4164-01-P

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 [INSERT DATE 60 AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. 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 more information about submitting a PMA.

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 [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. 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-5995 for "Effective Date of Requirement for Premarket Approval Applications for Blood Irradiators Intended to Prevent Metastasis." 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: https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

Docket: For access to the docket to read background documents 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:

I. Background--Regulatory Authorities

The FD&C Act, as amended, establishes 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. The three classes of devices are class I (general controls), class II (special controls), and class III (premarket approval).

Under section 513(d)(1) of the FD&C Act, devices that were in commercial distribution before the enactment on May 28, 1976, of the 1976 amendments (Medical Device Amendments of 1976, Pub. L. 94–295) (generally referred to as "preamendments devices") are classified after FDA (we or 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. FDA has classified most preamendments devices under these procedures.

A person may market a preamendments device that has been classified into class III through premarket notification procedures, without submission of a PMA until FDA issues an

administrative order under section 515(b) of the FD&C Act (21 U.S.C. 360e(b)) requiring premarket approval.

Section 515(f) of the FD&C Act provides an alternative pathway for meeting the premarket approval requirement. Under section 515(f), manufacturers may meet the premarket approval requirement if they file a notice of completion of a product development protocol (PDP) approved under section 515(f)(4) of the FD&C Act and FDA declares the PDP completed under section 515(f)(6)(B) of the FD&C Act. Accordingly, the manufacturer of a preamendments class III device may comply with a call for PMAs by filing a PMA or a notice of completion of a PDP. In practice, however, the option of filing a notice of completion of a PDP has rarely been used. For simplicity, although the PDP option remains available to manufacturers in response to a final order under section 515(b) of the FD&C Act, this document will refer only to the requirement for filing and obtaining approval of a PMA.

Section 515(b)(1) of the FD&C Act sets forth the process for issuing a final order. Specifically, prior to the issuance of a final order requiring premarket approval for a preamendments class III device, the following must occur: (1) publication of a proposed order in the *Federal Register*; (2) a meeting of a device classification panel described in section 513(b) of the FD&C Act; and (3) consideration of comments from all affected stakeholders, including patients, payors, and providers.

Section 515(b)(2) of the FD&C Act provides that a proposed order to require premarket approval shall contain: (1) the proposed order; (2) proposed findings with respect to the degree of risk of illness or injury designed to be eliminated or reduced by requiring the device to have an approved PMA, and the benefit to the public from the use of the device; (3) an opportunity for the submission of comments on the proposed order and the proposed findings; and (4) an opportunity to request a change in the classification of the device based on new information relevant to the classification of the device.

Section 515(b)(3) of the FD&C Act provides that FDA shall, after the close of the comment period on the proposed order,[1] consideration of comments received, and a meeting of a device classification panel described in section 513(b) of the FD&C Act, issue a final order to require premarket approval or publish a document terminating the proceeding together with the reasons for such termination. If FDA terminates the proceeding, FDA is required to initiate reclassification of the device under section 513(e) of the FD&C Act, unless the reason for termination is that the device is a banned device under section 516 of the FD&C Act (21 U.S.C. 360f).

A preamendments class III device may be commercially distributed without a PMA until 90 days after FDA issues a final order requiring premarket approval for the device, or 30 months after the classification of the device in class III under section 513 of the FD&C Act becomes effective, whichever is later (section 501(f)(2)(B) of the FD&C Act (21 U.S.C. 351(f)(2)(B)). Elsewhere in this issue of the *Federal Register*, FDA is proposing to classify blood irradiators intended for use in the irradiation of intraoperatively salvaged blood for cancer patients undergoing surgery to assist in the prevention of metastasis (blood irradiators intended to prevent metastasis) into class III. Therefore, if the proposed classification regulation and the order to require PMAs are finalized at the same time, a PMA for blood irradiators intended to prevent metastasis must be filed within the 30-month period because that will be the later of the two time periods. If a PMA is not timely filed for such devices, then the device would be deemed adulterated under section 501(f) of the FD&C Act.

Also, a preamendments device subject to the order process under section 515(b) of the FD&C Act is not required to have an approved investigational device exemption (IDE) (see part 812 (21 CFR part 812)) until the date identified by FDA in the final order requiring the filing of

[1] In December 2019, FDA began adding the term "Proposed amendment" to the "ACTION" caption for these documents to indicate that they "propose to amend" the Code of Federal Regulations. This editorial change was made in accordance with the Office of the Federal Register's interpretations of the Federal Register Act (44 U.S.C. chapter 15), its implementing regulations (1 CFR 5.9 and parts 21 and 22), and the Document Drafting Handbook.

a PMA for the device (assuming it complies with other applicable FDA requirements). At that time, an IDE is required prior to interstate distribution of the device only if a PMA has not been filed. If the manufacturer, importer, or other sponsor of the device submits an IDE application and obtains FDA approval, the device may be distributed for investigational use. If a PMA is not filed by the later of the two dates, and the device is not distributed for investigational use under an IDE or otherwise exempt from the PMA requirements, the device is subject to enforcement action.

II. Regulatory History of the Devices

After the enactment of the Medical Device Amendments of 1976, FDA undertook an effort to identify and classify all preamendments devices in accordance with section 513(d) of the FD&C Act. Consistent with the FD&C Act, FDA held a Radiological Devices Panel meeting regarding the classification of blood irradiators, with product code "MOT," on April 12, 2012 (2012 Panel) (Ref. 1). However, the 2012 Panel focused specifically on blood irradiators 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. The materials considered by the 2012 Panel noted that one device had been cleared at the time for the prevention of metastasis, but the classification of blood irradiators intended to prevent metastasis was not discussed at the 2012 Panel (Ref. 1).

On November 7, 2023, FDA held a Radiological Devices Panel meeting regarding the classification of blood irradiators intended to prevent metastasis (2023 Panel) (Ref. 2). FDA held the 2023 Panel to obtain input on the risks to health and benefits of blood irradiators intended to prevent metastasis. During the 2023 Panel meeting, FDA presented proposed risks to health for these devices. FDA identified risks which included some of the same risks that had been identified during the 2012 Panel for blood irradiators intended to prevent TA-GVHD relating to the device's hardware and software and some unique risks based on the device's intended use to

prevent metastasis. FDA noted that based on available information, long-term safety risks related to the device's intended use are unclear. In addition, there appears to be a lack of clinical data to demonstrate a clear clinical benefit from use of blood irradiators intended to prevent metastasis. The 2023 Panel was asked to recommend to FDA whether blood irradiators intended to prevent metastasis should be classified into class III (premarket approval), class II (special controls), or class I (general controls).

The 2023 Panel reviewed the list of risks to health provided by FDA for blood irradiators intended to prevent metastasis and agreed with the risks to health identified by FDA. The 2023 Panel also identified several additional risks to health posed by the device's intended use. The 2023 Panel agreed with FDA that the list of risks to health identified for this device type may not be exhaustive due to the limited reported clinical use of blood irradiators when used for the prevention of metastasis. The 2023 Panel also agreed that the benefits of irradiating intraoperatively salvaged blood for cancer patients undergoing surgery is unknown based on lack of scientific evidence.

The 2023 Panel recommended that blood irradiators intended to prevent metastasis be classified into class III because there was a lack of available evidence to determine that general and special controls are sufficient to provide reasonable assurance of safety and effectiveness, and these devices present a potential unreasonable risk of illness or injury given the lack of probable benefit. FDA agrees with the Panel's recommendation that blood irradiators intended for the prevention of metastasis be classified into class III subject to PMA. It is also FDA's position that there is a lack of available evidence to determine that general and special controls are sufficient to provide reasonable assurance of the device's safety and effectiveness, and that the device presents a potential unreasonable risk of illness or injury.

Elsewhere in this issue of the *Federal Register*, FDA is proposing to classify blood irradiators intended to prevent metastasis into class III. FDA has tentatively determined that requiring PMA approval, in addition to general controls, will provide reasonable assurance of the

safety and effectiveness of these devices. The proposed classification action would also establish the identification, classification, and regulatory controls for blood irradiators intended to prevent TA-GVHD. These devices have been subject to premarket review through a premarket notification (510(k)) submission and have been cleared for marketing if FDA considers the device to be substantially equivalent to a legally marketed predicate in accordance with section 513(i) of the FD&C Act. To date, FDA has cleared 16 of these devices and cleared only two devices of the device type that will be subject to the PMA requirements. For these two devices, the prevention of metastasis is a second intended use for the device in addition to the intended use to prevent TA-GVHD.

III. Dates New Requirements Apply

If FDA finalizes the proposed classification of blood irradiators intended to prevent metastasis, these devices will be classified into class III. In accordance with sections 501(f)(2)(B) and 515(b) of the FD&C Act, FDA is proposing to require that a PMA be filed with the Agency for blood irradiators intended to prevent metastasis by the last day of the 30th calendar month beginning after the month in which the classification of the device in class III becomes effective.

An applicant whose product was in commercial distribution before May 28, 1976, or whose product has been found to be substantially equivalent to such a product, may continue marketing such class III product during FDA's review of the PMA, provided that a PMA is timely filed. FDA intends to review any PMA for the device within 180 days. FDA cautions that under section 515(d)(1)(B)(i) of the FD&C Act, the Agency may not enter into an agreement to extend the review period for a PMA beyond 180 days, unless the Agency finds that ". . . the continued availability of the device is necessary for the public health."

Moreover, manufacturers must cease distribution of blood irradiators intended to prevent metastasis upon receiving a denial decision rendered on a PMA. In such circumstances, to resume distribution of devices for this indication, these manufacturers must receive PMA

approval for their devices. However, the product may be distributed for investigational use only if the requirements of the investigational device exemptions regulations in part 812 are met. The requirements for investigational use of significant risk devices include submitting an IDE application to FDA for review and obtaining approval. An IDE application under 21 CFR 812.30 is required to be approved before an investigation of the device may be initiated or continued. FDA, therefore, recommends that IDE applications be submitted to FDA at least 30 days before the date a PMA is required to be filed to avoid interrupting investigations.

IV. Devices Subject to This Proposal

Blood irradiators intended to prevent metastasis are used to irradiate intraoperatively salvaged blood *ex vivo* from cancer patients undergoing surgery to assist in the prevention of metastasis. Blood lost during surgery is collected using a suction device and may be processed or filtered before the blood irradiator is used to irradiate the blood to prevent the proliferation of cancer cells that may be present. The blood is then reinfused to the same patient either intraoperatively or post-operatively in an autologous blood transfusion. These devices include an x-ray or a sealed radiation source. FDA currently regulates these unclassified devices as devices requiring a 510(k) submission under product code MOT.

Elsewhere in this issue of the *Federal Register*, FDA is proposing to classify blood irradiators intended to prevent metastasis into class III. Blood irradiators are identified as follows: A blood irradiator device is a prescription device used to deliver a controlled radiation dose to blood or blood products. This generic type of device includes an x-ray or a sealed radiation source. Blood irradiators are class III when intended to irradiate intraoperatively salvaged blood in cancer patients undergoing surgery to assist in the prevention of metastasis.

In accordance with section 515(b)(2)(C) and (D) of the FD&C Act, interested persons are being offered the opportunity to comment or request a change on the Agency's proposed classification of blood irradiators intended to prevent metastasis published elsewhere in this *Federal Register*.

V. Proposed Findings With Respect To Risks and Benefits for Blood Irradiators Intended To Prevent Metastasis

As required by section 515(b) of the FD&C Act, FDA is publishing its proposed findings regarding: (1) the degree of risk of illness or injury designed to be eliminated or reduced by requiring that these devices have an approved PMA and (2) the benefits to the public from the use of the devices. These findings are based on the reports and recommendations of the 2023 Panel, and any additional information that FDA has obtained. Additional information regarding the risks can be found below, as well as in the proposed rule published elsewhere in this issue of the *Federal Register*, proposing to classify these devices into class III.

Based on this information, FDA has identified the following risks to health of 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*:[2] 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. 3). Insufficient presence of safety controls or interlocks within irradiator design may result in unintended exposure.

[2] The original 2023 Panel materials denoted this risk as "Unintended radiation exposure to the operator and public". We have updated the title of this risk to health to expressly reflect other persons who may be at risk of such exposure (e.g., patients, bystanders); the description of this risk to health is identical to what was included in the 2023 Panel materials.

- *Electrical shock*:[3] 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

[3] 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 for blood irradiators intended to prevent TA-GVHD in the proposed rule; the description of this risk to health is identical to what was included in the 2023 Panel materials.

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. 4). 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.

A. Summary of Data

FDA conducted a query of the Manufacturer and User Facility Device Experience (MAUDE) database and the Medical Device Report (MDR) database from 1984 through September 25, 2023, to identify adverse events related to use of blood irradiators, with product code MOT, which includes blood irradiators intended to prevent TA-GVHD and blood

irradiators intended to prevent metastasis. The query resulted in the identification of five unique MDRs related to blood irradiators during that time period. No direct adverse events to patients were reported. FDA also conducted a query of Accidental Radiation Occurrences (AROs) reports during this time period. There were no AROs reported for devices under product code MOT. The MDR and ARO analyses showed few device malfunctions over the lifetime of use for these devices. Following these queries, FDA received one report of adverse events related to high current safety interlock system switch failures reported to result in superficial (first-degree) burns. FDA conducted updated queries for MDRs on July 7, 2025, and for AROs on November 7, 2024 and August 4, 2025. No additional reports were identified.

FDA reviewed recalls reported under product code MOT from November 2002 to June 22, 2025. There were two recalls for devices under product code MOT during that time period. The first recall was to complete a cooling system retrofit to preclude overheating and failure of the device. The recall was terminated May 13, 2012. [4] The second recall was 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)[5] because an interlock was not directly linked to the door. 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.

Additionally, FDA conducted a systematic literature review for articles published between January 1, 2002, and April 20, 2023, to identify and gather relevant published information regarding the safety and effectiveness of blood irradiators intended to prevent metastasis. The review identified 10 articles which were determined to be relevant to the safety and effectiveness of blood irradiators used to prevent metastasis. (Ref. 2, Executive Summary at

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

[5] 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.

pp. 11-12). No articles provided information on the safety assessment of blood irradiators intended to prevent metastasis. No articles definitively evaluated the effect of salvaged blood irradiation on tumor recurrence or metastasis. Further, the articles showed a lack of consensus on the specific dose to use, and for which cancer type and surgical procedure. FDA also conducted an additional literature search on September 23, 2024 for articles published since the prior search using the same search terms and filters and found no additional articles relevant to the safety and effectiveness of blood irradiators intended to prevent metastasis published since the prior search. Consequently, FDA tentatively concludes there is inadequate information characterizing the safety and effectiveness of blood irradiators intended to prevent metastasis to establish special controls. The 510(k) clearances of these devices were based solely on nonclinical information and determinations of substantial equivalence to a preamendments device. In light of the available information regarding the risks to health with no information supporting the benefit of these devices, general controls, including the 510(k) requirement, appear inadequate to support a reasonable assurance of safety and effectiveness for these devices.[6]

On November 7, 2023, FDA convened the Radiology Device Panel (2023 Panel) described in section II (Ref. 2). The 2023 Panel members agreed that there is a lack of clinical data to demonstrate a clinical benefit regarding the use of blood irradiators intended to prevent metastasis. The 2023 Panel 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 blood irradiators intended to prevent metastasis present an unreasonable risk of illness or injury to the patient, especially given the lack of probable benefit. Additionally, the 2023 Panel consensus was that special controls could not be established to mitigate the risks to health associated with the device

[6] The first blood irradiator that included an intended use to prevent metastasis was found to be substantially equivalent to a previously cleared device (i.e., the predicate), which 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 proposed order, and for the reasons described in section V, FDA is proposing to separately classify these two device types.

given the very limited data available. As such, the panelists agreed that blood irradiators intended to prevent metastasis should be classified as class III.

B. Benefits of the Device

As radiation is able to cause DNA damage in radiation-sensitive cancer cells and prevent those cells from proliferating (Ref. 5), the purported benefit of the use of blood irradiators intended to prevent metastasis is to prevent cancer cells present in the irradiated intraoperatively salvaged blood from causing metastasis after being reinfused into the patient. However, available evidence is inadequate to draw any definitive conclusions about the safety or effectiveness of this intended use (Ref 2). FDA is not aware of clinical evidence supporting the benefit of the use of blood irradiators intended to prevent metastasis. FDA is proposing a PMA be filed to require that manufacturers demonstrate that a reasonable assurance of safety and effectiveness exists for blood irradiators intended to prevent metastasis.

C. Risks to Health

The risks associated with blood irradiators intended to prevent metastasis includes damage to blood or blood components from radiation, unintended radiation exposure to the operator and public, electrical shock, mechanical crush or injury, 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, delayed or lack of re-transfusion of irradiated blood or blood components, induction of a new cancer due to irradiation of the blood components, 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 2023 Panel that there is a lack of probable benefit for these devices based on available information and has tentatively determined that 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 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. FDA further agrees that because insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness, blood irradiators intended to prevent metastasis should be class III subject to PMA.

VI. PMA Requirements

A PMA for blood irradiators intended to prevent metastasis must include the information required by section 515(c)(1) of the FD&C Act and 21 CFR 814.20. Such a PMA should also include a detailed discussion of the risks identified in section V, as well as a discussion of the effectiveness of the product for which premarket approval is sought. In addition, a PMA must include all data and information on the following: (1) any risks known, or that should be reasonably known, to the applicant that have not been identified in this document; (2) the effectiveness of the device that is the subject of the application; and (3) full reports of all preclinical and clinical information from investigations on the safety and effectiveness of the device for which premarket approval is sought (see section 515(c)(1)(A) of the FD&C Act; 21 CFR 814.20(b)(8)).

A PMA must include valid scientific evidence to demonstrate reasonable assurance of the safety and effectiveness of the blood irradiator to prevent metastasis for its intended use (see 21 CFR 860.7(c)(1)). FDA defines valid scientific evidence in 21 CFR 860.7(c)(2).

To present reasonable assurance of safety and effectiveness of blood irradiators intended to prevent metastasis, FDA tentatively concludes that manufacturers should submit performance testing, including clinical studies of their product, to support PMA approval. Existing published clinical literature relevant to the product may also be leveraged as part of the PMA submission.

In addition, FDA strongly encourages manufacturers to meet with the Agency early through the Q-Submission Program[7] for any assistance in preparation of their PMA.

VII. 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.

VIII. Paperwork Reduction Act of 1995

While this proposed order contains no collection of information, it does refer to previously approved FDA collections of information. The previously approved collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3521). The collections of information in 21 CFR part 814, subparts A through E, have been approved under OMB control number 0910-0231; and the collections of information in part 812 have been approved under OMB control number 0910-0078.

IX. Proposed Effective Date

FDA is proposing that any final order based on this proposal become effective on the date of its publication in the *Federal Register* or at a later date if stated in the final order.

X. Opportunity To Request a Change in Classification

Before requiring the filing of a PMA or notice of completion of a PDP for a device, FDA is required by section 515(b)(2)(D) of the FD&C Act to provide an opportunity for interested persons to request a change in the classification of the device based on new information relevant to the classification of the device. A request for a change in the classification of blood irradiators for the prevention of metastasis, as described in this document, should be provided in response to

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[7] *See* FDA guidance, "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program; Guidance for Industry and Food and Drug Administration Staff." May 29, 2025, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program.

the proposed rule issued elsewhere in this issue of the *Federal Register* and contain the information required by 21 CFR 860.123, including new information relevant to the classification of the device.

XI. 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 are also 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.

*1. Radiological Devices Panel "April 12, 2012: Meeting Materials FDA Generated - Blood Irradiators." Available at https://wayback.archive-it.org/7993/20170403223422/https:/www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/RadiologicalDevicesPanel/ucm299053.htm.

*2. Radiological Devices Panel, "November 7, 2023: Radiological Devices Panel of the Medical Devices Advisory Committee Meeting." Available at https://www.fda.gov/advisory-committees/radiological-devices-panel/2023-meeting-materials-radiological-devices-panel.

*3. National Cancer Institute. "Risk Factors - Radiation" (2019). Available at: Risk Factors: Radiation - NCI (canchttps://www.cancer.gov/about-cancer/causes-prevention/risk/radiationer.gov) (last accessed September 5, 2025).

4. Hall EJ and Giaccia, A. (2011) Radiobiology for the Radiologist. 7th Edition, Lippincott Williams & Wilkins, Philadelphia. Chapter 2: Molecular Mechanisms of DNA and

Chromosome Damage and repair, pp. 12-34, and Chapter 10: Radiation Carcinogenesis, pp. 135-158.

5. Joiner, M. and van der Kogel, A. (Eds) (2009), Basic Clinical Radiobiology. 4th Edition, CRC Press, London. Chapter 3: Cell Death After Irradiation: How, When and Why Cells Die (BG Wouters), pp. 27-40 and Chapter 7 (D Zips): Tumour Growth and Response to Radiation, pp. 78-101.

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. Amend § 892.7000, as proposed to be added in Docket No. FDA-2025-N-5996, published elsewhere in this issue of the *Federal Register*, by adding paragraph (b)(2)(i) to read as follows:

§ 892.7000 Blood irradiator devices.

* * * * *

(b) * * * * *

(2) * * * * *

(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 EFFECTIVE DATE OF 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.

Grace R. Graham,

Deputy Commissioner for Policy, Legislation, and International Affairs.

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