Classification of Blood Irradiators for the Prevention of Metastasis

Presenter
Justina Tam, PhD
Division of Health Technology 8C: Radiological Imaging & Radiation Therapy Devices
Office of Health Technology 8: Radiological Health
Office of Product Evaluation and Quality Center for Devices and Radiological Health
Food and Drug Administration

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Outline

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- Indications for Use
- Regulatory History
- Clinical Background
- Literature Review
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- Risks to Health
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Device Description

- Blood irradiator for the prevention of metastasis
  - Intended use: Irradiation of intra-operatively salvaged blood for cancer patients undergoing surgery to assist in the prevention of metastasis
  - Delivers ionizing radiation to *ex vivo* blood or blood products

- Radiation-emitting methods for FDA-cleared blood irradiators:
  - **X-ray**
    - Focus of this panel
    - Regulations - Electronic Product Radiation Control (EPRC): 21 CFR 1020.40 Cabinet x-ray systems
  - Radioisotope (e.g., Cobalt-60 or Cesium-137)

- These are a subset of blood irradiator devices currently cleared under product code “MOT”.

Device Description

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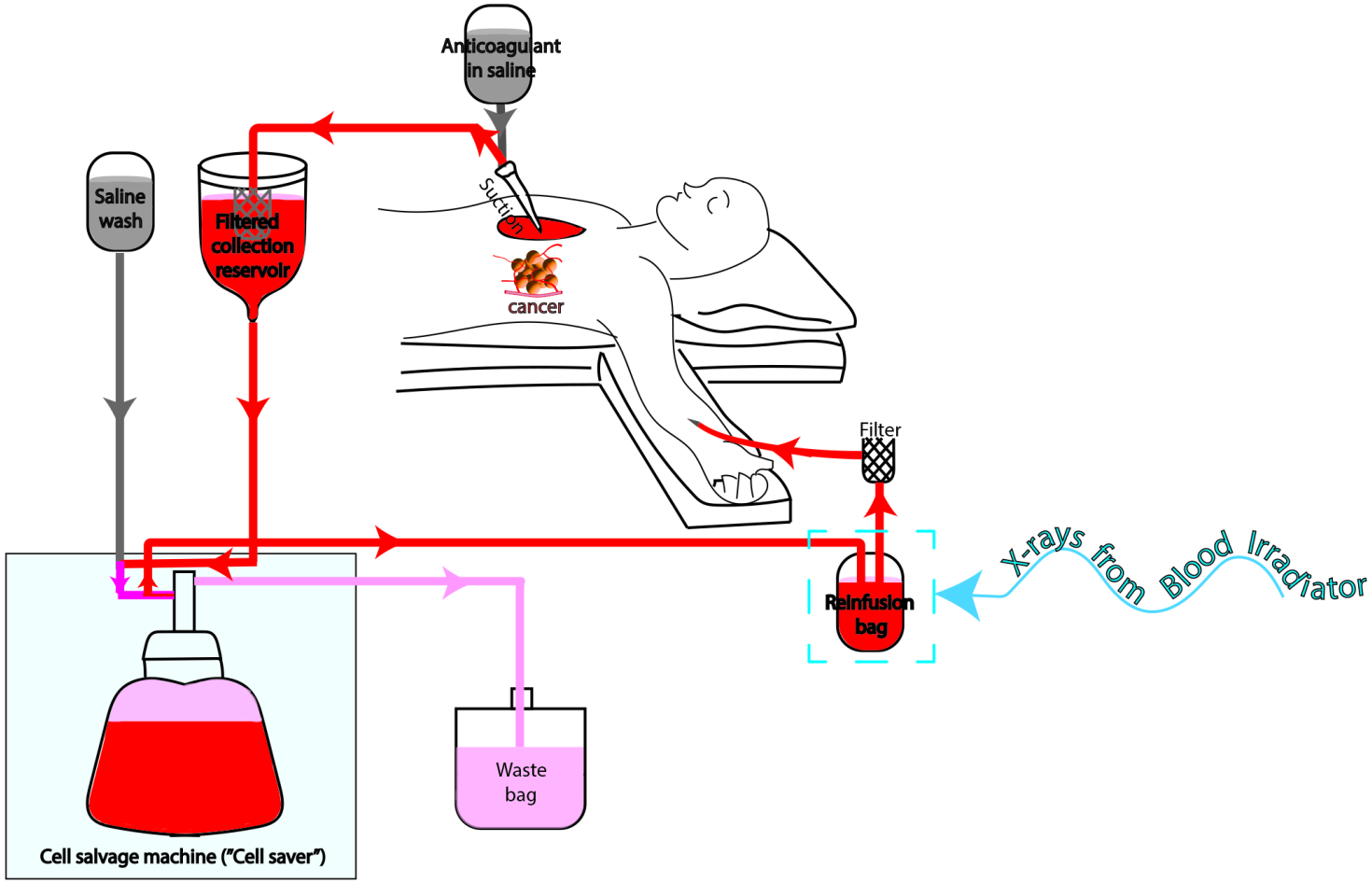
Procedure: Intra-operative Cell Salvage during Cancer Surgery

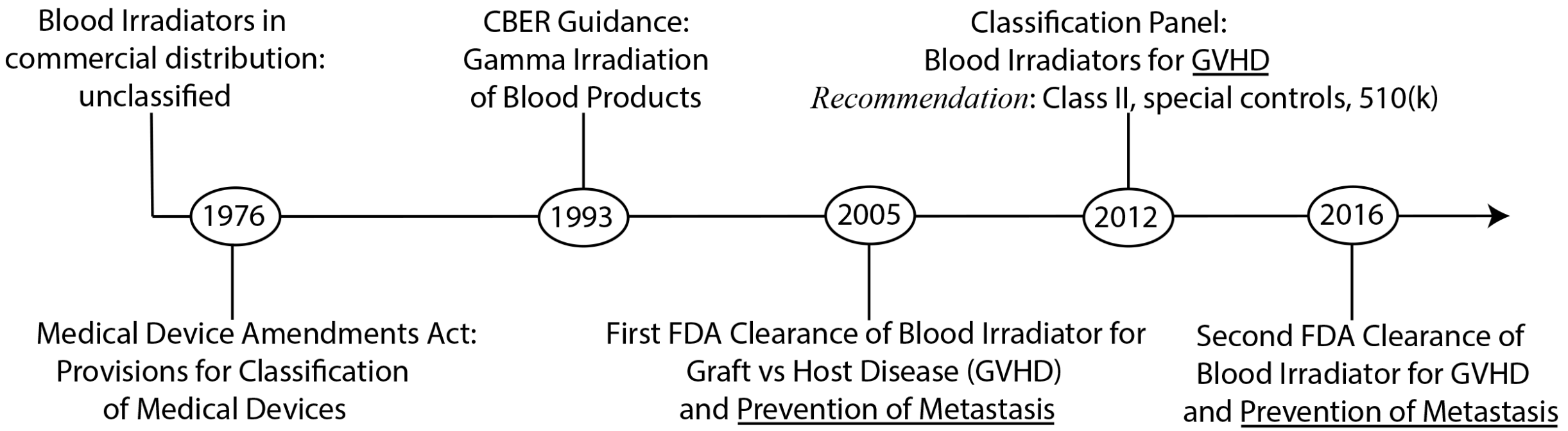


- Salvaged blood is irradiated to prevent cancer cells from proliferating
- Technique of irradiating intraoperatively salvaged blood from cancer patients for the prevention of metastasis does not appear to be widely used

Indications for Use

- Blood irradiators for the prevention of metastasis have been cleared as prescription use devices for the following indications for use:
  - **The [device] is intended for use in the irradiation of intra-operatively salvaged blood for cancer patients undergoing surgery to assist in the prevention of metastasis.**

Regulatory History



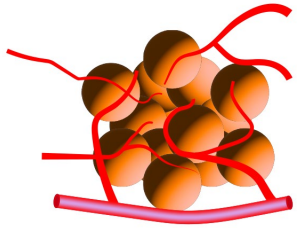
In the 2012 panel, the classification of blood irradiators for the prevention of metastasis was not discussed.

Regulatory History

- 2012 Panel: Additional indication for the “prevention of metastasis” was noted for one (1) of the 12 cleared devices at the time.
- Current panel:
  - Indication for the “prevention of metastasis” may involve new risks related to blood irradiators for the prevention of graft versus host disease (GVHD).
  - **Discuss current landscape of product technology, indications for use, safety and effectiveness, and risks to health, on which to base the classification of blood irradiators for the prevention of metastasis.**

Clinical Background

- Cancer
  - Second leading cause of death in the U.S.[1]
  - Metastasis: Tumors may spread via vascular or lymphatic system
- Oncologic Surgery
  - Significant blood loss may occur
    - Blood Transfusion:
      - Allogenic: From a compatible donor
      - Autologous: Salvaged blood from the cancer patient is re-infused back into the patient during or immediately after surgery
      - Radiation results in removal of leukocytes and tumor cells: Leukocytes (white blood cells), such as T-cells, and tumor cells are more sensitive to radiation than other blood components (e.g., red blood cells).
      - Leukocyte reduction filters: reduce the concentration of white blood cells (WBCs)



The difference in radiation sensitivity between other blood components and leukocytes or tumor cells can be exploited to remove activated T-cells to prevent transfusion-associated graft-versus-host disease (TA-GVHD) or to kill tumor cells.

1. U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on 2022 submission data (1999-2020): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; https://www.cdc.gov/cancer/dataviz, released in June 2023.

Clinical Background

- Patient Outcomes
  - Cancer patients, in general: Overall survival
  - Cancer patients undergoing surgery following the irradiation of intra-operatively salvaged blood to assist in the prevention of metastasis: Risk of post-operative infections, tumor recurrence, or metastasis

- Currently Available Treatments
  - Standard: Allogenic blood transfusion - from a compatible donor
  - Intra-operative blood salvage
    - “Cell saver” or “Cell recovery” – To salvage red blood cells, blood is separated, washed, and concentrated.
  - Leukocyte depletion filters – FDA-cleared devices for the removal of white blood cells (leukocytes) from blood components; may also remove cancer cells

- Alternatives to Intra-operative Blood Salvage
  - Pre-operative donation – autologous donation by the cancer patient prior to surgery
  - Hemodilution – dilution of the patient’s blood with a water- and mineral-based solution
  - Post-operative salvage

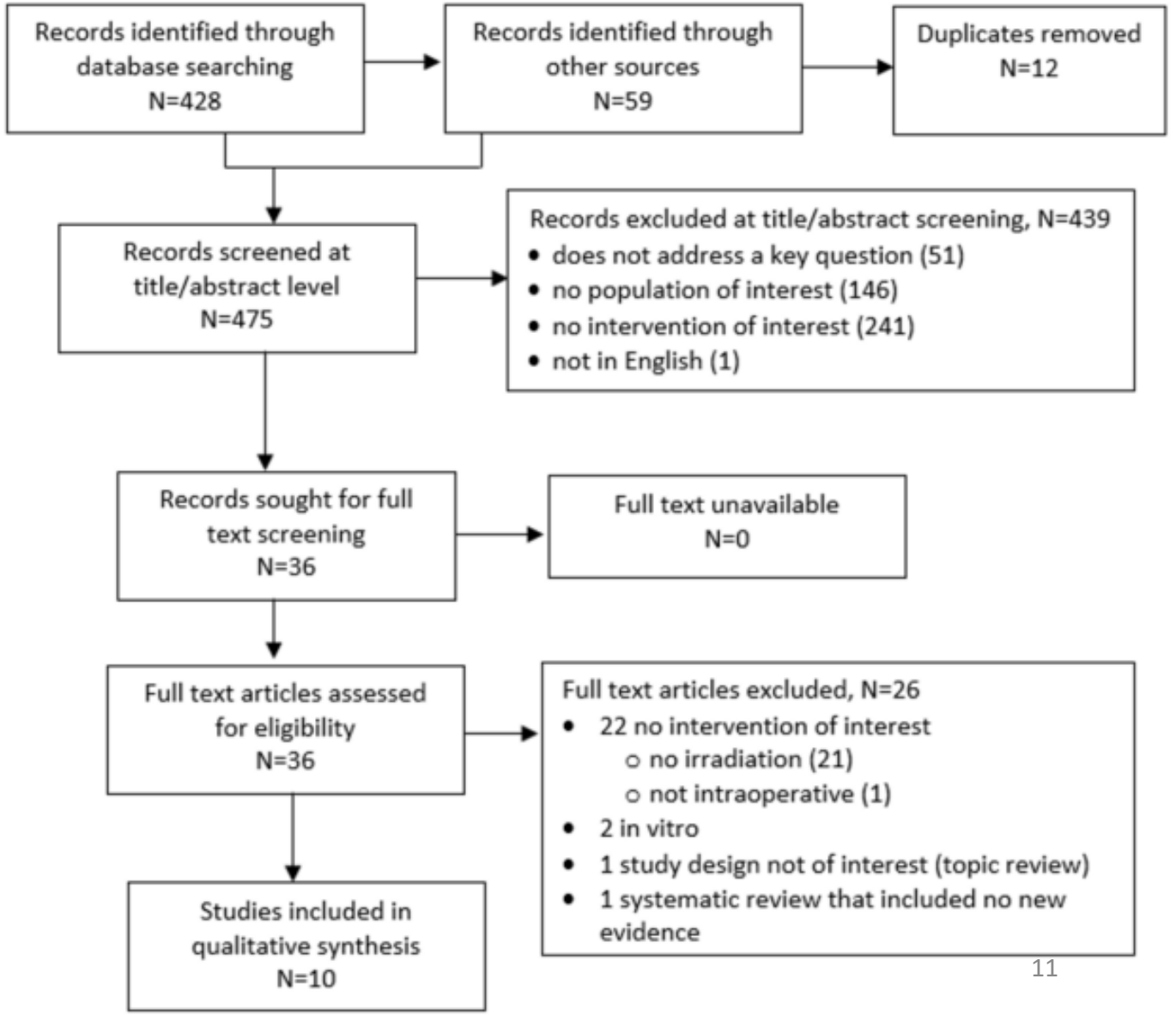
- **Primary Objection to Intraoperative Blood Salvage in Oncologic Patients:** Possibility that tumor recurrence and metastasis may occur from re-transfused malignant cells

Literature Review

- Systematic literature review was conducted:
  - Safety and effectiveness of blood irradiators for the prevention of metastasis
  - Published between January 1, 2002 and April 20, 2023.
  - Limited to publications in English and excluded studies where blood was not recovered intraoperatively from a human or animal subject with malignancy.
  - Radiation sources: x-ray and radioisotope
  - Blood irradiator device function and design are the same regardless of indication (prevention of Graft versus host disease (GVHD) or metastasis)

Literature Review

- After removal of duplicates, the search yielded 475 records.
- After filtering the results for relevance and inclusion/exclusion criteria, **10 records** were studied.



Literature Review – Safety Assessment

- Risks or Performance issues: No reports
- Observation: Blood irradiation took additional time
  - Hansen et al 1999 and 2003: 50Gy in 6 – 15 minutes
  - Weller et al 2021: Duration from irradiation to re-transfusion was < 20 minutes

Literature Review – Effectiveness Assessment

- **FDA Conclusion:** Effect of salvaged blood irradiation on tumor recurrence or metastasis was not definitively evaluated

- Effectiveness of irradiation on tumor recurrence
  - Weller et al 2021
  - Results: No significant difference in tumor recurrence with or without irradiation.
  - Limitation: All patients received allogenic transfusions of red blood cells, fresh frozen plasma, and platelets.

- Effectiveness of irradiation on damage to tumor cells
  - Hansen et al 1999, and Poli et al 2008
  - Results: Irradiation damaged tumor cells so that they were no longer proliferative or showed evidence of DNA metabolism, or that tumor cells were not detected after washing, filtration, and irradiation.
  - Limitations:
    - No examination of the *in vivo* prevention of metastasis
    - Inconsistent results within patients

Literature Review – Summation

- **Available evidence is inadequate to draw definitive conclusions about the safety or effectiveness of the use of blood irradiators to irradiate intraoperatively salvaged blood for the prevention of metastasis**
  - Safety: No articles provided information on the safety assessment
  - Effectiveness: No articles provided definitive information on the effect of salvaged blood irradiation on metastasis
- Search limitations:
  - Low number of relevant studies – only three (3) observational studies, all outside the U.S.
  - No randomized control trials
  - No mention of the FDA-cleared (K051065, K161324) blood irradiators for the prevention of metastasis
- Dose: Lack of consensus on specific dose to use, and for which cancer type and surgical procedure
  - Reported doses were 25 – 50Gy.

Medical Device Reports

- Medical Device Reporting (MDR): the mechanism for the FDA to receive significant medical device adverse events from:
  - Mandatory reporters (manufacturers, importers, and user facilities)
  - Voluntary reporters (healthcare professionals, patients, consumers)

Medical Device Reports

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- MDR reports can be used effectively to:
  - Establish a qualitative snapshot of adverse events for a specific device or device type
  - Detect actual or potential device problems used in a “real world” setting/environment, including:
    - rare, serious, or unexpected adverse events
    - adverse events that occur during long-term device use
    - adverse events associated with vulnerable populations
    - off-label use
    - user error

Medical Device Reports

- Limitations
  - Under reporting of events
  - Potential submission of incomplete, inaccurate, untimely, unverified, or biased data
  - Incidence or prevalence of an event cannot be determined from this reporting system alone
  - Confirming whether a device actually caused a specific event can be difficult based solely on information provided in a given report
  - MAUDE data does not represent all known safety information for a reported medical device

Medical Device Reports

- MAUDE (Manufacturer And User Facility Device Experience) Database reviewed for product code “MOT”(Irradiator, blood to prevent graft versus host disease and to prevent metastasis) with no date limitation through September 25, 2023.
- The search resulted in the identification of 7 unique MDRs:
  - 5 related to blood irradiators
    - 2: Low x-ray output; Root causes were isolated electrical or mechanical malfunctions.
    - 1: Suggestion to upgrade failure alarm
    - 2: No narrative, and thus could not be analyzed
  - 1 malfunction of film used to identify the radiation dose delivered
  - 1 miscategorized MRI coil

- Accidental Radiation Occurrences (AROs)
  - 21 CFR 1002.20
  - No AROs were reported for devices under product code MOT.

- **Conclusion: MDR and ARO analyses showed few device malfunctions.**

Recall History

- The Medical Device Recall database contains medical device recalls classified since November 2002.
- Since January 2017, it may also include correction or removal actions initiated by a firm prior to review by the FDA.
- The status is updated if the FDA identifies a violation and classifies the action as a recall and again when the recall is terminated.
- FDA recall classification (resulting in the posting date) may occur after the firm recalling the medical device product conducts and communicates with its customers about the recall.

Recall History

- Recalls are classified numerical designation I, II, or III (relative degree of health hazard presented)
  - A Class I recall is a situation in which there is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death.
  - A Class II recall is a situation in which use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote.
  - A Class III recall is a situation in which use of or exposure to a violative product is not likely to cause adverse health consequences.

Recall History

- One (1) recall for devices under product code “MOT” (not time restricted):
  - Z-2251-2016: Class II Recall
    - Non-compliant with the associated performance standards within 21 CFR Subchapter J Radiological Health: an interlock was not directly associated with the movement of the door.
- **Conclusion: No evidence that blood irradiators as medical devices pose a serious health hazard.**

Risks

FDA has identified the following risks to health associated with blood irradiators for prevention of metastasis

Identified Risk	Description/Examples
Presence of proliferative malignant cells in re-transfused blood due to incorrect dose or improper dose of radiation delivered	1) Incorrect dose of radiation identified to be effective may result in tumor cell survival leaving proliferative (able to function, grow, and divide) tumor cells present in the blood. 2) Device malfunction or lack of adequate maintenance, dosimetry or quality assurance checks, could lead to improper dose of radiation delivered to the blood or blood components resulting in incomplete tumor cell death and presence of proliferative tumor cells in the blood. 3) Operator error, including improper loading of the sample canister containing the blood or blood component, incorrect time entered into the user interface resulting in improper dose of radiation delivered leading to presence of proliferative tumor cells in the blood.
Worsened control of oncologic disease or patient prognosis	Irradiating blood or blood component may cause an immune response that negatively impacts cancer outcome or patient recovery or survival.
Damage to 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 affects red cell viability.

Risks

FDA has identified the following risks to health associated with blood irradiators for prevention of metastasis

Identified Risk	Description/Examples
Unintended radiation exposure to the operator and public	1) Device malfunction, lack of adequate maintenance, 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. 2) Insufficient presence of safety controls or interlocks within irradiator design may allow x-ray tube to generate x-rays when it should be shut off, resulting in unintended exposure.
Electrical shock or burn	Electrical malfunction of the device or user 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.

Risks

FDA has identified the following risks to health associated with blood irradiators for prevention of metastasis

Identified Risk	Description/Examples
Delayed or lack of re-transfusion of irradiated blood or blood component	Use of device inherently adds time to re-transfusion procedure and device malfunction, or operator error could add additional delay or risk of giving salvaged blood that was not irradiated. 1) Delayed re-transfusion of the blood or blood component to the patient could occur due to device malfunction, including from mechanical, electrical, or software malfunctions, or use error. 2) Operator error or device malfunction could lead to blood not being irradiated or being irradiated to incorrect dose, both of which would not kill tumor cells. In addition, operator error or device malfunction could result in over-irradiation, thereby impairing blood function. These could lead to the blood not being suitable for patients and not being given for re-transfusion
Mechanical or crush injury	Mechanical or crush injury may result from shielded doors being closed, impinging on operator.

Risks

- Blood irradiators intended for the prevention of metastasis
  - Unclear long term safety risks: cancer outcome, patient recovery, or survival
  - Risks may not be mitigated by special controls
  - Ability to have more stringent postmarket oversight typically associated with Class III devices recommended.

Risks

- Blood irradiators intended for the prevention of metastasis
  - **Proposed Classification: Class III, PMA devices**
  - FDA proposes that blood irradiators for the prevention of metastasis meet the statutory definition of a Class III device because:
    - Insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of their safety and effectiveness; and
    - Blood irradiators for the prevention of metastasis present a potential unreasonable risk of illness or injury based on the limited clinical information that has been obtained.

Proposed Classification

- 892.XXXX Blood irradiator for the prevention of metastasis

  (a) Identification. Blood irradiator devices for the prevention of metastasis are prescription devices used to deliver a controlled radiation dose to blood or components salvaged during surgery to assist in the prevention of metastasis in cancer patients. It is not intended to be used for cancer treatment or therapy.

  (b) Classification. Class III (premarket approval)

Questions to Panel

Questions 1 to Panel

According to 21 CFR 860.7(d)(1), "[t]here is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use" [emphasis added].

In addition, according to 21 CFR 860.7(e)(1), "[t]here is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results" [emphasis added].

Questions 1a to Panel

Please address the following questions regarding the risks to health posed by blood irradiator devices intended for use in the irradiation of intra-operatively salvaged blood for cancer patients undergoing surgery to assist in the prevention of metastasis (hereafter "blood irradiators for the prevention of metastasis"):

Questions 1a to Panel

i. FDA has identified the following risks to health for blood irradiators for the prevention of metastasis based upon literature and our search of adverse events submitted through Medical Device Reports (MDRs). However, given the limited reported clinical use of these devices in intra-operative blood salvage procedures, this list may not be exhaustive:

Questions 1a to Panel

Identified Risk	Description/Examples
Presence of proliferative malignant cells in re-transfused blood due to incorrect dose or improper dose of radiation delivered	1) Incorrect dose of radiation identified to be effective may result in tumor cell survival leaving proliferative (able to function, grow, and divide) tumor cells present in the blood. 2) Device malfunction or lack of adequate maintenance, dosimetry or of quality assurance checks, could lead to improper dose of radiation delivered to the blood or blood components resulting in incomplete tumor cell death and presence of proliferative tumor cells in the blood. 3) Operator error, including improper loading of the sample canister containing the blood or blood component, incorrect time entered into the user interface resulting in improper dose of radiation delivered leading to presence of proliferative tumor cells in the blood.
Worsened control of oncologic disease or patient prognosis	Irradiating blood or blood component may cause an immune response that negatively impacts cancer outcome or patient recovery or survival.
Damage to 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 affects red cell viability.

Questions 1a to Panel

Identified Risk	Description/Examples
Unintended radiation exposure to the operator and public	1) Device malfunction, lack of adequate maintenance, 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. 2) Insufficient presence of safety controls or interlocks within irradiator design may allow x-ray tube to generate x-rays when it should be shut off, resulting in unintended exposure.
Electrical shock or burn	Electrical malfunction of the device or user 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.

Questions 1a to Panel

Identified Risk	Description/Examples
Delayed or lack of re-transfusion of irradiated blood or blood component	Use of device inherently adds time to re-transfusion procedure and device malfunction, or operator error could add additional delay or risk of giving salvaged blood that was not irradiated. 1) Delayed re-transfusion of the blood or blood component to the patient could occur due to device malfunction, including from mechanical, electrical, or software malfunctions, or use error. 2) Operator error or device malfunction could lead to blood not being irradiated or being irradiated to incorrect dose, both of which would not kill tumor cells. In addition, operator error or device malfunction could result in over-irradiation, thereby impairing blood function. These could lead to the blood not being suitable for patients and not being given for re-transfusion
Mechanical or crush injury	Mechanical or crush injury may result from shielded doors being closed, impinging on operator.

Questions 1a to Panel

- Some of the identified risks could occur from the reported device-related adverse events related to incorrect dose of radiation delivered to the blood products due to low x-ray tube output.
- As the dose of radiation necessary to remove proliferative tumor cells is unclear, the effects on the blood and blood products are unknown.
- The literature review did not identify any articles that discussed risks or performance issues related to any identified blood irradiator device used for the prevention of metastasis.
- No definitive 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).
- 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, this list of risks may not be exhaustive.

Please comment on whether you agree with inclusion of these identified risks in the overall risk assessment of blood irradiators for the prevention of metastasis.

In addition, please comment on whether you believe that any additional risks should be included in the overall risk assessment of this device.

Questions 1a to Panel

ii. Given the available information, **please comment on whether there is a reasonable assurance of safety for blood irradiators for the prevention of metastasis.**

Questions 1b to Panel

b) Based on the information FDA could obtain, we are aware of little data that supports the assessment of effectiveness of blood irradiators for the prevention of metastasis. The most commonly cited evidence is the *in vitro* data examining the effect of radiation on tumor-derived cell lines mixed with red cells or with blood shed during cancer surgery.

Please comment on whether there is a reasonable assurance of effectiveness for blood irradiators for the prevention of metastasis.

Questions 2 to Panel

Section 513(a) of the Food, Drug, and Cosmetic Act states a device should be Class III if:

- insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of its safety and effectiveness, AND
- the device is 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, or the device presents a potential unreasonable risk of illness or injury.

A device should be Class II if:

- general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness, AND
- there is sufficient information to establish special controls to provide such assurance.

Questions 2 to Panel

A device should be Class I if:

- general controls are sufficient to provide reasonable assurance of safety and effectiveness, OR
- insufficient information exists to:
  - determine general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device, or
  - establish special controls to provide such assurance, BUT
    - is 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
    - does not present a potential unreasonable risk of illness or injury.

Questions 2a to Panel

Please discuss the following questions:

a. FDA believes that blood irradiators for the prevention of metastasis presents an unreasonable risk of illness or injury. There is a lack of evidence supporting effectiveness and a large amount of uncertainty surrounding the patient benefit from the device. Although limited information was available, based on the literature search conducted and the evidence obtained from review of the MAUDE database, FDA has identified the following risks: presence of proliferative tumor cells with the use of blood irradiators for the prevention of metastasis and potential increase in cancer recurrence or worsening of patient prognosis due to immunological response to irradiation or irradiated blood. Active malignancy is considered a relative contraindication for the use of intraoperative blood salvage, with an absence of definitive evidence to suggest a lack of adverse outcomes such as metastasis. There is also no definitive evidence showing that irradiation of intraoperatively salvaged blood is able to prevent metastasis in patients. From the information provided in the literature review, it is unclear what dose of radiation could effectively be used to irradiate intraoperatively salvaged blood to prevent metastasis, or if that dose would be the same for all cancer types and all surgical procedures. **Therefore, the risk of injury is unreasonable given the lack of probable benefit.**
   i. **Do you agree with this assessment? If not, please explain why.**

Questions 2b to Panel

Please discuss the following questions:

b. FDA believes that insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness of blood irradiators for the prevention of metastasis. **Given the limited information available on the safety and effectiveness of these devices, FDA does not believe that special controls can be established to mitigate the risks to health associated with these devices.**

i. Do you agree with this assessment?

A. If you agree with this assessment, please identify the type of performance data, including any type of clinical information, that you believe would be necessary to provide reasonable assurance of safety and effectiveness.

ii. If you disagree with this assessment, please identify the valid scientific evidence available in support of a reasonable assurance of safety and effectiveness of blood irradiators for the prevention of metastasis.

A. In addition, please identify the special controls that could be established that you believe would be sufficient to mitigate the risks to health and provide reasonable assurance of safety and effectiveness of blood irradiators for the prevention of metastasis.

End of Panel Questions