(1)(B) of the FD&C Act).

[5] The Raycell X-ray Blood Irradiator device was found to be substantially equivalent to a previously cleared device that has an intended use for the prevention of TA–GVHD only. At this time, FDA does not have records identifying a preamendments device with an intended use other than to prevent TA–GVHD. As reflected in this NPRM, and for the reasons described in Sections V.B–C of this preamble, FDA is proposing to separately classify these two device types.

Class III devices are those devices for which insufficient information exists to determine that general controls (controls authorized by or under sections 501, 502, 510, 516, 518, 519, or 520 of the FD&C Act or any combination of such sections) and special controls would provide a reasonable assurance of safety and effectiveness, and are purported or represented for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, or present a potential unreasonable risk of illness or injury (section 513(a)(1)(C) of the FD&C Act.

FDA refers to devices that were in commercial distribution before the 1976 amendments as ''preamendments devices.'' The procedures for classification of such devices are prescribed in sections 513(b)–(d) of the FD&C Act (21 U.S.C. 360c(b)–(d)). FDA classifies these devices after the Agency has: (1) received a recommendation from the appropriate device classification panel (which are part of the FDA Medical Devices Advisory Committee); (2) published the panel's recommendation and a proposed regulation classifying the device for comment; and (3) published a final regulation classifying the device (section 513(d)(1) of the FD&C Act. FDA has classified most preamendments devices under these procedures.

A preamendments device that has been classified into class III only requires premarket notification and not approval of a PMA until FDA issues a final order under section 515(b) of the FD&C Act (21 U.S.C. 360e(b)) requiring premarket approval. FDA is also proposing, by proposed order published elsewhere in this issue of the **Federal Register**, to require the filing of a PMA for blood irradiators intended to prevent metastasis.

Blood irradiators that include an x-ray source are radiation-emitting electronic products and, accordingly, also are subject to the Electronic Product Radiation Control requirements of the FD&C Act (sections 531 through 542 (21 U.S.C. 360hh through 360ss)) (originally enacted as the Radiation Control for Health and Safety Act of 1968), and its implementing regulations. This includes compliance with certain performance standards found in 21 CFR 1020.40 for cabinet x-ray systems, pursuant to the authority found in section 534 of the FD&C Act (21 U.S.C. 360kk). A blood irradiator that includes an x-ray source meets the definition of a cabinet x-ray system found in 21 CFR 1020.40(b)(3) because it consists of an x-ray tube installed in an enclosure intended to contain at least that portion of material, in this case blood or blood components, being irradiated, provides radiation attenuation, and excludes personnel from its interior during generation of x radiation.

Blood irradiators that include a radionuclide sealed radiation source (sealed radiation source) may be subject to regulatory requirements of the Nuclear Regulatory Commission (NRC) pursuant to its authority under the Energy Reorganization Act of 1974 (42 U.S.C. 5801 *et seq.*).

C. History of This Rulemaking

As previously described, blood irradiator devices are unclassified, preamendments devices. These devices have been subject to premarket review through a 510(k) submission and have been cleared for marketing if FDA found the device to be substantially equivalent to a legally marketed predicate in accordance with section 513(i) of the FD&C Act (21 U.S.C. 360c(i)). FDA has cleared a total of 16 devices within the scope of this classification action. Consistent with the FD&C Act, FDA convened the Radiological Devices Advisory Panel at two meetings regarding the classification of blood irradiators.

1. 2012 Radiological Devices Advisory Panel

On April 12, 2012, FDA convened the 2012 Panel to secure recommendations regarding risks and benefits presented by blood irradiators as well as the appropriate classification and regulatory controls that should apply to this device type (Ref. 1). At the meeting, FDA requested that the 2012 Panel consider whether blood irradiators intended to prevent TA–GVHD fit the statutory definition for a class II device. The 2012 Panel considered the information about this device type provided by FDA, including results and analysis from a literature search and search of known adverse events (Ref. 1). The 2012 Panel considered both types of blood irradiators intended to prevent TA–GVHD: the x-ray tube blood irradiators and the sealed radiation source blood irradiators. The 2012 Panel did not issue a recommendation as to the classification of blood irradiators intended to prevent metastasis.

At the 2012 Panel meeting, FDA presented information on the identified risks to health and proposed mitigation measures for blood irradiators intended to prevent TA–GVHD. FDA-identified risks to health included improper radiation dose to blood or blood products, radiation exposure to the user, and electric shock. FDA proposed mitigation measures for the identified risks to health, which included premarket review of indications for use and design specifications, and compliance with the CBER Memorandum (Ref. 3). The CBER Memorandum provides recommendations to blood establishments on manufacturing, quality control procedures, labeling and other aspects of manufacturing irradiated blood and blood products. FDA also suggested in 2012 Panel materials, as a mitigation for certain risks to health, compliance with NRC regulations and certain regulations of states that have entered into agreements with NRC that govern radioactive isotopes and their safe use (collectively referred to in the remainder of this proposed rule as ''NRC regulations''), which would apply to blood irradiators that use a sealed radiation source. During the 2012 Panel meeting, FDA presented the additional risk of damage to blood or blood components from radiation. This risk is associated with a shorter shelf life for irradiated blood and blood components, as noted in the CBER Memorandum and discussed at the 2012 Panel.

The 2012 Panel agreed with the FDA-identified risks to health associated with blood irradiators intended to prevent TA–GVHD. Several of the 2012 Panel members suggested additional risks of mechanical or crush injury from door closure and dose inhomogeneity. For dose inhomogeneity, multiple Panel members expressed a concern that a large dose inhomogeneity could result in the blood or blood product receiving an ineffective dose of radiation. The main concern was the ability to deliver 25 gray (Gy) of radiation targeted to the central portion of the container and to achieve a 15 Gy minimum dose at any other point within the container, as recommended in the CBER Memorandum, for all contents in the irradiation exposure chamber for all possible fillings. Several of the 2012 Panel members also expressed concern for safety and security in terms of using the device and adequate training of personnel. FDA has interpreted concerns about safety and security to be about operator error and lack of safety controls on the device to protect against exposure to the radiation source. There was some disagreement among the 2012 Panel members as to whether manufacturer-provided personnel training should be a special control because of the challenge it puts on manufacturers and on facilities' ability to perform their own training.

The 2012 Panel members suggested that the risks to health associated with improper radiation dose, including not

achieving minimum dosing throughout the irradiated blood and blood components due to dose inhomogeneity, could be mitigated by performance standards and design controls (Ref. 1, 2012 Panel transcript at 187–189). FDA interprets this discussion to mean performance testing to demonstrate that the device performs as intended under anticipated conditions of use, and certain labeling information. For dose inhomogeneity, the 2012 Panel members also recommended periodic demonstration of the dose uniformity and a recommended dosimetric evaluation interval. Based upon the 2012 Panel discussion, FDA interprets periodic demonstration of the dose uniformity at recommended intervals to mean the inclusion of a recommended quality assurance program by the manufacturer, that manufacturers provide information about dosimetric distribution measured both in air and with the canister or exposure chamber filled with water, and that manufacturers provide information about decay and residual strength of the sealed radiation source, where applicable. The 2012 Panel also suggested some indication of dose rate and a manufacturer provided method for identifying if the proper dose of radiation is delivered. To mitigate against the risk of exposure to the sealed radiation source, which may be caused by operator error or lack of safety controls on the device, the 2012 Panel suggested adding a special control requiring safety and security that limits who can operate the device. Some of the 2012 Panel-recommended mitigations were suggested by the CBER Memorandum.

The consensus of the 2012 Panel was that class I (general controls) alone would not be adequate to provide a reasonable assurance of safety and effectiveness for blood irradiators intended to prevent TA–GVHD and that special controls could be identified. The 2012 Panel agreed that the CBER Memorandum, although intended for blood establishments manufacturing irradiated blood products, provided a good resource to develop special controls for both sealed radiation source and x-ray source devices. The 2012 Panel noted that blood irradiators are an established technology to prevent TA–GVHD in transfused patients, and that blood establishments' implementation of the recommendations in the CBER Memorandum, together with the performance standards found in 21 CFR 1020.40 for cabinet x-ray systems, which would include x-ray source blood irradiators, had resulted in few published problems and no reported adverse events in literature over a long period of time when the device was used at the CBER recommended dosage level. The 2012 Panel recommended that blood irradiators intended to prevent TA–GVHD be classified into class II to provide reasonable assurance of safety and effectiveness of these devices.

FDA tentatively agrees with the 2012 Panel's recommendation that general controls and special controls are needed to provide reasonable assurance of safety and effectiveness of blood irradiators intended to prevent TA–GVHD and that this device be classified into class II. General controls are insufficient to provide reasonable assurance of safety and effectiveness of this device type based on the fatal nature of TA–GVHD and risk of the disease if the radiation exposure does not inactivate the lymphocytes present in the blood. Identification of the dose of radiation necessary to inactivate lymphocytes, pre-market data requirements showing that the blood irradiator is capable of delivering this radiation dose to the blood and blood components, and labeling requirements including required quality control processes are necessary to mitigate the identified risks to health. Accordingly, FDA is proposing to classify blood irradiators intended to prevent TA–GVHD into class II (special controls).

2. 2023 Radiological Devices Panel of the Medical Devices Advisory Committee

On November 7, 2023, FDA convened the 2023 Panel to make recommendations regarding the risks and benefits presented by blood irradiators intended to prevent metastasis as well as the appropriate classification and regulatory controls that should apply to these devices (Ref. 2). At the meeting, FDA requested that the 2023 Panel consider whether blood irradiators intended to prevent metastasis fit the statutory definition for a class III device. The 2023 Panel considered the information provided by FDA about blood irradiators intended to prevent metastasis, including results and analysis from a literature search and search of known adverse events (Ref. 2).

During the 2023 Panel meeting, FDA presented information on the identified risks to health for blood irradiators intended to prevent metastasis as well as proposed mitigation measures. FDA identified similar risks to health related to the device hardware and software as blood irradiators intended to prevent TA–GVHD, which are similar in design and function. Specifically, these risks to health included: damage to blood components from radiation, unintended (non-therapeutic) radiation exposure to the operator and public, electric shock or burn, and mechanical or crush injury. FDA also identified unique risks to health posed by the intended use of blood irradiators intended to prevent metastasis, including presence of proliferative malignant cells in re-transfused blood due to incorrect dose or improper dose of radiation delivered, worsened control of oncologic disease or patient prognosis, and delayed or lack of re-transfusion of irradiated blood or blood component.

FDA's search of literature for blood irradiators intended to prevent metastasis for the 2023 Panel returned a limited number of articles (Ref. 2, FDA Executive Summary, Appendix D). None of the articles identified as part of the systematic literature search provided information on the safety assessment of the use of these devices for prevention of metastasis. No articles provided definitive information on the effect of salvaged blood irradiation on metastasis. Moreover, the literature showed a lack of consensus on the specific dose to use (reported doses were 25–50 Gy) to render tumor cells nonviable, and for which cancer type and surgical procedure (Ref. 2, Presentation (Classification of Blood Irradiators for the Prevention of Metastasis)). Several articles observed that blood irradiation took additional time to perform (Ref. 2, Presentation (Classification of Blood Irradiators for the Prevention of Metastasis)). At the meeting, FDA indicated that because long-term safety risks, such as the cancer outcome, patient recovery, or survival, are unclear based upon the available information, these risks to health may not be effectively mitigated by special controls. Further, based on the available information, there appears to be a lack of clinical data to demonstrate a clear clinical benefit from use of the blood irradiators intended to prevent metastasis.

The 2023 Panel agreed with the FDA-identified risks to health for blood irradiators intended to prevent metastasis. The 2023 Panel identified several additional risks to health related to the device's intended use, including: risk of induction of a new cancer due to irradiation of the blood or blood components, risk of induction of mutations in cells irradiated more than once (*i.e.,* if blood was salvaged and re-transfused multiple times during the surgical procedure), risks associated with the volume of blood that may need to be irradiated and the additional operating procedure time, and risks

associated with usability including irradiating the salvaged blood outside the operating room and the potential for blood to be incorrectly labeled or misidentified. The 2023 Panel also noted that it is unclear whether risks to health related to the device's intended use can be exhaustively identified.

The 2023 Panel consensus was that insufficient information exists to determine that class I (general controls) and class II (special controls) are sufficient to provide reasonable assurance of safety and effectiveness for blood irradiators intended to prevent metastasis. The 2023 Panel members suggested that risks to health associated with the device's hardware and software were similar to those for blood irradiators intended to prevent TA–GVHD because device function and design were the same. However, the risks to health associated with the device's intended use—for the prevention of metastasis in cancer patients receiving intraoperatively salvaged blood—could not fully be identified or mitigated with general and special controls given the very limited data available. In addition, there are uncertainties about the effective radiation dose, including whether the dose would be the same for all cancer types and all surgical procedures. Regarding the benefit and risk assessment, the 2023 Panel consensus was there is no definitive evidence showing that irradiation of intraoperatively salvaged blood is effective to prevent metastasis in patients. As a result, the risk of injury is unreasonable given the lack of probable benefit. The 2023 Panel recommended that these devices be classified into class III (premarket approval).

FDA agrees with the 2023 Panel that risks to health of blood irradiators for the prevention of metastasis cannot fully be identified or mitigated with special controls given the very limited data available and that there is a potential unreasonable risk of illness or injury for these devices given the lack of probable benefit. For the reasons stated by the 2023 Panel, FDA has tentatively determined that general controls and special controls are not sufficient to provide reasonable assurance of safety and effectiveness of blood irradiators intended to prevent metastasis. FDA is proposing that these devices be classified into class III.

IV. Legal Authority

The Agency is proposing this classification under the authority of the FD&C Act (21 U.S.C. 301 *et seq.*). Specifically, the relevant authority related to the proposed classification includes sections 513(a) through (d) of the FD&C Act (21 U.S.C. 360c(a) through (d)), regarding device classes, classification, and panels; and section 515 (21 U.S.C. 360e), regarding PMAs.

V. Description of the Proposed Rule

We are proposing to amend subpart G of 21 CFR part 892 by adding § 892.7000 to classify blood irradiators, currently categorized under the product code MOT, with sub-sections for blood irradiators intended to prevent TA–GVHD, including those intended to inactivate leukocytes and/or lymphocytes to prevent TA–GVHD, and blood irradiators intended to prevent metastasis, in accordance with section 513(d) of the FD&C Act (21 U.S.C. 360c(d)) and section 701(a) of the FD&C Act (21 U.S.C. 371).

A. Device Description

A blood irradiator is a prescription device used to deliver a controlled radiation dose to blood or blood products. Prescription devices are exempt from the requirement for adequate directions for use for the layperson under section 502(f)(1) of the FD&C Act (21 U.S.C. 352(f)(1)) and 21 CFR 801.5, as long as the conditions of 21 CFR 801.109 are met. This generic type of device may include an x-ray or a sealed radiation source. Blood irradiators intended to prevent TA–GVHD are used to deliver a controlled radiation dose to blood or blood products prior to transfusion to prevent TA–GVHD. Blood irradiators intended to prevent metastasis are used to irradiate intraoperatively salvaged blood *ex vivo* for cancer patients undergoing surgery to assist in the prevention of metastasis.

B. Risks to Health and Public Health Benefits

In evaluating the risks to health associated with use of blood irradiators intended to prevent TA–GVHD and blood irradiators intended to prevent metastasis, FDA considered information from the 2012 Panel and 2023 Panel, respectively, including risks identified in the CBER Memorandum (Ref. 3); postmarket data regarding blood irradiators with product code MOT, including adverse event reports in the MAUDE database; CDRH's Medical Device Recalls database, and the published scientific literature, some of which is discussed in FDA's executive summaries for the 2012 and 2023 Panel meetings (Refs. 1 and 2).

For blood irradiators intended to prevent TA–GVHD, in addition to the literature analysis conducted for the 2012 Panel meeting, FDA conducted literature searches on January 25, 2024, and September 23, 2024, for articles published since the 2012 Panel meeting about these devices. These literature searches identified nine additional relevant articles (Refs. 4–12). The information from the contemporary literature analyses is consistent with the findings of the prior literature analysis presented at the 2012 Panel meeting. For blood irradiators intended to prevent metastasis, in addition to the literature analysis conducted for the 2023 Panel meeting, FDA conducted a contemporary literature search on September 23, 2024, for articles published since the prior search for the 2023 Panel meeting. One new paper was identified (Ref. 13). The information from the 2024 literature analysis is consistent with the findings of the prior literature analysis presented at the 2023 Panel meeting.

FDA's search of the MAUDE and MDR databases for the 2012 and 2023 Panel meetings for product code MOT, which includes blood irradiators intended to prevent TA–GVHD and blood irradiators intended to prevent metastasis, identified five MDRs related to blood irradiators reported in MAUDE. Two MDRs contained no information, one was a suggestion for devices to include an audible alarm, and two noted low x-ray tube output that may have resulted in less than 15 Gy being delivered to all locations within the irradiation canister. No direct adverse events to patients were reported. Following these searches, FDA received one additional report describing multiple adverse events on May 14, 2024. The adverse events were related to high current safety interlock system switch failures that were reported to result in superficial (first-degree) burns. For blood irradiators intended to prevent TA–GVHD, the proposed special controls covering demonstration of appropriate functioning of safety systems, including interlocks, and electrical safety testing are designed to mitigate this risk to health. During the same time period, there were no accidental radiation occurrences (AROs) reported under 21 CFR 1002.20 for devices with product code MOT containing x-ray tubes. FDA conducted updated queries for MDRs on July 7, 2025, and for AROs on November 22, 2024 and August 4, 2025. No additional reports were identified.

FDA also reviewed recalls reported under product code MOT from November 2002 to June 22, 2025. There were two product recalls during that time period. The first recall was a class 3 recall to complete a cooling system

retrofit to preclude overheating and failure of the device. The recall was terminated May 13, 2012.[6] The second recall was a class 2 recall, for non-compliance with the associated performance standards within 21 CFR Subchapter J Radiological Health. Specifically, the device failed to comply with the performance standard for cabinet x-ray systems (21 CFR 1020.40).[7] To address this issue, the company completed repairs during annual routine preventive maintenance visits at the users' sites to minimize downtime, and the recall was terminated August 1, 2017.

1. Risks to Health and Public Health Benefits for Blood Irradiators Intended To Prevent TA–GVHD

As noted in Section III.C.1, for blood irradiators intended to prevent TA–GVHD, the 2012 Panel members suggested additional risks to health of mechanical crush and injury, dose inhomogeneity, and safety and security in terms of using the device and adequate training of personnel, which FDA has interpreted to be about operator error and a lack of safety controls to protect against exposure to the radiation source. FDA agrees that there is a risk to health of mechanical or crush injury from door closure and has added it as a separate risk category. The design of blood irradiators includes an amount of shielding sufficient to prevent radiation exposure to the operator, causing the door to be atypically heavy. FDA also agrees that dose inhomogeneity may pose a risk that not all blood and blood products placed in the device receive an effective dose of radiation. However, FDA does not believe that dose inhomogeneity needs to be added as a separate category of risk to health. Instead, FDA included this risk to health within the description of the risk of improper radiation to blood or blood products, with mitigations included in the proposed special controls to address this concern. FDA included risks to health posed by operator error and a lack of safety controls on the device within ''Improper radiation dose to blood or blood products'' and ''Unintended radiation exposure to the operator and others,'' respectively. Safety controls include device access controls that may be hardware or software controlled. FDA modified the risk category from ''Radiation exposure to the user'' to ''Unintended radiation exposure to the operator and others'' to expressly capture risk to other persons in the vicinity of the device in addition to the direct operator and to clarify that the exposure is unintended (*i.e.,* it is not part of the limited degree of radiation exposure that is anticipated and accepted when using a device that works via ionizing radiation).

Based upon the information described above, FDA identified the following risks to health for blood irradiators intended to prevent TA–GVHD:

- *Damage to blood or blood components from radiation:* Irradiation of whole blood and red blood cells causes damage to red blood cells and lymphocytes within the blood. Radiation damages the membrane of red blood cells leading to higher concentrations of potassium in plasma, hemolysis (destruction of red blood cells), and decreased red blood cell viability and survival.
- *Improper radiation dose to blood or blood products:* Failure to deliver a proper radiation dose to the intended target can result in immunologically active cells in transfused blood or blood products, which may result in TA–GVHD, which is often fatal. Delivery of an improper dose could result from multiple causes including: inability of the device to deliver 25 Gy of radiation targeted to the central portion of the container or a 15 Gy minimum dose at any other point within the container; dose inhomogeneity; malfunction of the device; lack of adequate maintenance, dosimetry or quality assurance checks; electrical fault, electromagnetic interference, or mechanical fault; or operator error causing improper dose delivery, including improper loading of the sample canister and incorrect exposure time entered into the user interface.
- *Unintended radiation exposure to the operator and others:* Device malfunction, lack of adequate maintenance, inadequate shielding, or safety control or interlock failure could allow the operator to access the radiation source resulting in physical injury and/or exposure of the operator or other nearby persons to radiation. Exposure to ionizing radiation has been shown to increase cancer risk (Ref. 14). Insufficient presence of safety controls or interlocks within irradiator design may result in unintended exposure.
- *Electrical shock:* Electrical malfunction of the device or operator contact with an energized portion may result in electrical shock or burns. This can occur when there are insufficient or malfunctioning safety controls or interlocks.
- *Mechanical crush or injury:* Blood irradiators contain shielding materials to prevent excess radiation emission outside the device causing the device itself and many components to be heavy. Operator inattention or placement of body parts where they can be impinged by the device may result in physical injury to the operator.

In evaluating benefits associated with the use of blood irradiators intended to prevent TA–GVHD, FDA considered information from the 2012 Panel regarding the classification of blood irradiators intended to prevent TA–GVHD and the published scientific literature. The information indicated that blood irradiation is an accepted method to prevent TA–GVHD by inactivation of T-lymphocytes to prevent post-transfusional proliferation and has been widely used for this purpose since the 1970s (Ref. 1, Executive Summary, Appendix A, Section III.A).

2. Risks to Health and Benefits to Public Health for Blood Irradiators Intended To Prevent Metastasis

As noted in Section III.C.2, in addition to the risks to health that FDA presented at the 2023 Panel for blood irradiators intended to prevent metastasis, Panel members suggested additional risks to health: risk of induction of a new cancer due to irradiation of the blood or blood components, risk of induction of mutations in cells irradiated more than once (*i.e.,* if blood was salvaged and re-transfused multiple times during the surgical procedure), risks associated with the volume of blood that may need to be irradiated and the additional operating procedure time, and risks associated with usability including irradiating the salvaged blood outside the operating room and the potential for blood to be incorrectly labeled or misidentified. FDA agrees with the additional risks to health identified by the 2023 Panel. However, FDA does not believe that induction of mutations in cells irradiated more than once needs to be added as a separate category of risk to health. FDA views this risk as a subset of the risk of induction of a new cancer due to the irradiation of the blood or blood components. Multiple irradiations may lead to a greater chance of a cell being damaged. Should this damage result in negative changes in the cell, the risk to the patient would be induction of a new cancer if cells are malignantly transformed. Accordingly,

[6] For details about termination of a recall see 21 CFR 7.55.

[7] A blood irradiator that includes an x-ray source meets the definition of a cabinet x-ray system found in § 1020.40(b)(3) because it consists of an x-ray tube installed in an enclosure intended to contain at least that portion of material, in this case blood or blood components, being irradiated, provides radiation attenuation, and excludes personnel from its interior during generation of x radiation.

we have included the risk of induction of mutations in cells within the description of the risk ''Induction of a new cancer due to irradiation of the blood or blood components.''

We have included the risk associated with the volume of blood that may need to be irradiated with the description of the risk to health ''Delayed or lack of re-transfusion of irradiated blood or blood components.'' Irradiation of the blood adds time to the intraoperative procedure, after salvage and filtration have occurred. Depending how much blood is removed for re-transfusion and when it is re-transfused during the procedure, irradiation may need to occur multiple times. In addition, FDA has updated the wording of the risk to health ''Damage to blood components from radiation'' to ''Damage to blood or blood components from radiation'' to better reflect the variety in the product re-transfused (*e.g.,* blood with plasma proteins and clotting factors, washed red blood cells). The term blood component was originally used to specify that it was a blood component (*i.e.,* lymphocyte or red blood cell) that was damaged by irradiation. FDA also updated the wording of the risk to health ''Unintended radiation exposure to the operator and public'' to ''Unintended radiation exposure to the operator and others'' to clearly reflect other persons who may be at risk of such exposure (*e.g.,* patients, bystanders).

Based on the information described in this Section V.B., FDA has identified the following risks to health associated with blood irradiators intended to prevent metastasis:

- *Damage to blood or blood components from radiation:* Irradiation of whole blood and red blood cells causes damage to red blood cells and lymphocytes within the blood. Radiation damages the membrane of red blood cells leading to higher concentrations of potassium in plasma, hemolysis (destruction of red blood cells), and decreased red blood cell viability and survival.
- *Unintended radiation exposure to the operator and others:* Device malfunction, lack of adequate maintenance, inadequate shielding, or safety control or interlock failure could allow the operator to access the radiation source resulting in physical injury and/or exposure of the operator or other nearby persons to radiation. Exposure to ionizing radiation has been shown to increase cancer risk (Ref. 13). Insufficient presence of safety controls or interlocks within irradiator design may result in unintended exposure.
- *Electrical shock:*[8] Electrical malfunction of the device or operator contact with an energized portion may result in electrical shock or burn. This can occur when there are insufficient or malfunctioning safety controls or interlocks.
- *Mechanical or crush injury:* Blood irradiators contain shielding materials to prevent excess radiation emission outside the device causing the device itself and many components to be heavy. Operator inattention or placement of body parts where they can be impinged by the device may result in physical injury to the operator.
- *Presence of proliferative malignant cells in re-transfused blood due to incorrect dose or improper dose of radiation delivered:* Incorrect dose of radiation identified to be effective or improper dose of radiation delivered due to operator error, device malfunction, lack of adequate maintenance, or lack of dosimetry or quality assurance checks, may result in tumor cell survival leaving proliferative (*i.e.,* able to function, grow, and divide) tumor cells present in the blood.
- *Worsened control of oncologic disease or patient prognosis:* Irradiating blood or blood components may cause an immune response that negatively impacts cancer outcome or patient recovery or survival.
- *Delayed or lack of re-transfusion of irradiated blood or blood components:* Use of the device inherently delays re-transfusion and lengthens the duration of the operating procedure with larger volumes of blood irradiated adding a larger amount of additional operating procedure time. Device malfunction, including from mechanical, electrical, or software malfunctions, or operator error could lead to improper or no irradiation of the blood or blood components, which could add additional delay if the malfunction or error results in the salvaged blood not being suitable for re-transfusion into the patient. Delay in re-transfusion could increase risk to patients depending on their blood volume at any given point in the procedure. Longer operating times are associated with increased risks, including prolonged exposure to anesthesia and greater risk of infection.
- *Induction of a new cancer due to irradiation of the blood or blood components:* Irradiation of nucleated cells may result in malignant transformation as ionizing radiation exposure causes DNA damage that may result in downstream biologic effects (*e.g.,* mutation, cell killing or carcinogenesis) (Ref. 15). Permanent DNA damage could result in the cells becoming malignant. Quantitative risk assessment of this phenomenon occurring in irradiated blood for the prevention of metastasis has not been performed. If blood salvage and processing, including irradiation, occurs multiple times, blood cells may be exposed to ionizing radiation multiple times. If those cells are returned into the body this could result in induction of a new cancer.
- *Risks associated with usability including irradiating the salvaged blood outside the operating room and the potential for blood to be incorrectly labeled or misidentified:* Included in this risk to health are issues with operating the device in a way that results in an incorrect blood product being given to the patient. For example, should blood irradiation be performed in a manner where blood or blood products from multiple patients are irradiated at one time, if the bags are labeled with the wrong patient information, or are thought to be irradiated, but are not, this could result in the patient receiving a transfusion of the wrong blood. This could include operator error or inadequate usability testing of the points of interaction between the device and the operator, including displays and instructions for use.

In evaluating benefits associated with the use of blood irradiators intended to prevent metastasis, FDA considered information from the 2023 Panel regarding the classification of blood irradiators intended to prevent metastasis and the results of published scientific literature searches performed on April 20, 2023 and September 23, 2024. The information indicated that there appears to be a lack of clinical data to demonstrate that irradiating intraoperatively salvaged blood is able to prevent metastasis in patients and therefore there is no clear clinical benefit from use of the blood irradiators intended to prevent metastasis.

C. Proposed Classification and FDA's Findings

Based on FDA's experience with blood irradiators intended to prevent TA-GVHD, including those intended to inactivate leukocytes and/or lymphocytes to prevent TA-GVHD, the 2012 Panel's recommendations, and other available information, FDA is proposing to classify blood irradiators

[8] The original 2023 Panel materials denoted this risk as ''Electrical shock or burn.'' We have updated the title of this risk to health to be consistent with the similar risk discussed earlier in this proposed rule for blood irradiators intended to prevent TA–GVHD; the description of this risk to health is identical to what was included in the 2023 Panel materials.

intended to prevent TA-GVHD into class II. FDA is proposing to classify blood irradiators intended to prevent TA-GVHD into class II because general controls alone are insufficient to provide reasonable assurance of the safety and effectiveness of these devices (see Section III.C.1) as presented and discussed during the 2012 Panel meeting (Ref. 1). FDA also believes there is sufficient information to establish special controls to mitigate the risks to health of the device. FDA has tentatively determined that the special controls, in addition to general controls, will provide reasonable assurance of the safety and effectiveness of blood irradiators intended to prevent TA-GVHD. Blood irradiators intended to prevent TA-GVHD would be subject to 510(k) requirements under section 510(k) of the FD&C Act (21 U.S.C. 360(k)).

Based on FDA's experience with blood irradiators intended to prevent metastasis, the 2023 Panel's recommendations, and other available information, FDA is proposing to classify blood irradiators intended for use in irradiating intraoperatively salvaged blood of cancer patients undergoing surgery to prevent metastasis into class III. FDA is proposing this classification because FDA believes that insufficient information exists to determine that general controls and special controls would provide reasonable assurance of safety and effectiveness for these devices and, based upon assessment of benefits and risks, blood irradiators intended to prevent metastasis present a potential unreasonable risk of illness or injury. FDA does not believe the special controls proposed for blood irradiators intended to prevent TA-GVHD are sufficient to provide reasonable assurance of safety and effectiveness for blood irradiators intended to prevent metastasis. FDA has identified additional risks to health posed by the intended use for prevention of metastasis, as described in section V.B.2, for which it does not have adequate information to establish special controls. Additionally, FDA agrees with the 2023 Panel that the identified risks for this intended use may not be exhaustive. Elsewhere in this issue of the **Federal Register**, FDA is proposing through a proposed order to require the filing of a PMA under section 515(b) of the FD&C Act. The proposed order will only be finalized if and when FDA finalizes this proposed rule classifying blood irradiators intended to prevent metastasis in class III.

VI. Proposed Special Controls for Blood Irradiators Intended To Prevent TA-GVHD

FDA is proposing the special controls identified in this section for blood irradiators intended to prevent TA-GVHD. FDA believes that these special controls, in addition to general controls, are necessary to provide a reasonable assurance of safety and effectiveness of these devices. Special controls for blood irradiators intended to prevent TA-GVHD were discussed at the 2012 Panel (Ref. 1, Executive Summary Table III). The consensus of the 2012 Panel was that the CBER Memorandum was a good resource for establishing special controls for these devices, including blood irradiators for TA-GVHD that use an x-ray source. The 2012 Panel concurred that the recommendations described in the CBER Memorandum provided sufficient guidance for a reasonable assurance of safety and effectiveness for this device type with some additional risk mitigations suggested by the 2012 Panel (Ref. 1, Transcript at 196).

The proposed special controls listed below for blood irradiators intended to prevent TA-GVHD include some risk mitigations and special controls proposed and recommended at the 2012 Panel meeting. FDA agrees with the 2012 Panel that certain recommendations suggested by the CBER Memorandum would support reasonable assurance of safety and effectiveness of blood irradiators to prevent TA-GVHD. As a result, the proposed risk mitigations and special controls for blood irradiators intended to prevent TA-GVHD include controls that are recommended in the CBER Memorandum for blood banks that FDA has determined are appropriate for and adaptable to devices to mitigate the identified risks. The proposed special controls include items suggested by the CBER Memorandum that were specifically discussed by the 2012 Panel members as well as those that were not specifically discussed but that FDA has determined to be relevant to this classification action. The proposed special controls include performance testing; labeling information including a device description, specifying that the device is intended to prevent TA-GVHD, and a warning that elevated levels of potassium have been reported in irradiated blood; software verification, validation, and hazard analysis; and electrical and electromagnetic compatibility testing.

FDA agrees with those 2012 Panel members who suggested a special control to require manufacturer training of operators on device use is not necessary for reasonable assurance of safety and effectiveness for the device. FDA believes that the warnings and detailed procedures and information required by the proposed special controls in the labeling, including clear identification of intended operators, along with adequate warnings, are sufficient, together with other special controls, to mitigate against risks caused by operator error such as improper radiation dose to blood or blood products. FDA also notes 21 CFR 606.20, which among other things requires personnel responsible for the collection, processing, compatibility testing, storage or distribution of blood or blood components to have adequate training and experience, including professional training as necessary, or combination thereof, to assure competent performance of their assigned functions. There have been limited adverse events reported in the MAUDE database, including no reports that were a result of operator error. At this time, FDA believes a special control requiring separate operator safety training given by the manufacturer is unnecessary for reasonable assurance of safety and effectiveness of this device type.

FDA also disagrees with the 2012 Panel suggestion that a special control requiring a minimum dose homogeneity percentage and specification of a particular dose rate to be used when irradiating the blood or blood products is necessary for reasonable assurance of safety and effectiveness. FDA does not believe a minimum dose homogeneity percentage and specification of dose rate ensure that all blood within the container receive a minimum dose of 15 Gy of radiation, nor would they account for mechanisms implemented in device design to address dose inhomogeneity. Instead, to address risks from dose inhomogeneity, FDA is proposing special controls to ensure delivery of at least 25 Gy of radiation targeted to the central portion of the container and a minimum dose of at least 15 Gy at any other point within the container, and performance testing demonstrating conformance with the 25 Gy to the central portion of the container and 15 Gy minimum dose at any other point. FDA does agree with the Panel's suggestion that the manufacturer should provide information on the decay of the source and the residual strength of the source so that dose rate can be assessed. FDA also agrees with the Panel that the manufacturer should provide the dosimetric distribution. This information can be used by the operator

to make decisions on how to ensure requirements at individual blood irradiation facilities are met. FDA has included in the proposed special controls labeling controls that include information about the specifications of the device including: dose rate, dosimetric distributions including dose uniformity within each irradiation canister provided with the device, and a detailed procedure for identifying the proper loading configuration of blood and blood products in the canister.

As noted in Section III.C.1, at the 2012 Panel FDA suggested in the 2012 Panel materials compliance with NRC regulations as a mitigation for risks to health from improper radiation dose to blood and blood products, and radiation exposure to the user. We are not including compliance with NRC regulations as a special control in this proposed rule. FDA recognizes that devices containing sealed radiation sources and use of such devices by blood establishments may be subject to NRC regulations and that such regulations may have an effect on the safe use of the device. However, FDA believes that the proposed special controls for blood irradiators intended to prevent TA-GVHD, specifically, non-clinical performance testing demonstrating that the device performs as intended under anticipated conditions of use, which includes documentation demonstrating that safety features, including interlocks, access controls, and shielding perform as intended, labeling, and software verification, validation, together with general controls, are sufficient to provide reasonable assurance of safety and effectiveness of this device type.

Table 1 summarizes how each identified risk to health described in section V.B.1 would be mitigated by the proposed special controls. The mitigation measures in the table have been modified from those presented in Table III of the 2012 Panel Executive Summary during the 2012 Panel meeting (Ref. 1, Executive Summary). The language in Table 1 is more general and identifies the type of mitigation measure (*e.g.,* labeling) rather than the specific method (*e.g.,* ensure preventative maintenance program). The mitigation measures have also been modified to include the types of mitigation measures presented and identified at the 2012 Panel meeting (*e.g.,* compliance with the 1993 CBER Memorandum) with more clarity and specificity regarding the special controls needed to provide reasonable assurance of safety and effectiveness of the device.

Irradiation of blood and blood products to prevent TA-GVHD has been in routine use for decades. TA-GVHD occurs when viable T-lymphocytes in transfused blood or blood products engraft, multiply, and react against the tissues of the recipient. Gamma and x-ray radiation can abrogate the ability of lymphocytes to proliferate in vitro, and studies show that irradiation of at least 15 Gy (gamma irradiation) reduces lymphocyte response to mitogens by 90% (Refs. 3 and 16). The 1993 CBER Memorandum recommended that the dose of radiation delivered to the blood or blood product should be 25 Gy targeted to the central portion of the container and 15 Gy as the minimum dose delivered at any other point. To mitigate the risk of TA-GVHD in patients receiving a transfusion of blood or blood products due to the improper radiation dose being given to the blood or blood products, FDA believes that performance testing is needed to show that the device is capable of delivering the 25 Gy dose targeted to the central portion of the container and minimum 15 Gy dose at any other point within the container. To further mitigate against an improper dose of radiation being delivered to the blood or blood component, either due to operator error or device malfunction, the device function that allows the operator to identify if exposure was prematurely terminated must be validated, and any software functions must undergo software verification, validation, and hazard analysis. To further mitigate this risk, the device labeling must also include information that is needed by the operator to irradiate all contents of the container to the desired dose. This includes:

- A summary of the performance testing conducted that demonstrates that the device can deliver 25 Gy of radiation targeted to the central portion of the container and a minimum of at least 15 Gy of radiation at any other point within the container;
- A detailed procedure that allows the device operator to verify the minimum dose delivered during each use, the dose rate and dose delivered by the device to the container, and if the exposure has been prematurely terminated;
- A detailed procedure identifying the proper loading configuration of the blood or blood component within the canister and exposure chamber and isodose curves for each loading configuration;
- Information about the specifications of the device—the dosimetric distributions within each canister provided with the irradiator measured both in air and loaded with water equivalent material, including dose homogeneity; and
- Instructions for device maintenance.

To mitigate the risk of damage to the blood or blood components from radiation, FDA believes that the labeling must include appropriate warnings and limitations needed for safe use, including statements that irradiation reduces the shelf stability of blood and that elevated potassium levels have been reported in irradiated red blood cell products.

To mitigate the risk of radiation exposure to the operator from the device, FDA believes that documentation is needed to demonstrate that the device performs as intended under anticipated conditions of use, including safety features of the device, which include its interlocks, access controls, and radiation shielding. For any safety features controlled by software, software verification, validation and hazard analysis of the features must be performed to ensure that these features perform as intended under anticipated conditions of use. Finally, to further mitigate this risk, FDA believes that labeling must include an identification of the safety features that enable operators to protect themselves and other nearby persons from unnecessary radiation exposure and the details of their specifications.

To mitigate against electrical shock or burns, FDA believes that adequate performance testing must demonstrate the electrical safety, mechanical safety, thermal safety, and electromagnetic compatibility of any electrical components of the device.

Finally, to mitigate against the risk of mechanical crush injury, FDA believes that labeling must include adequate warnings indicating that improper placement of hands or limbs could result in a mechanical crush injury.

Further, FDA believes that the special controls proposed for blood irradiators intended to prevent TA-GVHD, in addition to the general controls, mitigate the risks to health and are necessary to provide reasonable assurance of safety and effectiveness.

TABLE 1—IDENTIFIED RISKS TO HEALTH AND PROPOSED MITIGATION MEASURES FOR BLOOD IRRADIATORS INTENDED TO PREVENT TA-GVHD

Identified risks to health	Mitigation measures
Damage to blood or blood components from radiation	• Labeling.
Improper radiation dose to blood or blood products	• Performance testing and descriptive information. • Software verification, validation, and hazard analysis. • Labeling.
Unintended radiation exposure to the operator and others	• Performance testing and descriptive information. • Software verification, validation, and hazard analysis. • Labeling.
Electrical shock	• Electrical safety, mechanical safety, and thermal safety testing. Electromagnetic compatibility testing.
Mechanical crush or injury	• Labeling.

VII. Premarket Approval for Class III Devices

FDA has determined that insufficient information exists to determine that general controls and special controls would provide a reasonable assurance of safety and effectiveness for blood irradiators intended to prevent metastasis and that these devices present a potential unreasonable risk of illness or injury based on the limited clinical information that is available. FDA found no evidence that the physical aspects (hardware and software) of blood irradiators intended to prevent metastasis pose a potential unreasonable risk of illness or injury. However, we found no available information about the short- and long-term safety risks presented by the intended use of blood irradiators intended to prevent metastasis, including cancer outcome, patient recovery, or survival. Given the limited reported clinical use of blood irradiators for the irradiation of intraoperative blood salvaged from cancer patients to assist in the prevention of metastasis in the published literature, the list of risks to health currently identified in this proposed classification action may not be exhaustive. For effectiveness, FDA found no definitive available evidence showing that irradiation of intraoperatively salvaged blood is able to prevent metastasis in patients or that it does not trigger an immunological response that could worsen patient prognosis (promote recurrence or invasiveness, or surgical recovery). In addition, the dose of radiation necessary to remove proliferative tumor cells is unclear, and the effects on the blood and blood products are unknown. Given the uncertainty about the extent of risks posed by the device, the lack of evidence supporting effectiveness, and a large amount of uncertainty surrounding the patient benefit from the device, FDA is proposing to classify blood irradiators intended to prevent metastasis into class III.

As required by section 515(b) of the FD&C Act, FDA is publishing elsewhere in this issue of the **Federal Register** a proposed order to require the filing of a PMA, which will be finalized if this classification action is finalized and these devices for this intended use are classified into class III. The proposed order also contains FDA's proposed findings regarding: the degree of risk of illness or injury designed to be eliminated or reduced by requiring that blood irradiators intended to prevent metastasis have an approved PMA when intended for use that includes delivering a controlled radiation dose to irradiate intraoperatively salvaged blood of cancer patients undergoing surgery to prevent metastasis and the benefit to the public from use of the device.

These findings are based on the reports and recommendations of the advisory committees (panels) for the classification of these devices along with information submitted to the public docket, postmarket data, adverse event reports in the MAUDE and MDR databases, information in CDRH's Medical Device Recalls database, and published scientific literature.

VIII. Proposed Effective/Compliance Dates

FDA proposes that any final rule based on this proposed rule become effective 30 days after its date of publication in the **Federal Register**. If this classification action is finalized, FDA proposes the implementation strategy set forth below.

A. Devices That Are Proposed To Be Classified Into Class II

- Blood irradiators intended to prevent TA-GVHD proposed to be classified into class II that have *not* been legally marketed prior to the effective date of any final rule, or blood irradiators intended to prevent TA-GVHD that have been legally marketed, but are required to submit a new 510(k) under 21 CFR 807.81(a)(3) because the device is about to be significantly changed or modified and have not submitted such 510(k) by the effective date of any final rule: FDA is proposing that manufacturers would have to obtain 510(k) clearance before marketing the new or modified device and would be required to comply with the applicable special controls as of the effective date. We believe that 30 days is a reasonable effective date given that FDA would not have received updated submissions regarding, and therefore would not have familiarity with, the noncompliant devices in this category, and given the concern about the probable consequences of device failure, including TA-GVHD, which can result in patient death.
- Blood irradiators intended to prevent TA-GVHD proposed to be classified into class II that have been legally marketed prior to the effective date of any final rule and are not about to be significantly changed or modified in a manner that requires a 510(k), and blood irradiators intended to prevent TA-GVHD for which 510(k) submissions have been submitted before the effective date of any final rule: FDA generally does not intend to enforce compliance with the special control requirements, including the labeling requirements, for a period of 12 months following the effective date of the final rule, although FDA intends to carefully assess the application of this policy to any devices for which submissions are made between the date of publication of the final rule and the effective date. If a manufacturer were to market such a device after 12 months following the effective date of the final rule, and that device did not comply with the special controls, the enforcement discretion policy described above would no longer apply, meaning FDA would evaluate enforcement action against such a manufacturer under its usual approach. FDA believes that a period of one year from the effective date of this final rule would be appropriate for manufacturers

to come into compliance with such requirements, as we are generally familiar with these devices and we believe changes for existing devices to come into compliance are generally limited to minor labeling changes. We also believe this compliance period is appropriate to accommodate the reliance interests of manufacturers who have developed products and submitted premarket notifications based on the previous regulatory status quo, under which blood irradiators are subject to 510(k) requirements but not special controls. FDA believes this approach would help ensure the efficient and effective implementation of the classification action, if finalized as currently proposed.

B. Devices That Are Proposed To Be Classified Into Class III

• If this proposal to classify blood irradiators intended to prevent metastasis in class III and the related proposed order to require the approval of a PMA are finalized, blood irradiators intended to prevent metastasis by delivering a controlled radiation dose to irradiate intraoperatively salvaged blood of cancer patients undergoing surgery to prevent metastasis would be considered adulterated if either a PMA is not filed with FDA prior to the last day of the 30th calendar month beginning after the month in which the classification of the device into class III becomes effective or a PMA is filed but approval is denied, suspended, or withdrawn (see section 501(f)(1)(A) and 501(f)(2)(B) of the FD&C Act (21 U.S.C. 351(f)(1)(A) and (2)(B))).

In this event, the device can no longer be introduced into interstate commerce (see, *e.g.,* section 301(a) of the FD&C Act (21 U.S.C. 331(a))) unless it meets a relevant exemption, such as the exemption for investigational use devices. The requirements of the investigational device exemption regulations are set forth in 21 CFR part 812.

IX. Preliminary Economic Analysis of Impacts

We have examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, Executive Order 14192, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4).

Executive Orders 12866 and 13563 direct us to assess all benefits and costs of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits. Rules are economically significant under Executive Order 12866 if they have an annual effect on the economy of $100 million or more; or adversely affect in a material way the economy, a sector of the economy, productivity, competition, jobs, the environment, public health or safety, or State, local, or tribal governments or communities. The Office of Information and Regulatory Affairs has determined that this proposed rule is not a significant regulatory action under Executive Order 12866.

Executive Order 14192 requires that any new incremental costs associated with certain significant regulatory actions ''shall, to the extent permitted by law, be offset by the elimination of existing costs associated with at least 10 prior regulations.'' This proposed rule, if finalized as proposed, is not expected to be an Executive Order 14192 regulatory action because this rule is not significant under Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because net annualized compliance costs of the proposed rule are more than 1 percent of average annual revenues and unquantified effects are uncertain, we find that the proposed rule will have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (Section 202(a)) requires us to prepare a written statement, which includes estimates of anticipated impacts, before proposing ''any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any 1 year.'' The current threshold after adjustment for inflation is $187 million, using the most current (2024) Implicit Price Deflator for the Gross Domestic Product. This proposed rule would not result in an expenditure in any year that meets or exceeds this amount.

The proposed rule, if finalized, would classify blood irradiators (unclassified, preamendments devices) into two classes based on intended use. It would classify blood irradiators intended to prevent TA-GVHD into class II (special controls) and blood irradiators intended to prevent metastasis into class III (premarket approval application). The proposed special controls for blood irradiators intended to prevent TA-GVHD are already generally practiced by manufacturers of currently cleared devices, with the primary change consisting of the labeling special controls. FDA believes that the proposed special controls, together with the general controls in the FD&C Act, would provide reasonable assurance of the safety and effectiveness of these devices and help ensure that all new devices meet the same standards as the currently marketed devices. FDA has determined that general controls and special controls together are insufficient to provide reasonable assurance of safety and effectiveness for blood irradiators intended to prevent metastasis, and that these devices present a potential unreasonable risk of illness or injury. Separately, FDA also is issuing a proposed order requiring the filing of a PMA for blood irradiators intended to prevent metastasis.

Quantified benefits of the proposed rule, if finalized, would consist of cost savings to industry and FDA from a reduction in the quantity and time burden of informal inquiries related to blood irradiators intended to prevent TA-GVHD. We also estimate cost savings to industry and FDA from a reduction in the number of 510(k) submissions necessitating requests for additional information from FDA before and during review. Industry and FDA could incur costs associated with premarket approval for current and future blood irradiators intended to prevent metastasis. Industry would incur costs to prepare and submit PMAs and annual and supplemental reports and costs to undergo facility inspections. In turn, FDA would incur costs to review and respond to PMAs and annual and supplemental reports, and costs to inspect facilities. We quantify the associated user fees for these PMAs and annual and supplemental reports as transfers from industry to FDA. We additionally quantify one-time costs to industry to read and understand the proposed rule and the proposed order requiring the filing of a PMA, as well as one-time costs to industry to revise labeling.

We summarize the quantified benefits and costs of the proposed rule, if finalized, in Table 2. We estimate that the annualized benefits over 10 years would range from $84 to $180,268 at a 7 percent discount rate, with a primary estimate of $90,176, and from $86 to $184,271 at a 3 percent discount rate, with a primary estimate of $92,178. The annualized costs would range from $0.68 million to $1.51 million at a 7 percent discount rate, with a primary estimate of $1.07 million, and from $0.66 million to $1.53 million at a 3 percent discount rate, with a primary estimate of $1.07 million.

TABLE 2—SUMMARY OF BENEFITS, COSTS, AND DISTRIBUTIONAL EFFECTS OF THE PROPOSED RULE
[Millions of 2024 dollars]

Category	Primary estimate	Low estimate	High estimate	Units			Notes
				Year dollars	Discount rate	Period covered (years)	
Benefits:							
Annualized Monetized	$0.09	$0.0001	$0.18	2024	7	10	Estimated benefits are cost savings.
($m/year).	0.09	0.0001	0.18	2024	3	10	
Annualized Quantified ..	.....	.....	.....	.....	.....	.....	
	.....	.....	.....	.....	.....	.....	
Qualitative							
Costs:							
Annualized Monetized	1.07	0.68	1.51	2024	7	10	
($m/year).	1.07	0.66	1.53	2024	3	10	
Annualized Quantified ..	.....	.....	.....	.....	.....	.....	
	.....	.....	.....	.....	.....	.....	
Qualitative							
Transfers:							
Federal Annualized	0.05	0.03	0.07	2024	7	10	User fee payments associated with premarket ap-
Monetized ($m/year).	0.05	0.03	0.07	2024	3	10	proval for class III blood irradiator devices.
	From: Blood irradiator device industry			To: FDA			
Other Annualized Mon-	.....	.....	.....	.....	.....	.....	
etized ($m/year).	.....	.....	.....	.....	.....	.....	
Effects:							
State, Local, or Tribal Government: None.							
Small Business: Quantified effects of more than 1 percent of average annual revenues and uncertain unquantified effects.							
Wages: None.							
Growth: None.							

We estimate that the present value of total benefits over 10 years would range from $0.001 million to $1.35 million at a 7 percent discount rate, with a primary estimate of $0.68 million, and from $0.001 million to $1.62 million at a 3 percent discount rate, with a primary estimate of $0.81 million. The present value of total costs would range from $5.09 million to $11.38 million at a 7 percent discount rate, with a primary estimate of $8.06 million, and from $5.80 million to $13.41 million at a 3 percent discount rate, with a primary estimate of $9.39 million.

In line with Executive Order 14192, in Table 3 we estimate present and annualized values of costs, cost savings, and net costs over a perpetual time horizon. We estimate that this proposed rule would generate $570,338 in annualized net costs at a 7 percent discount rate, discounted relative to year 2024, over a perpetual time horizon.

TABLE 3—EXECUTIVE ORDER 14192 SUMMARY TABLE
[Millions of 2024 dollars, discounted over a perpetual time horizon relative to year at a 7 percent discount rate]

	Primary estimate	Low estimate	High estimate
Present Value of Costs	$9.21	$4.59	$14.54
Present Value of Cost Savings	1.06	0.001	2.12
Present Value of Net Costs	8.15	4.59	12.42
Annualized Costs	0.64	0.32	1.02
Annualized Cost Savings	0.07	0.0001	0.15
Annualized Net Costs	0.57	0.32	0.87

Note: Due to uncertainty regarding future impacts of the proposed rule, if finalized, we assume that undiscounted costs and cost savings in years 10 through infinity would equal costs and cost savings in year 9. We assume that costs and cost savings would begin to accrue in 2028 (year 0).

We have developed a Preliminary Economic Analysis of Impacts that assesses the impacts of the proposed rule. The full preliminary analysis of economic impacts is available in the docket for this proposed rule (Ref. 17) and at *https://www.fda.gov/about-fda/economics-staff/regulatory-impact-analyses-ria.*

X. Analysis of Environmental Impact

We have determined under 21 CFR 25.34(b) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

XI. Paperwork Reduction Act of 1995

FDA tentatively concludes that this proposed rule contains no new collection of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

XII. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. We have determined that this proposed rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we conclude that the proposed rule does not contain policies that have federalism implications as defined in the Executive Order and, consequently, a federalism summary impact statement is not required.

XIII. Consultation and Coordination with Indian Tribal Governments

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13175. We have tentatively determined that the rule does not contain policies that would have a substantial direct effect on one or more Indian Tribes, on the relationship between the Federal Government and Indian Tribes, or on the distribution of power and responsibilities between the Federal Government and Indian Tribes. The Agency solicits comments from tribal officials on any potential impact on Indian Tribes from this proposed action.

XIV. References

The following references marked with an asterisk (*) are on display at the Dockets Management Staff (see **ADDRESSES**) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they also are available electronically at *https://www.regulations.gov.* References without asterisks are not on public display at *https://www.regulations.gov* because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. Although FDA verified the website addresses in this document, please note that websites are subject to change over time.

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List of Subjects in 21 CFR Part 892

Medical devices, Radiation protection, X-rays.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, we propose that 21 CFR part 892 be amended as follows:

PART 892—RADIOLOGY DEVICES

■ 1. The authority citation for part 892 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 360*l,* 371.

■ 2. Add § 892.7000 to subpart G to read as follows:

§ 892.7000; Blood irradiator devices.

(a) *Identification.* A blood irradiator device is a prescription device used to deliver a controlled radiation dose to blood or blood products to prevent transfusion-associated graft-versus-host disease through delivery of a radiation dose to blood or blood products prior to transfusion or to irradiate intraoperatively salvaged blood in cancer patients undergoing surgery to assist in the prevention of metastasis. This generic type of device includes an x-ray or a sealed radionuclide radiation source.

(b) *Classification.*

(1) Class II (special controls) when intended to prevent transfusion-associated graft-versus-host disease through delivery of a radiation dose to blood or blood products prior to transfusion. The special controls for this device are:

(i) Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use and must include:

(A) Documentation demonstrating that the device delivers a dose of at least 25 Gy of radiation targeted to the central portion of the container.

(B) Documentation demonstrating that the device delivers a minimum dose of at least 15 Gy of radiation at any other point within the container.

(C) Documentation demonstrating that safety features, including interlocks, access controls, and shielding, perform as intended.

(D) Validation of the method that allows the operator to identify if the exposure has been prematurely terminated.

(ii) Software verification, validation, and hazard analysis must be performed.

(iii) Performance testing must demonstrate the electrical safety, mechanical safety, thermal safety, and electromagnetic compatibility of any of the electrical components of the device.

(iv) Labeling must include:

(A) The intended use statement must specify that the device is intended to prevent transfusion-associated graft-versus-host disease.

(B) A summary of the performance testing conducted demonstrating that the device can deliver 25 Gy of radiation targeted to the central portion of the container and a minimum of at least 15 Gy at any other point within the container.

(C) A detailed procedure allowing the device operator to verify:

(*1*) The minimum dose delivered during each use;

(*2*) The dose rate and dose delivered by the device to the container; and

(*3*) If the exposure has been prematurely terminated.

(D) Identification of the safety features that enable operators to protect themselves and other nearby persons from unnecessary radiation exposure and details of their specifications.

(E) A detailed procedure for identifying the proper loading configuration of the blood or blood products within the canister and exposure chamber and isodose curves for each loading configuration.

(F) Information about the specifications of the device including:

(*1*) Dosimetric distributions, including dose uniformity, within each irradiation canister provided with the irradiator measured both in air and loaded with water equivalent material;

(*2*) Dose rate; and

(*3*) For radionuclide sealed radiation source irradiators, the strength of the source and the dose correction factor.

(G) Instructions for device maintenance, including:

(*1*) A recommended schedule of maintenance; and

(*2*) A recommended quality assurance program to ensure that the device continues to meet its specifications.

(H) A warning statement indicating that irradiation reduces the shelf stability of blood and blood products.

(I) A warning statement indicating that elevated potassium levels have been reported in irradiated red blood cell products.

(J) A warning statement indicating that improper placement of hands or limbs could result in a mechanical crush injury.

(2) Class III (premarket approval) when intended to irradiate intraoperatively salvaged blood in cancer patients undergoing surgery to assist in the prevention of metastasis.

(i) *Date premarket approval application (PMA) or notice of completion of product development protocol (PDP) is required.* A PMA or notice of completion of a PDP is required to be filed with the Food and Drug Administration on or before [DATE OF THE LAST DAY OF THE 30TH FULL CALENDAR MONTH AFTER EFFECTIVE DATE OF FINAL RULE], for any blood irradiator as identified in paragraph (b)(2) of this section that was in commercial distribution before May 28, 1976, or that has, on or before [DATE OF THE LAST DAY OF THE 30TH FULL CALENDAR MONTH AFTER THE EFFECTIVE DATE OF THE FINAL RULE], been found to be substantially equivalent to any blood irradiator, that was in commercial distribution before May 28, 1976. Any other blood irradiator identified in paragraph (b)(2) of this section shall have an approved PMA or declared completed PDP in effect before being placed in commercial distribution.

Robert F. Kennedy, Jr.,

Secretary, Department of Health and Human Services.

[FR Doc. 2026–05320 Filed 3–17–26; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 892

[Docket No. FDA–2025–N–5995]

Effective Date of Requirement for Premarket Approval Applications for Blood Irradiators Intended To Prevent Metastasis

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed amendment; proposed order.

SUMMARY: The Food and Drug Administration (FDA) is proposing to require the filing of a premarket approval application (PMA) for blood irradiators intended to irradiate intraoperatively salvaged blood for cancer patients undergoing surgery to assist in prevention of metastasis, which are unclassified, preamendments devices. FDA is summarizing its proposed findings regarding the degree of risk of illness or injury designed to be eliminated or reduced by requiring the devices to meet PMA requirements of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and the benefits to the public from use of the devices.

DATES: Either electronic or written comments on the proposed order must be submitted by May 18, 2026. FDA intends that, if a final order based on this proposed order is issued, anyone who wishes to market blood irradiators intended for use in the irradiation of intraoperatively salvaged blood for cancer patients undergoing surgery to assist in the prevention of metastasis must submit a PMA prior to the last day of the 30th calendar month beginning after the month in which the classification of the device in class III became effective. See section III for the effective date of any final order that may publish based on this proposed order. See section VI of this document for