SUMMARY MINUTES

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

RADIOLOGICAL DEVICES ADVISORY COMMITTEE MEETING

MEDICAL DEVICES ADVISORY COMMITTEE

November 7, 2023
9:00 a.m. EST

Attendees

Chairperson

John Carrino, MD, MPH
Vice-Chairman
Radiology and Imaging
Weill Cornell Medicine - New York, NY

Voting Members

Suan Ascher, MD
Professor of Radiology
Georgetown University School
Of Medicine - Washington, DC

J. Daniel Bourland, MSPH, PhD
Professor Department of Radiation
Oncology, Biomedical Engineering
And Physics
Wake Forest University School of Medicine - Winston-Salem, NC

Grace Hyun J. Kim, PhD
Professor in Residence
Department of Radiological
Sciences & Biostatistics
University of California - Los Angeles, CA

Elizabeth Krupinski, PhD
Professor and Vice-Chair
For Research Department of
Radiology & Imaging Services
Emory University - Atlanta, GA

Stephen Solomon, MD
Professor and Chief
Department of Radiology
Weill Cornell Medicine - New York, NY

Margarita Zuley, MD
Professor of Radiology
Vice-Chair, Quality and Strategic Development
University of Pittsburgh
Medical Center - Pittsburgh, PA

Consultants

John Hess, MD, MPH
Professor of Laboratory
Medicine and Pathology
University of Washington
School of Medicine - Seattle, WA

Louis Kavoussi, MD, MBA
Professor of Urologic Surgery
The Arthur Smith Institute
For Urology
Northwell Health - Lake Success, NY

Victor van Berkel, MD
Division Chief of Thoracic Surgery
University of Louisville
School of Medicine - Louisville, KY

Jonathan Waters, MD
Anesthesiologist
Professor of Anesthesiology and Bioengineering
University of Pittsburg - Pittsburgh, PA

Marjan Burma, MD
Professor of Pharmaceutical Sciences
University of Arkansas for Medical Sciences - Little Rock, AR

Temporary Non-Voting Members

Andy Chen, MD
Assistant Professor
Department of Medicine/Hematology &
Medical Oncology
Knight Cancer Institute
Oregon Health & Science University - Portland, OR

Joseph Cullen, MD
Professor of Surgery
Department of Surgery
Iowa City VA Medical Center - Iowa City, IA

Jorge Nieva, MD
Associate Professor of Clinical Medicine
University of Southern California - Los Angeles, CA

Edward Snyder, MD
Professor of Laboratory Medicine
Assistant Cancer Center Director
Yale School of Medicine - New Haven, CT

Daniel Song, MD
Professor Radiation Oncology
And Molecular Sciences
John Hopkins University - Baltimore, MD

Industry Representative

John Jaeckle, MS
Chief Regulatory Affairs
Engineer & Strategist
GE Healthcare - Brookfield, WI

Consumer Representative

Karen Rue, RN-BC, MBA
Gerontology Nurse/Owner
Aging Life Care Professional
Hailind Consulting, LLC - Lafayette, LA

Patient Representative

Natalie Compagni-Portis, PsyD, MFT
Psychologist
Private Practice - Oakland, CA

FDA Participants

Julie Sullivan, PhD
Director
Division of Radiological
Imaging and Radiation Therapy Devices
CDRH - Silver Spring, MD

Designated Federal Officer

Jarrod Collier, MS
Office of Management
CDRH - Silver Spring, MD

FDA Presenters

Scott McFarland, J.D.
Regulatory Counsel Immediate Office
CDRH/OPEQ, FDA - Silver Spring, MD

Justina Tam, MD
Lead Reviewer
Division of Radiological Imaging
and Radiation Therapy Devices
Office of Radiological Health
CDRH's Office of Product Evaluation and Quality Silver Spring, MD

Open Public Hearing Speakers

Diana Zuckerman, PhD
President of the National Center for Health Research

CALL TO ORDER & INTRODUCTIONS

Dr. Carrino, the Panel's chairperson, called the meeting to order, advised that the panel members participating in today's meeting have received training in FDA device law and regulations, and announced the agenda for the meeting: to discuss and make recommendations on the classification of blood irradiator devices for the prevention of metastasis, which are currently unclassified pre-amendments devices, to Class III, that is general controls and premarket approval.

Dr. Carrino asked committee members and the FDA attending virtually to introduce themselves.

CONFLICT OF INTEREST STATEMENT & APPOINTMENT OF NON-VOTING MEMBERS

Upon completion of introductions, **Jarrod Collier,** the Designated Federal Officer, read the conflict of interest statement and made general announcements, noting that based on the agenda for today's meeting and all financial interests reported by the panel members and consultants, no conflict of interest waivers have been issued. **Mr. John Jaeckle** is serving as the industry representative, acting on behalf of all related industry. **Mr. Jaeckle** is employed by GE Healthcare. **Jarrod Collier** reminded all members and consultants that if the discussions involve any other products of firms not already on the agenda for which the FDA participant has a personal or imputed financial interest, that participant needs to exclude themselves from such involvement and their exclusion will be noted for the record.

Jarrod Collier advised that for the duration of the radiological devices panel meeting on November 7, 2023, **Drs. Andy Chen, Natalie Compagni-Portis, Joseph Cullen, Jorge Nieva**, **Edward Snyder**, and **Daniel Song** have been appointed to serve as temporary non-voting

members. **Jarrod Collier** noted for the record that **Drs. Chen, Cullen**, and **Song** serve as consultants. **Dr. Nieva** serves as a voting member, and **Dr. Compagni-Portis** serves as a patient representative to the Oncologic Drugs Advisory Committee at the Center for Drug Evaluation and Research. **Dr. Snyder** serves as a consultant to the Blood Products Advisory Committee at the Center for Biologics Evaluation and Research. These individuals are special government employees or regular government employees who have undergone the customary conflict of interest review and have reviewed the materials to be considered at this meeting.

The meeting was handed back to **Dr. Carrino**, who advised they had two additional introductions. He also stated there would be another panel member joining later, and they would do an introduction at that time. The two additional panel members were **Jonathan Waters** and **Marjan Burma.**

OPEN PUBLIC HEARING

Jarrod Collier read the open public hearing disclosure process statement and turned the meeting back over to **Dr. Carrino. Dr. Carrino** stated that there was one request to speak, and they have five minutes allotted for their comment.

Dr. Diana Zuckerman noted that these devices have been treated as 510(k) devices since 1976, which has not resulted in scientific data of either safety or effectiveness, nor have there been studies to indicate that it improves patient outcomes. She asked given the lack of evidence of benefits, what are the risks? There are a few adverse events reported to FDA's MDR system, and everyone agrees that adverse events are underreported, but the FDA has identified numerous serious risks.

Dr. Zuckerman advised that most patients and surgeons assume that these products are proven and safe, but would they choose them if they knew how little scientific evidence there is regarding safety or effectiveness? She urged FDA to categorize these as Class III and to require a PMA.

FDA PRESENTATION - CLASSIFICATION OVERVIEW - SCOTT MCFARLAND

Dr. Carrino announced the open public hearing was closed and turned it over to FDA for their presentations.

Dr. Scott McFarland reiterated the purpose of the panel meeting is regarding the classification of devices that are currently unclassified, specifically for one pre-amendments unclassified device type. **Dr. McFarland** provided a high-level overview of the medical device classification process, which forms the basis for the discussion. He explained the three classes of medical devices: Class I, Class II, and Class III. Devices are classified based on the controls necessary to mitigate the risks associated with the device type. Class I devices are only subject to general controls, Class II are subject to both general and special controls, and Class III are subject to general controls and pre-market approval. He noted that importantly, a device should be placed in the lowest class whose level of control provides reasonable assurance of safety and effectiveness.

Class I devices are those devices for which general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device. General controls are basic requirements that apply to all medical devices and are outlined in the Federal Food, Drug, and Cosmetic Act. Some examples include meeting establishment registration and device listing requirements, following good manufacturing practices, adhering to record keeping and reporting requirements, and ensuring the devices are not misbranded or adulterated. A few examples of Class I devices include scintillation gamma cameras, radiographic head holders, radiographic anthropomorphic phantoms, and radiographic bill marking systems.

There's an alternative pathway to determine that a device is Class I. Class I devices could also be devices that cannot be classified into Class III because they're not life sustaining, life supporting, or of substantial importance in preventing impairment of human health, and they do not present a potential unreasonable risk of illness or injury. And these devices cannot be classified into Class II because insufficient information exists to establish special controls to provide reasonable assurance, safety, and effectiveness.

Class II devices are those devices which cannot be classified into Class I because general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness of the device, and for which there is sufficient information to establish special controls to provide such assurance. There are many types of special controls, but some examples include performance testing, sterilization validation, and device specific labeling requirements. These special controls, in combination with the general controls previously described, provide reasonable assurance of safety and effectiveness for Class II devices. Examples of Class II devices include full field digital mammography systems, radiological computer aided triage and notification software, and rectal balloon for prostate immobilization devices.

Class III devices are those which cannot be classified in Class II because insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device, and the devices are life sustaining or life supporting or are of substantial importance in preventing impairment of human health or present a potential unreasonable risk of illness or injury. Class III devices typically require premarket approval through a premarket approval application, or PMA, prior to being marketed. Examples of Class III devices include transilluminator for breast evaluation devices, digital breast tomosynthesis systems, and radioactive microsphere devices.

A flowchart was presented that walks the general decision-making process for each of the classes that were discussed. **Dr. McFarland** advised they start by determining whether general controls are sufficient to provide reasonable assurance of safety and effectiveness. If so, the device can be appropriately regulated in Class I. If not, they ask whether there is sufficient information that allows them to be able to develop special controls that, in combination with the general controls, provide reasonable assurance of safety and effectiveness. If so, the device can be appropriately regulated in Class II. If not, then it would be Class III if the device is life supporting or life sustaining or if it is of substantial importance in preventing impairment of human health or if it presents a potential unreasonable risk of illness or injury. If the device is not life supporting or life sustaining or of substantial importance in preventing impairment of human

health and does not present a potential unreasonable risk of illness or injury, they end up back at a Class I designation.

Dr. McFarland shifted panel's focus to the classification process for blood irradiators for prevention of metastasis, a pre-amendments unclassified device type, which will be discussed today. He provided a few quick definitions. What is a pre-amendments device? A pre-amendments device is a device which was introduced into interstate commerce prior to May 28th, 1976, or the date of enactment of medical device amendments to the Federal Food, Drug, and Cosmetic Act. An unclassified device is a pre-amendments device that was not classified by the original classification panels and for which no classification has subsequently been conducted. Thus, no classification regulation currently exists, which is the purpose of this panel meeting: to formally classify these unclassified devices.

Dr. McFarland noted while these devices are not classified, they are currently brought to market through the 510(k) process. He explained the steps FDA has to complete before reamendments on classified devices will be classified. FDA asked the panel to provide input on the classification of blood irradiators for prevention of metastasis and whether they should be classified into Class III, Class II, or Class I. The input should include an identification of the risk to health presented by the device type, a discussion of whether the device is life supporting, life sustaining, or of substantial importance in preventing impairment of human health, or if it presents a potential unreasonable risk of illness or injury. The panel will also be asked to discuss whether general controls alone are sufficient to provide reasonable assurance of safety and effectiveness for the device type. If not, does sufficient information exist to develop special controls, and what should those special controls be, that in combination with the general controls, provide reasonable assurance of safety and effectiveness for the device type?

Following this panel meeting, FDA has several steps to follow before making a determination. If FDA determines that the devices can be appropriately regulated as Class I or Class II devices, the devices may continue to be marketed. If, however, FDA determines that they fall into a Class III designation, a separate call for PMAs will also be published. Existing devices may remain on the market until a specified date, at which point a PMA would need to be submitted in order to continue marketing. If this PMA is not approved, existing devices would be considered misbranded and must be removed from commercial distribution.

FDA PRESENTATION - BLOOD IRRADIATORS for the PREVENTION of METASTASIS - DR. JUSTINA TAM

Dr. Justina Tam presented information regarding FDA's efforts to classify blood irradiators for the prevention of metastasis. She advised that FDA is looking for thoughts and recommendations on the appropriate regulatory classification for these devices. **Dr. Tam** advised that these devices be classified as Class III.

Blood irradiators for the prevention of metastasis are devices that are intended to irradiate intraoperatively salvaged blood in cancer patients that are undergoing surgery to assist in the prevention of metastasis. These irradiators deliver a desired dose of ionizing radiation to ex vivo blood or blood products. All of the FDA cleared blood irradiators use one of two radiation

sources: an x-ray tube or a radioisotope source, commonly Cobalt-60 or Cesium-137. For this classification panel, we are only focusing on the x-ray tube source because only devices with x-ray sources are currently cleared for the indication of preventing metastasis.

Regarding existing regulations, blood irradiators that use x-ray tubes are subject to the requirements of the electronic product radiation control provisions under the FD&C Act, including those for cabinet x-ray systems, under 21 C.F.R. 1020.40. Blood irradiators for the prevention of metastasis are a subset of devices currently cleared under product code MOT. A schematic of the surgical procedure illustrating how the device is used was presented. During cancer surgery, sometimes there is significant blood loss. One method of managing the patient's blood loss is to collect the blood that is lost during surgery via a suction device. This suctioned blood may then be filtered and processed before being irradiated to prevent the proliferation of cancer cells in this ex vivo blood while salvaging the red blood cells for reinfusion. Based on the literature and device information gathered, it does not appear that this technique of irradiating intraoperatively salvaged blood from cancer patients for the prevention of metastasis is widely used.

Blood irradiators for the prevention of metastasis have been cleared for the following indication. The device is intended for use in the irradiation of intraoperatively salvaged blood for cancer patients undergoing surgery to assist in the prevention of metastasis. Regarding the regulatory history of blood irradiators, blood irradiators are a pre-amendment unclassified device type. This means that this device type was marketed prior to the Medical Device Amendments Act of 1976. It was not classified by the original classification panels. Currently, these devices are being regulated through the 510(k) pathway and are cleared for marketing if their intended use and technological characteristics are substantially equivalent to a legally marketed predicate device. Because these devices are unclassified, there is no regulation associated with the product code.

In 1993, the Center for Biologics Evaluation and Research, CBER, published a guidance regarding license amendments and procedures for the gamma irradiation of blood products. X-ray based blood irradiators, which are the focus of this classification panel, have generally been manufactured and used in a manner that accords with the recommendations in that guidance. Blood irradiators as medical devices are among the few medical devices that are jointly regulated by CBER and the Center for Devices and Radiological Health, CDRH. To date, two 510(k)s have been cleared as blood irradiators for the prevention of metastasis through the premarket notification 510(k) pathway. The first 510(k) was cleared in 2005, and the second 510(k) was cleared in 2016. For additional details on these cleared devices, please refer to the Executive Summary, Section 2.

Between the times of these clearances, in 2012, FDA presented information to the Radiological Devices Panel of the Medical Devices Advisory Committee to help classify blood irradiators intended to irradiate blood and blood products to prevent graft versus host disease, including risks and potential mitigation measures. Following the discussion, the panel recommended that the agency classify blood irradiators for the prevention of graft versus host disease as Class II medical devices with special controls and requiring 510(k) premarket notification. In this 2012 panel, the classification of blood irradiators for the prevention of

metastasis was not discussed. In the 2012 panel, although the classification of blood irradiators for the indication of the prevention of metastasis was not discussed, this additional indication was briefly noted for one of the 12 cleared devices at the time. Because this additional indication of the prevention of metastasis may involve new risks, FDA is convening this classification panel to discuss the current landscape of product technology, indications for use, safety and effectiveness, and risks to health, on which to base classification of blood irradiators for the prevention of metastasis.

Cancer is the second leading cause of death in the U.S. Tumors may spread via the vascular or lymphatic system from the original location in a process called metastasis. One method to treat cancer is with surgery. Between leukocytes and tumor cells, compared to other blood components such as red blood cells, can be exploited by irradiating blood to remove activated T cells to prevent transfusion associated graft versus host disease or kill tumor cells within the salvaged blood. During oncologic surgery, if patients experience significant blood loss and require a blood transfusion, an alternative to allogenic blood transfusion is to use salvaged blood from the cancer patient and reinfuse this salvaged blood back into the patient. The blood can also be passed through a leukocyte reduction filter to reduce the concentration of white blood cells. For this panel, we are discussing irradiation of the blood that would be performed by blood irradiator devices after the intraoperative blood salvage and before re-transfusion.

In general, the primary outcome measures for patients with cancer is overall survival. For cancer patients receiving irradiated intraoperatively salvaged blood, the outcomes may include the risk of postoperative infections, tumor recurrence, or spread of cancer, in other words, metastasis. Regarding currently available treatments for most patients, the standard treatment is allogenic blood transfusion for blood loss during surgery or for low post-operative hemoglobin levels. Alternatively, a patient may undergo intraoperative blood salvage, which may use cell saver or cell recovery technologies to separate, wash, and concentrate salvaged red blood cells, which are then re-infused back into the patient using microaggregate or lithocyte depletion filters.

Leukocyte depletion filters are FDA cleared devices for the removal of white blood cells from other blood components. These leukocyte depletion filters also have the ability to remove cancer cells. Alternatives to intraoperative cell salvage include preoperative donation by the patient or other intraoperative techniques like hemodilution or postoperative salvage. These strategies may be used to avoid allogenic transfusion and may be used preferentially for patients with religious or safety concerns. The primary objection to using intraoperatively salvaged blood in oncologic patients undergoing surgery is the possibility that malignant cells in the operative field may be re-transfused back into the patient and result in tumor recurrence or metastasis.

FDA conducted a literature review to identify any published information between January 1, 2002, and April 20th, 2023, regarding the safety and effectiveness of blood irradiators for the prevention of metastasis. Searches were limited to publications in English and excluded studies where blood was not recovered intraoperatively from a human or animal subject with malignancy. Additionally, as both radioisotope and x-ray sources are known to produce ionizing radiation that damages DNA and stops the proliferation of cancer cells, blood irradiators using either radiation source were included in the literature search. Because the FDA cleared blood

irradiators and product code MOT are similar in design and function to those intended for the prevention of metastasis, any literature referencing the use of blood irradiator was analyzed. The search yielded 487 records, but after duplicates were removed, 475 unique records were screened for relevance. In the end, 10 records were found to meet inclusion/exclusion criteria and were determined to be relevant to the safety and effectiveness of blood irradiators used to prevent metastasis. Regarding safety, none of the articles discussed risks or performance issues related to any identified blood irradiator used for the prevention of metastasis. However, while not specifically an adverse event, multiple papers identified that irradiating blood took additional time. Regarding effectiveness, conclusion is that the effect of salvaged blood irradiation on tumor recurrence and metastasis was not definitively evaluated in any of the articles. Only one article examined the effect of irradiation on metastasis. However, the effect of irradiation of salvaged blood on tumor recurrence could not be definitively evaluated because of a limited sample size and the fact that all patients, whether they received autologous transfusions or not, received allogenic transfusions. The available evidence is inadequate to draw definitive conclusions about the safety or effectiveness of blood irradiators for the prevention of metastasis.

The MDR system provides FDA with information on medical device performance from patients, healthcare professionals, consumers, and mandatory reporters, manufacturers, importers, and device user facilities. The FDA receives MDRs of suspected device associated deaths, serious injuries, and certain malfunctions. Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the submission of incomplete, inaccurate, untimely, unverified, duplicated, or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone, due to potential underreporting of events and lack of information about the frequency of device use. The existence of an adverse event report does not definitely establish a causal link between the device and the reported event. Because of multiple limitations, MDRs comprise only one of the FDA's tools for assessing device performance. As such, MDR numbers and data should be taken in the context of the other available scientific information.

To further contribute to the benefit risk assessment of blood irradiators for the prevention of metastasis, the agency reviewed individual MDRs to identify adverse events related to the use of blood irradiators entered through September 25, 2023. The search resulted in the identification of seven unique MDRs. Of the seven MDRs, there were five related to blood irradiators, one related to a malfunction of film, and one miscategorized device. Of the five MDRs that were related to blood irradiators, two were related to low x-ray tube output, which may have resulted in less than 50 gray being delivered to all locations within the device canister. The root causes were determined to be isolated electrical and mechanical issues. The other three MDRs either contain no narrative or were a suggestion to upgrade all devices to provide an audible alarm or computer-generated message to designate a serious mechanical failure. Additionally, an analysis of accidental radiation occurrences, AROs, was performed. Per 21 C.F.R. 1002.20, manufacturers of radiation emitting electronic products must report to FDA all accidental radiation occurrences reported to or known to the manufacturer. No AROs were found. Overall, the MDR and ARO analyses showed few device malfunctions over the lifetime of use for these devices.

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 may occur after the firm recalling the medical device product conducts and communicates with its customers about the recall. Therefore, the recall information posting date, create date, identified on the database indicates the date FDA classified the recall. It does not necessarily mean that the recall is new. Recalls are classified into a numerical designation, I, II, or III, by the FDA, to indicate the relative degree of health hazard presented by the product being recalled. A review of the medical device recall database found one recall for devices under product code MOT. The search was performed without a time restriction up to September 27, 2023. The Class II recall was for an x-ray based blood irradiator intended for the prevention of transfusion associated graft versus host disease. The device did not comply with the associated performance standards within 21 C.F.R. subchapter J because an interlock was not directly linked to the door. The recall analysis did not provide evidence that blood irradiators as medical devices pose a serious health hazard.

To determine the appropriate classification for blood irradiators for the prevention of metastasis, we identified the risks associated with these devices. To identify the risks, we reviewed MDRs, recall information, and the literature analysis, as previously discussed, and the information available to FDA regarding cleared devices. Here are the seven risk categories we've identified for blood irradiators for the prevention of metastasis: The proliferative malignant cells in re-transfused blood due to incorrect dose or improper dose of radiation delivered. Second, a 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. Thirdly, 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. Damage to blood components from radiation. Radiation damages the membrane of red blood cells, leading to higher concentrations of potassium and plasma, hemolysis, destruction of red blood cells, and affects red cell viability. Unintended radiation exposure to the operator and public. Electrical shock or burn. Delayed or lack of re-transfusion of irradiated blood or blood components. Mechanical or crush injury.

Based on the available information, it is unclear if identified risks may have long term safety consequences, such as the cancer outcome, patient recovery, or survival. These risks may not be mitigated by special controls. Ability to have more stringent post market oversight typically associated with Class III devices, such as annual reports and reports of manufacturing changes, is believed to be needed. FDA proposes that blood irradiators intended 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. Additionally, blood irradiators intended for the prevention of metastasis present a potential unreasonable risk of illness or injury based on the limited clinical information that has been obtained.

Q&A FOR FDA PRESENTERS

Dr. Carrino introduced panel member Elizabeth Krupinski had joined and had her introduce herself and provide her affiliation, and then he opened it up for clarifying Q&A for the FDA presenters. **Dr. Compagni-Portis** asked what training is required. **Dr. Sullivan** responded that currently no specific user is identified. It would likely be someone with knowledge of radiation. **Dr. Compagni-Portis** asked if there is information about the difference between the use in solid tumors or blood cancers. **Dr. Sullivan** advised that based on literature research, there is not information about the difference.

Dr. Bourland asked if this consideration applies to both x-ray and gamma devices or only x-ray, were the two approved devices x-ray or gamma, and if classification is changed, approximately how many of those devices may have to eventually be removed from market? **Dr. Sullivan** responded that they are looking to classify specifically x-ray based irradiators, the two approved devices are both x-ray based, and they don't have a number of devices. They don't believe this is a commonly used indication for the device.

Dr. Nieva inquired about time and increased operating room time. Is that unique to this device, or does any operative red cell salvage process take an equivalent amount of time? He also asked about a mention that the purpose of these devices was in some way psychological and asked if there is quantitation around how many patients choose irradiation as their decision to avoid allogenic transfusion. **Dr. Sullivan** stated there may be member of the panel that know a bit more, but the time provided was noting the time for irradiation specifically. She didn't remember a mention of the psychological as part of benefit risk analysis, and they don't have that information.

Dr. van Berkel questioned why is FDA requesting reclassification now when these have been out for a while, and there was a meeting in 2012 and nothing was done then either. What changed? Was there an adverse event? Is FDA clearing a backlog? **Dr. Sullivan** explained that this specific indication was not discussed during previous 2012 panel. That panel focused on transfusion graft versus host disease. FDA is trying to get currently unclassified devices to be classified because it causes public health concern if they don't have adequate controls of those devices.

Dr. Zuley asked if FDA classified this as Class III, would the reviews be focused more specifically, instead of all cancers, to really try and subset to understand who may benefit more or less? **Dr. Sullivan** explained that she couldn't speak to the future, but for a PMA device, they would have to show safety and effectiveness from that specific device and in the specific intended population that they would be interested in. So she believes there would be more tumor specific or cancer specific information.

Dr. Waters, based on his experience, has concerns about the delay that it would take to move a unit from the OR to the irradiator and then return of that unit of blood back to operating room. **Dr. Sullivan** again explained that PMA process would require the device to show safety and effectiveness within intended use population, and that although they have some ideas of what

they would be considering clinically meaningful or how to measure benefit or effectiveness, such as overall survival or time to recurrence or metastasis, this is something they would like panel's input on as well. **Dr. Waters** followed up with what time frame would PMA require for this to be done. **Dr. Sullivan** responded that it would likely be a number of years. After this process if panel recommended Class III and FDA took up that recommendation, then FDA has several steps to complete before they could make a call for PMAs, and it's usually at least a year to allow for time for PMA to be submitted and reviewed.

Karen Rue asked again about how long before potentially gathering enough data. **Dr. Sullivan** advised if all steps were taken, then it would be up to the manufacturers who wanted this indication to collect the data and come in with a PMA submission. So if there was no interest in coming forward for this indication, then they may not see a PMA. **Dr. Kavoussi** asked about reimbursement if this were left alone and unregulated. **Dr. Sullivan** advised FDA doesn't get into questions of reimbursement. That would be their CMS agency. If no one wanted this indication and there was no PMA for this indication, the 510(k)s for the blood irradiators used to prevent transfusion assisted graft versus host disease would still remain on the market. She advised FDA is still taking the recommendations from the 2012 panel and looking at the literature to come up with an updated proposed rule for those devices. So if they wanted to continue to use the blood irradiators to prevent transfusion associated graft versus host disease, there would be no disruption in the presence of those devices being out on the market. **Dr. Kavoussi** raised concerns about potential for abuse for financial reasons and potential for abuse based on some soft literature from other countries.

Dr. Zuley advised that volume of blood needing treated also needs to be discussed to determine efficacy. **Dr. Song** asked since this would still have approval for GVHD and physicians are not restricted to off-label use, then once could still treat patients with this despite it not being marketed for that. **Dr. Sullivan** confirmed his understanding is correct. **Dr. Jaeckle** shared some comments such as there could be grounds made to reduce actual radiation time. He also advised that of the identified seven hazards or potential risks, most of them are not unique to such a device and are routinely handled in other devices by Class II special controls. He also advised that going for a PMA is a costly endeavor, and a company would have to look at getting a return on their investment of time and money, and if these are in limited use, it's unlikely somebody would submit for a PMA.

PANEL QUESTIONS AND DELIBERATIONS

Dr. Carrino called the meeting back to order after a break, made a few announcements, and asked **Dr. Justina Tam** to read the questions that the panel will deliberate on. Question 1: According to 21 CFR 860.7(d)(1), there is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probably 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 probably 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), there 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").

Question 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 last may not be exhaustive: the risks include the 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, damage to blood components from radiation, unintended radiation exposure to the operator and public, electrical shock or burn, delayed or lack of re-transfusion of irradiated blood or blood component, mechanical or crush injury. 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 risk 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.

Question 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.

Question 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.

Dr. Krupinski advised that for question 1, she definitely agrees with the inclusion of all of those risks and stated it may not be exhaustive. She feels some of the ones during their discussion should be added. Getting to question two, she doesn't feel there is a lot of evidence that this is an effective device. **Dr. Jorge Nieva** advocated for operating room time to be added as a risk. He stated that as for the other questions, there is obviously no evidence that this works for the indication. He is concerned that "the horse is out of the barn" and people are doing this anyway without the use of these devices, but he doesn't feel anything should be labeled with this benefit giving everything known about how tumor cells circulate and the incomplete information regarding immunologic effects.

Dr. Natalie Compagni-Portis also agrees with the list of risks, and she agrees with the other panel members that they don't know what the risks are. She appreciates **Dr. Nieva's** comment about the "horse out of the barn," and she feels they are trying to "contain this horse." She implored the panel and FDA to utilize the precautionary principle and not let this get any further without having the data needed about safety and effectiveness. She feels that too often controls haven't been utilized to keep patients safe, or patient's vulnerabilities have been used or even exploited their hope for a cure and longer life to use them as guinea pigs with regard to devices and drugs where the risks and treatments are unknown and benefits are unproven. They all share the same goal of patient safety, so controls need to be utilized to make sure of that.

Dr. Zuley agrees with all of the risks put forth by FDA and would like to suggest three additional ones that colleagues mentioned during panel discussions: first being induction of a new cancer from irradiating the cells, second being immunotherapy, induction of some mutation of cells that inadvertently are radiated twice, and the last being the potential risk of billing for a procedure that has not been shown to be safe and effective. She does not feel the safety and effectiveness of this device for this indication has been shown. **Dr. Carrino** clarified for purposes of summarizing that in addition to the identified risks, she was advising to add risk of potential for induction of cancer within the irradiated blood product, and induction of mutation. And the safety and effectiveness comment was for deciding regarding Class III. **Dr. Zuley** confirmed.

Dr. Bourland agrees with the identified risks, especially the last one that states it is not an exhaustive list. He does believe there is some additional risk of logistics. **Dr. Carrino** clarified that he was stating that if there's a certain dose limit, we will want to know what amount of radiation is going to be applied, and the vendor has to support use for that dose. **Dr. Carrino** confirmed with FDA about separating work flow from safety and effectiveness. He asked if workflow or embodiment of the device and how it's used plays into what the panel can comment on for answering the questions. **Dr. Sullivan** confirmed that would be relevant. They are looking for the panel to evaluate usability and human factors so the device can be used by the potential user in the correct manner.

Dr. Kim commented the importance of a dose ranging study to understand more how it works in the human body. **Dr. Carrino** confirmed she was talking about if the vendors were looking at using multiple doses or multiple levels of radiation, they would need to know how that might affect the product or the patient, and they would want to provide a range or a number that

they ensure the device is going to deliver that amount. **Dr. Krupinski** added to **Dr. Kim** that it's also the type of cancer and the stage of cancer as well.

Dr. Carrino summarized question one that it's the panel's feeling that there is no reasonable assurance of effectiveness of blood irradiators for the prevention of metastasis. He asked **Dr. Sullivan** if this summary was adequate. She confirmed.

Dr. Carrino summarized for 1a: The panel agrees that all of the identified risks should be included. There were some additional risks mentioned, so the panel thinks it would be important to include the risk of either inducing cancer or mutation within the irradiated specimen or blood volume, are there specific dose effects with what the vendor would be proposing for the doses. Risks would also include the usability, the risk of handling the blood product such as transferring it from the OR to another facility. Those are risks the panel would endorse adding. He asked **Dr. Sullivan** if this is adequate. She confirmed.

Dr. Carrino summarized 1b - Panel feels that there is not a reasonable assurance of effectiveness for the blood irradiators and certainly with consideration of potential for PMA, they would want a rigorous study design with the same goals as surgery that is curative. **Drs. Kim** and **Zuley** again added comments about subsets for cancer type and cancer stage. **Dr. Carrino** clarified that panel believes there is not a reasonable assurance of effectiveness based on the evidence out there at this time.

The panel moved to Question 2. Does the panel agree with the assessment that the risk of injury is unreasonable given the lack of probably benefit. **Dr. Krupinski** and **Dr. Bourland** agree.

Dr. Carrino summarized 2a that the panel agrees with this assessment, and they have explained why. **Dr. Song** added concerns about the wording of parts of the statement. **Dr. Sullivan** advised if there is something incorrect that would need to be updated to be able to agree, they would want to know what that is, but just pointing out that you don't agree for a particular reason, that's all they need to know. **Dr. Nieva** expressed concern about the active malignancy sentence. **Dr. Carrino** advised panel suggestion is to remove the sentence that goes 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. **Dr. Carrino** summarized that with the two modifications that were just mentioned, panel would agree with this assessment.

Dr. Sullivan clarified where the panel wanted to change could to should? Is it thought that there is a sort of maximum dose that could be given to kill everything. Panel responded the latter. **Dr. Carrino** asked if this is now adequate, and **Dr. Sullivan** confirmed.

Panel moved on to 2b i. and 2b ii. **Dr. Zuley** wanted to go back to 2a. She feels something should be added about the volume of blood treated. She advised she was speaking about the sentence, it is unclear what dose of radiation should effectively be used to irradiate intraoperatively salvaged blood and add "what volume would be safe," or something like that.

Dr. Carrino stated that is now their third edit, and asked **Dr. Sullivan,** with those three edits, is the summary adequate. **Dr. Sullivan** agreed.

Panel moved on to 2b i. **Dr. Compagni-Portis** agrees with the assessment and feels performance data is needed around overall survival. There needs to be controlled studies to analyze and assess the benefit and the risks. **Dr. Krupinski** added what they have talked about before, which is the different types of cancers and stages. **Dr. Carrino** summarized the panel would state that they agree that they don't believe special controls can be established generally to mitigate the risks to health associated with these devices. The types of performance data would be outcome of randomized trials looking at two groups, how one does with the irradiated blood and potentially another one out. The clinical information has been emphasized on the type and stage of cancer and what the typical prognosis would be. There was some additional input.

Dr. van Berkel agrees with the statement that there's not enough info and this should be a Class II device, but cautioned against getting into the weeds on something that is perhaps not necessarily relevant to what they are talking about today. He doesn't feel that there is going to be a PMA for these devices, but given that this part is asking if someone were to design a trial, what are things that should be worried about from FDA's perspective, we would say something along the lines that panel would like clearly delineated clinical profile of the patients that would fit into this circumstance, and we would want both long term oncologic data suggesting benefit. Because you don't want someone to read all of these suggestions and miss something that wasn't mentioned that wasn't thought of. He feels the panel has brought up excellent points, but it would be up to the company going for the application to work through these things.

Dr. Chen asked FDA if they would consider modifying the label for irradiators that are approved for the prevention of transfusion associated graft versus host disease to clarify that they are not intended for us for prevention of metastasis to discourage off-label use of that unless an investigator wants to design a study for it?

Dr. Sullivan thanked him for the feedback and advised they would have to take this internally and see what they could do asking for some sort of limitation of an indication for the devices that were, for example, having this indication removed.

Dr. Carrino summarized that there have been lots of good comments from the panelists. He stated **Victor van Berkel** put it under a nice umbrella of getting the clinical profile but not to specify all the exact data elements right here. Panel agrees that given the limited information available on the safety and effectiveness, they do not believe special controls can be established. So that answers Question 2b i. Panel provided some examples and then also some framework for the clinical information. And **Dr. Carrino** thinks 2b ii is not applicable since the panel doesn't disagree. He asked **Dr. Sullivan** if that was adequate. She confirmed.

FDA SUMMATIONS, COMMENTS OR CLARIFICATIONS

Dr. Sullivan summarized the answers to the questions to make sure she captured everything from **Dr. Carrino's** summaries. There was no additional comments or additions or

corrections from the panel members. **Dr. Carrino** thanked the panel members and the FDA and adjourned the meeting.

I approve the minutes of this meeting as recorded in this summary.

John A. Carrino, M.D., M.P.H., F.A.C.R.

Digitally signed by John A. Carrino, M.D., M.P.H., F.A.C.R.
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September 25, 2023

I certify that I attended this meeting on November, 7, 2023 and that these minutes accurately reflect what transpired

Jarrod W. Collier -S

Digitally signed by Jarrod W. Collier -S
Date: 2023.12.19 12:42:54 -05'00'

Jarrod Collier, M.S.
Designated Federal Officer