FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DEVICES & RADIOLOGICAL HEALTH

Brief Summary of the Radiological Devices Panel of the Medical Devices Advisory Committee

November 7, 2023

Introduction:

The Radiological Devices Panel of the Medical Devices Advisory Committee for the Food and Drug Administration met on November 7, 2023 to discuss and make recommendations on the classification of blood irradiators for the prevention of metastasis, which are currently unclassified pre-amendment devices. This included a discussion of the known risks, safety/effectiveness concerns, and a general classification recommendation for the device.

FDA Questions/Panel Deliberations:

FDA Questions

1. 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].

a. 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"):

    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:

Identified Risk	Description/Examples
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 may result in tumor cell survival leaving proliferative (able to function, grow, and divide) tumor cells present in the blood. • 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. • 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.[1]
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.[2] 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.

[1] Gonzalez H, Hagerling C, Werb Z. Roles of the immune system in cancer: from tumor initiation to metastatic progression. Genes Dev. 2018;32(19-20):1267-84. doi: 10.1101/gad.314617.118. PubMed PMID: 30275043; PubMed Central PMCID: PMC6169832.

[2] "Recommendations Regarding License Amendments and Procedures for Gamma Irradiation of Blood Products". Dated July 22, 1993. Available at: https://www.fda.gov/files/vaccines%2C%20blood%20&%20biologics/published/Recommendations-Regarding-License-Amendments-and-Procedures-for-Gamma-Irradiation-of-Blood-Products.pdf

Unintended radiation exposure to the operator and public	• 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. • 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.
Delayed or lack of retransfusion of irradiated blood or blood component	Use of device inherently adds time to re-transfusion procedure. Device malfunction, or operator error could add additional delay or risk of giving salvaged blood that was not irradiated. • 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. • 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 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.

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. There is also 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 all the 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.

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

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.**

Panel Deliberations

The Panel agreed with inclusion of all FDA-identified risks in the overall risk assessment of blood irradiators for the prevention of metastasis. The Panel also expressed that the following risks should be added:

- Risk of induction of a new cancer due to irradiation of the 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.

There were differing opinions from the Panel on whether a reasonable assurance of safety could be established for blood irradiators for the prevention of metastasis with the right controls. The consensus appeared to be that risks associated with the blood irradiator device (hardware and software) could be mitigated with special controls. However, at this time, the risks associated with the intended use of the device – for the prevention of metastasis in cancer patients receiving intraoperatively salvaged blood – could not fully be identified or mitigated with special controls.

There was a consensus that there is not a reasonable assurance of effectiveness for these devices due to the very limited data available on their effectiveness and that such data is needed.

FDA Questions

1. 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.

   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.

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.[3,4,5] 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.**

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.**

[3] Waters JH, Yazer M, Chen Y-F, Kloke J. Blood salvage and cancer surgery: a meta-analysis of available studies. Transfusion. 2012;52(10):2167-73. doi: https://doi.org/10.1111/j.1537-2995.2011.03555.x.
[4] https://www.uptodate.com/contents/surgical-blood-conservation-blood-salvage#H380732602. Accessed September 27, 2023.
[5] Zaw AS, Bangalore Kantharajanna S, Kumar N. Is Autologous Salvaged Blood a Viable Option for Patient Blood Management in Oncologic Surgery? Transfus Med Rev. 2017;31(1):56-61. Epub 20160621. doi: 10.1016/j.tmrv.2016.06.003. PubMed PMID: 27421661.

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.**

Panel Deliberations

Overall, the Panel agreed that the risk of injury is unreasonable given the lack of probable benefit. However, there were three (3) comments on concerns with wording in FDA's question 2a. These wording concerns were regarding the statement that intraoperative blood salvage was a relative contraindication for active malignancy, the uncertainty as to the volume of blood that can be effectively irradiated, and the wording that it was unclear what dose should be used as this selection needs to balance effectiveness (i.e., cancer cell killing) with safety (unintended negative consequences of radiation on other blood components). The consensus was that the following was a more appropriate assessment of the unreasonable risk of injury or illness posed by blood irradiators for the prevention of metastasis:

FDA believes that blood irradiators for the prevention of metastasis present 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 type. 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. 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 should 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. It is also unclear what volume of blood would need to be irradiated to effectively prevent metastasis. Therefore, the risk of injury is unreasonable given the lack of probable benefit.

Overall, the Panel agreed that special controls could not mitigate the risks to health. The Panel discussed information that would be needed from trials to demonstrate safety and effectiveness including the appropriate radiation dose and appropriate blood volume (this could be expressed as a percentage of total blood volume). The Panel also suggested that data would be needed to determine the safety and effectiveness on various cancer types and stages and noted the importance of endpoints consistent with oncological goals (e.g., overall survival, disease free endpoint). There was a consensus the Panel wanted a clearly delineated clinical profile for

patients that benefit from use of irradiated salvaged blood along with an assessment of short and long-term outcomes.

Other comments were provided, including:

1) The level of quality of evidence should be consistent with the disease in the indication. For example, if patients are undergoing a surgical procedure with curative extent, then endpoints should be appropriate for a curative intent clinical trial.
2) Randomized controlled trials are needed to show that the benefit outweighs the risks.
3) Clearly delineate the patient population and the expected clinical benefit.
4) Need overall survival data and long-term follow-up data.
5) Consider subsets based on age group.
6) Based on the experience of irradiating ex-vivo blood to 25 Gy, it was noted that dose may impact effectiveness more than safety.

The Panel agreed with the FDA's assessment that special controls could not be established to mitigate the risks to health associated with the device. The panel agreed with FDA's proposed classification of class III (PMA).

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Transcripts may be downloaded from:
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OR

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