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FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

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RADIOLOGICAL DEVICES PANEL OF THE MEDICAL DEVICES ADVISORY COMMITTEE

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Via Web Conference

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Participants

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	Victor van Berkel, MD, Ph.D.	Division Chief of Thoracic Surgery, University of Louisville School of Medicine Louisville, KY
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Consumer Representative	Karen Rue, RN-BC, MBA	Gerontology Nurse/Owner Aging Life Care Professional, Hailind Consulting, LLC Lafayette, Louisiana
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Designated Federal Officer	Jarrod Collier, MS	Office of Management, CDRH

Table of Contents

Call to Order and Welcome

Dr. Carrino: Welcome. I would like to call this meeting of the radiological devices panel to order. I'm Dr. John Carrino. I'm the chairperson of the panel. I work as a musculoskeletal radiologist in New York at the hospital for special surgery and professor of radiology at Weill Cornell Medicine. I note for the record that the members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the panel members participating in today's meeting have received training in FDA device law and regulations. For today's agenda, the panel will 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. Before we begin, I would like to ask our distinguished committee members and FDA attending virtually to introduce themselves. Committee members, please turn on your video monitors, if you haven't done so already, and unmute your devices before you speak. When I call your name, please state your area of expertise and your position of affiliation. I introduced myself, and then next on the list is Susan Ascher.

Dr. Ascher: Good morning. My name is Susan Ascher. I'm a professor of radiology at Georgetown, and I'm a body imager.

Dr. Carrino: Next is John Daniel Bourland.

Dr. Bourland: Good morning. I'm Dan Bourland. I'm at Wake Forest University. I'm a medical physicist in the area of radiation oncology, radiation treatment and with some radiation sciences background and research.

Dr. Carrino: Next is Grace Hyun J. Kim.

Dr. Kim: Good morning. I'm a professor in radiological science and biostatistics at UCLA. I'm trained as a biostatistician and data scientist.

Dr. Carrino: Next is Stephen Solomon.

Dr. Solomon: Good morning. I'm Stephen Solomon. I'm the Chief of Interventional Radiology at Memorial Sloan Kettering in New York, and professor of radiology at Weill Cornell Medical College.

Dr. Carrino: Next is Margarita Zuley.

Dr. Zuley: Good morning. I'm Rita Zuley. I'm a professor of radiology at the University of Pittsburgh. I'm Vice-Chair of quality and Chief of breast imaging, which is my clinical practice.

Dr. Carrino: Next is John Jaeckle.

Dr. Jaeckle: Hi. I'm John Jaeckle, and I'm the Chief Regulatory Affairs Strategist and Engineer for GE Healthcare Imaging.

Dr. Carrino: Thank you. And I had Jaeckle correct during the practice, but.

Dr. Jaeckle: No worries. Thank you.

Dr. Carrino: Thank you. Next is Andy Chen.

Dr. Chen: Good morning. I'm Andy Chen. I'm at Oregon Health Science University. I'm a hematologist oncologist with expertise in bone marrow transplant and cell therapy.

Dr. Carrino: Next is Joseph Cullen.

Dr. Cullen: Hi. Joe Cullen here, professor in the Department of Surgery at the University of Iowa, and expertise in pancreatic cancer and metastasis.

Dr. Carrino: Next is John Hess.

Dr. Hess: I'm John Hess. I'm a blood banker at the University of Washington in Seattle. I have radiologic expertise as a hematologist oncologist using radioisotopes for developing blood products, these kinds of devices in blood banks and as a nuclear officer in the military.

Dr. Carrino: Next is Louis Kavoussi.

Dr. Kavoussi: Hi. I am Lou Kavoussi. I am the chairperson of urology for Hofstra Northwell. My area of expertise is minimally invasive urologic surgery.

Dr. Carrino: Next is Jorge Nieva.

Dr. Nieva: Hi. I'm Jorge Nieva. I'm a medical oncologist, section head of solid tumors, the University of Southern California, Norris Comprehensive Cancer Center.

Dr. Carrino: Thank you, Jorge. Next is Edward Snyder.

Dr. Snyder: Hi. I'm Ed Snyder. I'm a professor of laboratory medicine and blood bank director at Yale University and Yale New Haven Hospital and been dealing with blood irradiators pretty much for my full career.

Dr. Carrino: Next is Daniel Song.

Dr. Song: Good morning. I'm Daniel Song. I'm a radiation oncologist, a professor at Johns Hopkins University, and I lead the genitourinary oncology group there.

Dr. Carrino: Next is Victor van Berkel.

Dr. van Berkel: Hi. Good morning. I'm Victor van Berkel. I'm a professor of surgery at the University of Louisville. I'm the Division Chief for thoracic surgery. I'm doing mostly lung cancer operations and lung transplants.

Dr. Carrino: Next is Natalie Compagni-Portis.

Dr. Compagni-Portis: Good morning. My name is Natalie Compagni-Portis. I'm a psychologist working primarily in oncology. I've served as a patient representative with FDA for a number of years and also living with my own cancer diagnosis.

Dr. Carrino: Next is Karen Rue.

Ms. Rue: I'm Karen Rue. I'm consumer representative for this panel, and my areas of expertise are in maternal child as well as gerontology.

Dr. Carrino: Next is Julie Sullivan.

Dr. Sullivan: Hi. I'm Julie Sullivan. I am currently the Division Director of the Division of Radiological Imaging and Radiation Therapy in the Office of Radiological Health here at CDRH.

Dr. Carrino: Next is Jarrod Collier.

Mr. Collier: Good morning. My name is Jarrod Collier, and I am the Designated Federal Officer for today's radiological devices meeting. Thank you.

Dr. Carrino: Mr. Jarrod Collier, the Designated Federal Officer for today's radiological devices panel, will now provide the conflict of interest statement for today's meeting.

Unknown Speaker: Did you miss me?

Conflict of Interest Statement

Mr. Collier: Thank you, Dr. Carrino. Good morning, everyone. I will now read the conflict of interest statement. The Food and Drug Administration is convening today's meeting of the Radiological Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and consultants of the panel are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations. The following information on the status of this panel's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 are being provided to participants in today's meeting and to the public. FDA has determined that members and consultants of this panel are in compliance with federal ethics and conflict of interest laws.

Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have financial conflicts when it is

determined that the agency's need for a particular individual services outweighs his or her potential conflict of interest. Related to the discussions of today's meeting, members and consultants of this panel who are special government employees or regular federal employees have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and, for the purposes of 18 U.S.C. Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts/grants/CRADAs, teaching/speaking/writing, patents and royalties, and primary employment. For today's agenda, the panel will 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 general controls and premarket approval. 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 in accordance with 18 U.S.C. Section 208.

Mr. John Jaeckle is serving as the industry representative, acting on behalf of all related industry. Mr. Jaeckle is employed by GE Healthcare. We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all participants to advise the panel of any financial relationships they may have with any firms at issue. A copy of this statement will be available for review and will be included as part of the official transcript.

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. For the record, 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 appointments were authorized by Russell Fortney, Director of the Advisory Committee Oversight and Management Staff, on October 10, 2023. At this time, I will now turn the meeting back over to Dr. Carrino. Thank you.

Dr. Carrino: Thank you. Before we proceed, there's two additional introductions for people who are currently here, and then there will be one other panel member later who, when they join, we'll do that person's introduction. So let me get the chat. Okay. So the two additional people, one is Jonathan Waters.

Dr. Waters: Yeah. I thought you were saving the best for last. I'm John Waters. I'm an anesthesiologist, professor of anesthesiology and bioengineering at the University of Pittsburgh. So I'm in charge of the patient blood management program for the University of Pittsburgh, which includes approximately 7,000 autotransfusion or cell salvage cases annually. Thank you.

Dr. Carrino: Thanks. And next is Marjan Boerma.

Dr. Boerma: Yes. Thank you. This is Marjan Boerma. I'm a professor of pharmaceutical sciences at the University of Arkansas for medical sciences, and I study radiation biology.

Open Public Hearing

Dr. Carrino: Okay. At this time, we will proceed with the open public hearing portion of the meeting. Public attendees are given an opportunity to address the panel to present data,

information, or views relevant to the meeting agenda. Mr. Collier will now read the Open Public Hearing Disclosure Process Statement.

Mr. Collier: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. At this time, I will now turn the meeting back over to Dr. Carrino. Thank you.

Dr. Carrino: Thank you, Mr. Collier. Prior to the final date published in the Federal Register, the FDA received one request to speak. The speaker will have five minutes allotted for their comment. At this time, I'll ask Dr. Diana Zuckerman from the National Center for Health Research to begin her presentation.

Audio Visual (AV) technician (Jim Veizis): Diana, can you unmute, please.

Dr. Zuckerman: Yes. I was trying. I'm so sorry. Can you hear me now?

Dr. Carrino: Yes, we can.

Dr. Zuckerman: Okay. I really apologize. I'm Dr. Diana Zuckerman. I'm President of the National Center for Health Research. We scrutinize the safety and effectiveness of medical

products, and we don't accept funding from companies that make those products. So I have no conflicts of interest. In addition to my current work, my perspective reflects my post-doctoral training in epidemiology and public health, my training in bioethics, previous policy positions at HHS, and at a congressional committee with oversight over FDA, and as a faculty member and researcher at Yale and Harvard. I'm also a founding member of the Alliance for a Stronger FDA, which is a coalition of industry and non-profit organizations that work to ensure that the FDA has sufficient appropriations to fulfill its important mission. Thank you for the opportunity to speak today.

And since you have such impressive medical expertise on this panel, I will focus on policy issues that have important implications for patients, a goal that we all share. And since the FDA has spelled out their concerns, their specific concerns, about these devices in their written summary and will talk about them today, I will focus on the big picture. Number one, these devices have been treated as 510(k) devices since 1976, and that has not resulted in scientific data. In fact, FDA found very few studies of either safety or effectiveness, none of which were randomized controlled trials and none that evaluated a specific device used to prevent cancer metastasis.

Most important, number two, no studies indicate that the use of blood irradiators improves patient outcomes. So, given the lack of evidence of benefits, what are the risks? There are a few adverse event reports to FDA's MDR system, but that may be because the devices aren't used frequently and MDR reports are voluntary and everyone agrees that adverse events are underreported. We all know that surgeons are very busy and do not have strong incentives to report adverse events, especially when it isn't clear if a problem was caused by the device or by human error. Even so, the FDA has identified numerous serious risks, including incorrect or improper dose of radiation, damage to blood components caused by the radiation, and radiation

causing an immune response that's harmful to cancer patients. Device malfunction or poor design could result in unintended radiation, exposure of the operator or the public, or an electrical shock or burn. Several papers reported that blood irradiation took additional time, 15 to 20 minutes, and that can sometimes be harmful. Perhaps most important, most patients and surgeons assume that these products are proven safe and effective. Would they choose them if they knew how little scientific evidence there is regarding safety or effectiveness?

So the bottom line, these devices fit FDA's definition of Class III because, number one, insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of safety and effectiveness; and, number two, the devices are for a use which is of substantial importance in preventing impairment of human health. The FDA is asking if special controls would be sufficient instead of a PMA. They don't specify which special controls, but the problem here is that we don't know if the products have any benefits, regardless of how they are used. Would FDA impose special controls requiring evidence of effectiveness? And, if so, why not use a PMA instead? We don't know if either of the current products on the market is safe and effective, and we don't know if one is better than the other. That's why I encourage you to urge the FDA to categorize these as Class III and require a PMA, so that we will finally have well-designed clinical trials to determine safety and effectiveness.

And, in conclusion, I just want to mention that some might wonder if registries could be as good as clinical trials to study these devices that are already on the market. And registries can collect important information, but they don't have a control group. And this is especially problematic for a device that's not widely used since those who use blood irradiation to prevent metastasis may differ in important ways from those who do not. That's all I wanted to say. Thank you very much for the opportunity to speak today.

Dr. Carrino: Thank you for the comments. I now pronounce the open public hearing to be officially closed. And now we will proceed to the first FDA presentation.

FDA Presentation – Scott McFarland

Dr. Carrino: I would like to invite the FDA representative, Attorney Scott McFarland, to begin. The FDA representative will have ten minutes to present, and you may begin your presentation.

Mr. McFarland: Hello. My name is Scott McFarland, and I am a regulatory counsel within CDRH's Office of Product Evaluation and Quality. Today I'll be providing a high-level overview of the medical device classification process, which forms the basis for our discussion today. The purpose of this panel meeting will be regarding the classification of devices that are currently unclassified. Specifically for one pre-amendments unclassified device type, the panel will be asked to provide input to the FDA on the appropriate classification: Class III, Class II, or Class I. We begin by explaining the different classes of medical devices. 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 devices are subject to both general and special controls, and Class III devices are subject to general controls and premarket approval. These regulatory controls will be discussed in greater detail in the following slides. Importantly, a device should be placed in the lowest class whose level of control provides reasonable assurance of safety and effectiveness.

Now let's go into more detail about each of the classes. As mentioned previously, 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 that devices are not misbranded or adulterated. Most Class I devices do not require premarket review prior to being marketed. A few examples of Class I devices include scintillation (gamma) cameras, radiographic head holders, radiographic anthropomorphic phantoms, and radiographic film marking systems.

There's also 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 of 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. Typically, Class II devices require premarket notification, generally referred to as a 510(k) submission, prior to being marketed in the U.S. Within these 510(k) submissions, companies must include information demonstrating how the special controls for the specific device type are met.

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.

Here is a flow chart that walks through the general decision-making process for each of the classes that was just discussed. We start with 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, we ask whether there is sufficient information that allows us 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 will 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, we will end up back at a Class I designation.

Now we will shift our focus to the classification process for blood irradiators for prevention of metastasis, a preamendments unclassified device type, which will be discussed today. Before we walk through the process, here are a few quick definitions. First, what is a preamendments device? A preamendments device is a device which was introduced into

interstate commerce prior to May 28th, 1976, or the date of enactment of the 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. This brings us to the purpose of this panel meeting: to formally classify these unclassified devices. Please note that while these devices are not classified, they are currently brought to market through the 510(k) process.

Preamendments, unclassified devices will be classified once the FDA has taken the following steps. First, FDA will solicit input and a recommendation from the device classification panel, the purpose of this meeting. Second, FDA will publish, for comment, the Panel's recommendation, along with a proposed rule outlining FDA's proposed classification for the device. Finally, after taking into account public comments, the FDA will publish a final rule classifying the device.

What we ask from the panel today is 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. And if not, whether sufficient information exists to develop special controls and what those special controls should be that, in combination with the general controls, provide reasonable assurance of safety and effectiveness for the device type. Following this panel meeting, the FDA will consider all

available evidence, which includes the input received from this panel and the public. The FDA will then publish a proposed rule in the Federal Register proposing classification of this device type and seeking public comment on the proposal.

Finally, FDA will issue a final rule identifying the appropriate class. 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. I hope that this has provided you with sufficient background to set the stage for the forthcoming discussion. Thank you for your time and attention.

FDA Presentation – Dr. Justina Tam

Dr. Carrino: Okay. We will now proceed to the second FDA presentation. I would like to invite the FDA representative, Dr. Justina Tam, to begin the FDA presentation. You will have 25 minutes to present, and, Dr. Tam, you may begin your presentation.

Dr. Tam: Good morning. My name is Justina Tam, and I am a lead reviewer in the Division of Radiological Imaging and Radiation Therapy Devices within the Office of Radiological Health and CDRH's Office of Product Evaluation and Quality. Today I will be presenting information regarding our efforts to classify blood irradiators for the prevention of metastasis. These devices are currently unclassified. And we are looking for your thoughts and recommendations on the appropriate regulatory classification for these devices. This is the

outline for my presentation. These are the items that we will be discussing today where I will present information on why we recommend 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 CFR 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 is presented on this slide. 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 that we have 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. Our understanding is that x-ray based blood irradiators, which are the focus of this classification panel, have also 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 this 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.

Next, I will provide clinical background. 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 leukocyte 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.

We 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 in 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.

The number of each excluded criterion is summarized in the flow diagram to the right. 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. Hansen et al in 1999 and in 2003 noted that irradiation at 50 gray took approximately 6 to 15 minutes. And Weller et al in 2021 indicated that the duration from irradiation to re-transfusion took them less than 20 minutes. Regarding effectiveness, our 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 results of this study were that there was no significant difference in tumor recurrence between the groups that received autologous blood with or without irradiation. Additionally, there were two studies that provided evidence that blood irradiation could damage tumor cells such that there were no longer proliferative tumor cells or that they did not show evidence of DNA metabolism or that tumor cells were not detected after washing, filtration, and irradiation. However, these studies did not examine the in vivo prevention of metastasis in patients who received an autologous transfusion after radiation, and inconsistent results were found across samples from the same patients after each processing step. In summary, the available evidence is inadequate to draw definitive conclusions about the safety or effectiveness of blood irradiators for the prevention of metastasis.

There were limitations in the literature review. Of the ten relevant articles, only three were observational studies. Additionally, all three studies were conducted outside the U.S., so the results may not be generalizable to the U.S. population. There were no randomized controlled trials, and none of the articles mentioned the FDA cleared blood irradiators that are indicated for the prevention of metastasis. Additionally, regarding dose of irradiation use, the literature reported doses for blood irradiators for intraoperatively salvaged blood to assist in the prevention of metastasis in cancer patients ranged from 25 to 50 gray, but there is a lack of consensus in the literature from the recommendations from professional societies on a specific dose that should be used. Thus, 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 surgical procedures.

The next three slides provide background information for medical device reports or MDRs. 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. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues, and contribute to benefit risk assessments of these products. MDRs 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 or 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, or user error.

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. Finally, the existence of an adverse event report does not definitely establish a causal link between the device and the reported event. Because of these 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 CFR 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 Class I recall is a situation in which there is a reasonable probability that the use of or exposure to a violated product will cause serious adverse health consequences or death. The 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. Class III recall is a situation in which use of or exposure to a violative product is not likely to cause adverse health consequences.

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 CFR subchapter J because an interlock was not directly linked to the door. In conclusion, 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 have identified the risks associated with these devices. To identify the following 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 presence of proliferative malignant cells in re-transfused blood due to incorrect dose or improper dose of radiation delivered. This may occur through the incorrect dose of radiation that is identified to be effective, which may result in tumor cell survival, leaving proliferative (able to function, grow, and divide) tumor cells present in the blood.
- 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. This may occur when irradiation of the blood or blood components may cause an immune response that negatively impacts cancer outcome or patient recovery or survival.

- Damage to blood components from radiation. This may occur when 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 and plasma, hemolysis, destruction of red blood cells, and affects red cell viability.

Unintended radiation exposure to the operator and public. This may occur through device malfunction, lack of adequate maintenance or safety control, or interlock failure that 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. This may also occur through the insufficient presence of safety controls or interlocks within the irradiator design, which may allow the x-ray tube to generate x-rays when it should be shut off, resulting in unintended exposure.

- Electrical shock or burn. This may result during electrical malfunction of the device or when a user contacts an energized portion. This can also occur when there are insufficient or malfunctioning safety control or interlocks.
- Delayed or lack of re-transfusion of irradiated blood or blood components. This may occur because the use of the device inherently adds time to re-transfusion procedures and device malfunction, or operator error could add additional delays or risk of giving salvaged blood that was not irradiated. For example, delayed re-transfusion of the blood or blood components to the patient could occur due to device malfunction, including from mechanical, electrical, or software malfunctions or use error. Second, operator error or device malfunction could lead to blood not being irradiated or being irradiated to an 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. This may occur when shielded doors are being closed and impinging on the operator.

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.

Here is our proposed classification regulation for blood irradiators for the prevention of metastasis. Part A of the regulation defines the device as follows: 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. Part B of the regulation identifies the classification as Class III, premarket approval.

Dr. Carrino: Thank you. Dr. Tam, would you like to provide your additional comments now?

Dr. Tam: Sure. Thank you. I'll just add that we received feedback from a panel member on the meeting materials. We wanted to thank them and note that we used some imprecise language in a few spots within the presentation you just heard. There are a few slides that state blood irradiators for prevention of graft versus host disease. This should be for prevention of transfusion-associated graft versus host disease. Also, on slide 8, we want to note that radiation does not physically remove leukocytes and tumor cells, but ionizing radiation causes effects that may lead to cell death in these radiosensitive cells, and those dead cells will then be cleared by the body. Thank you.

Dr. Carrino: Thank you. I'd like to thank the FDA speakers, both speakers, for their presentations. Before we go on to the panel for clarifying questions, we have one more introduction. Elizabeth Krupinski joined, and if you could just state your name and affiliation.

Dr. Krupinski: Yeah. Elizabeth Krupinski, professor and vice-chair of research at Emory University in the Department of Radiology and Imaging Sciences.

Q & A for FDA Presenters

Dr. Carrino: Thank you. And I think with that, we've captured everybody on the panel and on the call, on the Zoom. So at this point, does anyone on the panel have any brief clarifying questions for the FDA presenters? I see Dr. van Berkel. We're going to use the hands, so if you can use the functionality of raising your hand, it then puts them in a queue, and I'll go through the queue in order. Dr. Compagni-Portis.

Dr. Compagni-Portis: Yes. Thank you. I'm wondering what type of training is required for someone who is using the device and who would that person be? I imagine this is happening in the OR, so what kind of training is, you know, on the device and with patients in these situations?

Dr. Sullivan: I guess I can take that question. So when we approve devices or clear devices, they are often cleared for use by a physician, and we may identify specific training that's necessary. Currently through the 510(k)s that have been cleared, there's no specific user identified. It would likely be someone with knowledge of radiation. It's unclear if this would be someone involved with a blood bank or someone with radiation expertise. But as far as the current clearances we have, we don't have the limitation to a particular physician type, but that is something that we could consider as part of the risks associated with this device. Now, if there

were a radionuclide source used, then there would be NRC license provisions that would be part of the device use.

Dr. Compagni-Portis: And do we know in the instances when this has been done, who is performing that task?

Dr. Sullivan: So we were unable to identify any current use of this in the United States. We reached out to a number of blood bank sites and didn't receive any feedback that this was currently being used. So it's unclear to us who the appropriate user would be, but as I noted earlier, this would really be able to be used by any licensed practitioner.

Dr. Compagni-Portis: And last question, which I think I know the answer to, but do we know anything about differences in blood cancers versus solid tumors with this process?

Dr. Sullivan: Based on our literature search, there was no information about the difference between the use in solid tumors or blood cancers.

Dr. Compagni-Portis: Thank you.

Dr. Carrino: Okay. Next is Daniel Bourland.

Dr. Bourland: Good morning. Thank you for the presentations. I had a couple questions. I was putting them in an email. Actually, there's more than a couple, and I'll try to select just a couple. Would this consideration apply to both x-ray and gamma devices or only x-ray. I saw x-ray identified or highlighted in the slide, but I didn't know if this would apply to gamma as well.

Dr. Sullivan: Can I just clarify? It's for the particular risks that we're identifying in the classification of this regulation today?

Dr. Bourland: Yes, was that an answer or not?

Dr. Sullivan: No, sorry. That was a question just clarifying that you're talking about what specific devices we're looking to classify today.

Dr. Bourland: Today, correct.

Dr. Sullivan: Okay. Yes, we're looking to classify specifically the x-ray based irradiators today.

Dr. Bourland: Okay. Very good. Thank you. And then on the history, it appears there were two devices approved in some manner. I couldn't quite tell if it was Class II device when they added metastasis at previous occasions. And are those x-ray or gamma?

Dr. Sullivan: Those are both x-ray based devices.

Dr. Bourland: Okay. Thank you. And then if the classification changed to III, those might have to eventually be removed from market or adjusted or something, but how many of such devices are there? Maybe it's the number of models, as well as the number of devices in the U.S. right now?

Dr. Sullivan: There are currently two different models that have been cleared through the 510(k) process as unclassified devices. Those are both represented in the executive summary. I don't remember exactly offhand which ones they are. And then the second part of your question I've now forgot.

Dr. Bourland: Well, it's just like how many? Is it like 20 throughout the U.S. that would be affected, existing right now, is what I'm talking about?

Dr. Sullivan: Right. So I don't have that number. As we noted, we don't believe this is a commonly used indication for the device, and so, if the decision was made that this should be a Class III device and go through the PMA process, there would be a call for PMAs. And the sponsor of those devices could clarify that if they wanted to have that indication or not.

Dr. Bourland: Very good. Thank you.

Dr. Carrino: Okay. Jorge Nieva.

Dr. Nieva: Yeah. My questions are about time and increased operating room time. Is that something that's unique to this device, these devices, or does any operative red cell salvage process take an equivalent amount of time? You know, you mentioned an additional 20 minutes

or so to operating room time. So is that something that's because of the irradiation, or is that something simply because of cell salvage?

Dr. Sullivan: The specific time that we were noting would be the time that it would take to irradiate the blood. There may be members of the panel or that we have behind the scenes that may know a little bit more about whether there would be surgical things occurring during that irradiation time. But the time that we provided was noting the time for irradiation specifically.

Dr. Nieva: Thank you. There was also a mention made of the purpose of these devices was in some way a psychological one. It reduced patient reluctance to undergo red cell salvage. Is there any quantitation around how many patients the use of irradiation affects their decision to avoid allogenic transfusion?

Dr. Sullivan: We don't have that information particularly. I'm not sure if that was Dr. Zuckerman who made that notice. I don't know that we used that in our benefit risk analysis within FDA.

Dr. Nieva: Thank you. That concludes my question.

Dr. Sullivan: Thank you.

Dr. Carrino: Okay. Next, Victor van Berkel.

Dr. van Berkel: Sure. Thank you. Thank you for the very thorough presentation. Just to perhaps respond to Dr. Nieva's question, as someone who uses Cell Saver a great deal, there is actually a fair bit of delay associated from just sucking the blood out to actually putting it back in the person. There is a reasonable amount of processing that needs to happen. And I guess the question is, and I don't know the answer to this, and it sounds like neither do our friends from the FDA, whether or not the radiation or the x-ray would be able to be given while that processing is occurring. And so it doesn't add much more than what you would do for Cell Saver anyways, or if it would have to be done separately and add an additional 20 minutes. So I'm not sure, I guess,

would be the right answer to that from someone who does a fair bit of that. My question for the FDA about this, perhaps this is a little bit silly, but why are we doing this now? Did something change? I guess these have been out in the world for a while. There was the meeting back in 2012. Was there an adverse event? Did a company say they wanted to start marketing it in this way, or are we just clearing a backlog of stuff? Or what happened?

Dr. Sullivan: Right. So this specific indication was not discussed during the previous 2012 blood irradiator panel. That panel focused on transfusion-associated graft versus host disease. And, as you noted, the agency is trying to get any currently unclassified devices to be classified because we note it can be a public health concern if we don't have the adequate controls of those devices.

Dr. van Berkel: Okay. So there's not a pressure from industry to do something? It's not like one of the people who's selling it is like we're excited about marketing this for this particular thing? It's just weird. It's just something that was sitting on the books as unclassified, and you don't like that so we're going to fix that?

Dr. Sullivan: Yes, the latter.

Dr. van Berkel: Got it. Thank you.

Dr. Carrino: Next is Margarita Zuley. Rita.

Dr. Zuley: Thank you. Thanks for the great presentations. I have a question about the patient population. We all know that there's an incredible diversity of types of cancers and subtypes of cancers. Patients are going to have incredibly different risks of circulating tumor in their bloodstream that might be cleared. They also may have received therapies that increase their individual risk of having cellular damage or be more prone to immune type responses. So the question that I have for FDA is, if this is classified as a type III device, would the reviews be

focused a little more specifically instead of it being all cancers to really try and subset this to understand people who may benefit more or less from such a therapy?

Dr. Sullivan: So I can't quite speak to what we would do in the future, but, for a PMA device, a Class III 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. One of the risks, and what you may have heard during our presentation, is that we do note that there isn't information about: is a specific cancer require a certain dose of radiation or show a proclivity to having more or less metastasis present after use. So I do believe that we would want to see tumor specific or cancer specific information.

Dr. Zuley: Thank you.

Dr. Carrino: Next is Jonathan Waters.

Dr. Waters: Yeah. In my introduction I mentioned that I'm in charge of about 7,000 auto transfusion cases a year with a fair amount of these cases being done in cancer, with gynecologic and neurologic cancers being the predominant forms of cancer that we salvage. I see no efficacy or impact of radiation on outcomes for patients. And we published data to that effect. What I do have concerns about is the delay that it would take to move a unit from the operating room to the irradiator and then the return of that unit of blood to that operating room. I have seen ABO mismatching where the unit of blood went to the wrong place and was transfused after processing in the blood bank. So I think that's a significant risk of moving the blood from the operating room to a remote location and the delay. I can process a unit of blood in about two minutes in the operating room by changing the processing speeds, but moving the unit of blood to a remote physical location can present quite a delay in somebody that is bleeding profusely, which is typically the case when you're implementing auto transfusion.

So I guess my question is really the PMA process to develop some form of trial to demonstrate effectiveness, because I know my German friends say that they basically agree that autotransfusion blood leaves patients with an equivalent or slightly better outcome than going to the blood bank for allogeneic blood. Their claim, though, is the irradiation provides better outcomes, and I'd like to see those studies before we proceed with any approval of these devices. So I guess that was my question is what does the PMA process require?

Dr. Sullivan: So I noted that the PMA process would require the device to show safety and effectiveness within the intended use population. As far as what we would be considering to be clinically meaningful or how we would measure benefit or effectiveness, we have considered things such as overall survival or time to recurrence or metastasis, things like reduction in allogenic blood use. But this is something that we would like to get the panel's input on as well.

Dr. Waters: And what time frame would the PMA require for this to be done?

Dr. Sullivan: Okay. So, after this process, if the panel recommended Class III and FDA took up that recommendation, it would likely be a number of years. We have to take your recommendation. We have to write a proposed final rule for the regulation. And then we would have to make a call for PMAs. And I think it's usually at least a year to allow for time for the PMA to be submitted and reviewed. And only after that would then the first device be potentially approved for this indication. So it may be some time before we would get there.

Dr. Waters: Thank you.

Dr. Carrino: Okay. Next, Karen Rue.

Ms. Rue: Hi. Dr. Zuley asked a lot of the questions, but along with what Dr. Waters just asked, if we have no idea that it's even being used in the United States, or if there's a desire, even once it's approved for study, how long are we talking about potentially gathering enough data if it's not even requested to be used?

Dr. Sullivan: So if the panel recommends Class III and FDA writes the rule, it would really be up to the manufacturers who wanted this indication to collect the data and then come in with a PMA submission. So if there was no interest in coming forward for this indication, then we wouldn't see a PMA. We note that a study to look at recurrence endpoints could take a number of years, as could overall survival endpoints.

Dr. Carrino: Okay. Next is Louis Kavoussi.

Dr. Kavoussi: Thank you for the great presentation, and I'm humbled to be part of this family today. A question I have is on a little different direction. It's a bit of a question editorial. If this were left alone, in terms of reimbursement, we know it's utilized somewhat for graft versus host. And if it is not regulated, could there be a danger of people saying, hey, this is a reimbursement? So my question is, if there are views associated with this, what is the reimbursement to the physician and to the institution, there are two different portions there, if you know it?

Dr. Sullivan: FDA doesn't usually get into questions of reimbursement. That would be our CMS agency. As far as 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. We are still taking the recommendations from the panel in 2012 and looking at the literature since then to come up with an updated proposed rule for those devices. So I guess what it comes down to is, if you 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. Does that sort of answer what you were looking for, or was there a second part?

Dr. Kavoussi: No, that did. I'm just concerned that if there is significant reimbursement associated with this, unfortunately, there's always the potential for abuse for financial reasons. And, again, in the urological realm, I'd be curious to hear Dr. Song if he's heard. I don't know of

this at all being common practice in urology. I really don't. And maybe of historical interest, remembering back from years and years ago, but if it is not truly studied well, et cetera, there is always the potential. Well, this is available. It's FDA cleared. There's a CMS code for it. It is being used on the graft versus host. And would there be the potential then for abuse based on some soft literature from other countries?

Dr. Carrino: I don't know if there's an answer to that, but we'll move on for the next one. Is that Edward Snyder?

Dr. Snyder: Yes. Thank you. It was an excellent presentation. Thank you very much for presenting it. Just a couple of comments rather than questions. If this device, the irradiation device, were to be in the operating room, probably it would be advisable for the transfusion medicine service to have some input because they have to reply to various oversight agencies of how blood is handled, whether it's coming out of the blood bank or it's being manipulated in an operative setting. So there would be some input from the blood bank. Whether a blood bank technologist would be in the operating room would be somewhat problematic. They're not in the operating room now for the cell saver activities as was mentioned.

A couple of other points. There is additional time that would take to do the irradiation process. These devices are very heavy. Having a gamma radiation device in the operating room is not even something that's reasonable because of the concerns about safety, and these devices are very highly regulated now. But having an x-ray device would be feasible, but it would have to either stay in the operating room or if, as Dr. Waters mentioned, the blood was brought out of the operating room to be irradiated elsewhere and then brought back in, it would have to be relabeled as an autologous unit to prevent just the kind of problems that Dr. Waters mentioned about the wrong kind of blood being given. So it would really delay dramatically the amount of time it took for this blood to come back into the operating suite in order to be re-infused, at least

in my opinion. So there are a lot of these other concerns that would need to be brought up as to practical aspects, but very important when someone's bleeding extensively and they need the blood back quickly. So those are just some comments.

Dr. Carrino: Okay. Thank you. Daniel Bourland.

Dr. Bourland: I'll speak very briefly. You know, dose rates typically are 3 to 8 gray a minute on these units. So just depends what dose you want to give. 30 gray to 50 gray means 5 to 15 minutes. That's the radiation time. Just thinking about some of these aspects. An x-ray self-shielded unit be about the size of a refrigerator, maybe three quarter height refrigerator, sitting in an OR area would obviously be best. I do not know that there are any designs that are integrated with the filtration aspect. Certainly maybe that's an opportunity. I don't know, but I do think it would, the blood would somehow be packaged and in place. And most of them are of a circular design where you put these things in a sample. Everything goes around in front of the radiation source. They're dual radiation. These are some of the logistics that would be important going forward. Just wanted to mention it.

Dr. Carrino: Thank you. Grace Kim.

Dr. Kim: Yes. Thank you for the presentation. When I read the intended for use, seems to be there are two parts within, because it's a pre-regulate one, so they put a lot of packages in there. There seems to be a special intensity required for the Class II, and if we think about in the prevention of metastasis, that's a big thing. It takes long time to clinical trial and by different solid and hemooncological cancer. So I'm thinking this one maybe we can suggest two steps. If they want to claim intent of use for prevention of metastasis, I'm thinking that we have to go Class III. But if they take out the metastasis part, and we can maybe focus in on Class II, how do the special control about radiation time to control and who's in charge of transport the blood and bring it back to safely during the surgery time. So I think we can maybe suggest two steps.

Dr. Sullivan: Thanks. So part of the way FDA determines where a device is regulated is that - is based on the intended use of the device. And so for this panel, we're specifically looking at the intended use of the blood irradiator for the prevention of metastasis in cancer patients. So I think, as you know, if we were just looking at the hardware and understanding the hardware, that may be an easier place to be able to identify special controls to make sure the hardware works as it should and delivers the dose that it's supposed to, but I think that where we've run into some trouble identifying the risks and identifying data to support the indication is really in that prevention of metastasis indication.

Dr. Kim: So we have to look at this whole thing when we decide Class III. Okay. I understand. And then if they don't come back for PMA, then this will be not being used, right?

Dr. Sullivan: Right. So the indication for use of this would just sort of no longer be part of the marketplace.

Dr. Kim: I see.

Mr. McFarland: Right. They'd have to either remove that indication or remove the device from the market.

Dr. Kim: So patient population have to use for 2012 the other Class II indicated one. Understood. Thank you.

Dr. Carrino: Okay. Next is Margarita Zuley.

Dr. Zuley: Thanks. Apologies for coming up with another question. It occurred to me in listening to this great conversation that we haven't discussed volume of blood that needs to be treated. So if we are saying that it's 10 to 15 minutes for a portion of blood, I'm not quite sure what that portion represents, has there been any consideration, and I would suggest that we actually do have this, where some portion of blood based on BMI or some other sort of patient based evaluation be used in the assessment to determine efficacy? Thanks.

Dr. Sullivan: Thank you. So I guess just to clarify, you would, for an effectiveness study, you would be looking to maybe have a sub-analysis of the amount of blood for each patient that was treated with irradiation and see if there was an effect on the volume of blood irradiated and transfused back into the patient?

Dr. Zuley: Yes, with the hypothesis that the more blood that's treated, the more likely there could be a risk or a benefit.

Dr. Sullivan: Thank you.

Dr. Carrino: Next, Daniel Song.

Dr. Song: Yeah. I just wanted to answer Dr. Kavoussi's question. I'm not aware of, at least in the GU or prostate cancer world, this being used. And then I think Dr. Zuley made a great point in terms of the percentage of blood being filtered or irradiated. If that's a small portion, one would imagine you're not processing the entire blood pool of the patient, then how much cumulative effect will there be on metastasis if you're only treating 5%, 10% of the blood? And I think, obviously, this is predicated on the hypothesis that these circulating tumor cells go up and that those lead to metastasis at the time of surgery, which I think is not yet known.

But I have a question for FDA in terms of given that this would still have approval for GVHD, and physicians are not restricted in terms of off-label use, then one could still, if your transplant surgeon colleague has one of these, you could still treat patients with this despite it not being marketed for that. And I just wanted to see if my understanding is correct on that.

Dr. Sullivan: Yes, your understanding is correct. Under the practice of medicine, you could decide to use the device in the care of that patient.

Dr. Carrino: Thanks. Next is John Jaeckle.

Dr. Jaeckle: Thanks everybody for the great questions and the presentations. I just have a couple of comments. One is regarding the irradiation time itself. I looked at the clearances that

are out there, and the current device only has a four kilowatt x-ray tube, which is relatively low power compared to other diagnostic imaging sources. So there could be grounds made to reduce the actual radiation time. And I know that's just a component of the overall time. Just wanted to point that out. Also, the FDA identified seven hazards or potential risks here. And I note that most of them are not unique to such a device and that they are routinely handled in other devices that produce ionizing radiation, and they're handled by Class II special controls. However, there are two unique risks that are specific to this. And I think that's what people are focusing on. And I think that's absolutely correct. And one third quick point, from an industry perspective, trying to go for a PMA is a very costly endeavor, and a company would have to look at are they going to get a return on that huge investment of time and money and whatnot? And it seems like if these are very limited in use, I would think that it's very unlikely somebody would submit for a PMA. Thank you.

Dr. Carrino: Thanks. Next is John Hess.

Dr. Hess: Yes. Thank you for the presentations. I'd like to address some questions to Jonathan Waters, specifically based on Dr. Bourland's and Dr. Snyder's comments. The device in my blood bank delivers 4 grays, and so I can irradiate a unit of blood in about six minutes to 25 gray. That's a Hodgkin's dose, thinking about it. A breast cancer dose of 5,000 rads or 50 gray, would take 12 minutes. And a sarcoma dose of say 75 gray would take 18 minutes. Now, I'm aware of a recent surgery in which 125 liters of blood were processed and put back into the patient. That's 25 blood volumes, and there's the chance that many of the units were radiated, many of the blood cells that went through would be radiated many times consecutively. What is your experience in the actual amount of blood that's used in these situations? And what are the kind of limits that are practical? I mean, obviously delaying blood use for 18 minutes to get six full bags of blood at 600 mL a piece means that radiating 125 units would take many hours.

What are the practical issues here? And, in the middle of surgery, what's the likelihood that somebody using that much blood in those desperate situations might feel compelled to stop the process in mid-irradiation just to keep the patient alive because they need the blood volume?

Dr. Waters: John, my personal record is 279 liters of blood being returned to a patient, and that was in a thoracic aorta that was ruptured. And the machines typically process 225 mLs per batch. So it's a lot of processing. Our average probably is more like one unit per case, so 225 mLs being processed at any one time on average. When we get into the big blood loss cases, we typically bring in two machines processing in parallel so that we can manage the volume. But it's one of my concerns with this irradiation is it's not particularly practical for the operating room environment. And the separation of the blood typically, at least in Germany, the way they do it is they send it to the blood bank for irradiation. And that poses risks of itself where it's separated from the patient. So I think some sort of study is warranted here.

Dr. Carrino: Thank you. Next is Elizabeth Krupinski.

Dr. Krupinski: Yeah. This is more of a naive question because I'm not a physiologist, I guess, or a molecular biologist, but with circulating cells from different types of cancers, do they react differently to radiation? I mean, for example, does breast cancer require a different dose than a prostate cancer, than brain cancer for these circulating cells? And if so, what are the implications for creating guidance around the level? If you know the particular type of cancer that you're after, do you have to adjust the dose that you're giving it? Maybe breast cancer circulating cells are harder to kill than those from prostate. Do we know that?

Dr. Song: I'll just jump on quickly and answer that. Yes, I mean, there are different radiation sensitivities for different cancer types. And I think that's something that needs to be investigated. I mean, one could take the experience with, for instance, stereotactic radiation, where very high doses of radiation are given in very few fractions or even single fractions to extrapolate what the

circulating tumor cell sensitivities for that specific cancer type might be. But it wouldn't necessarily translate. There could be several reasons why the dosing might be different for a circulating tumor cell versus a tumor cell that is already established as metastasis.

Dr. Carrino: Thank you.

Dr. Bourland: I'll add briefly to that just that I think radiosurgery as an example of a single fraction of radiation done. One day somewhat might be a model for this, and there are differences that can be relative to tumor type.

Dr. Carrino: Thank you both.

Dr. Stapleford: I could just say quickly, there's a pretty established dose that's generally used for radiating blood, and it's somewhere between 25 and 50 gray. I'm Liza Stapleford, I'm a radiation oncologist. So I don't know that dose is probably even really has mostly been sorted out, but not the critical factor, but I would just make a caveat. What we're talking about here is blood that's taken from the actual, generally speaking, well, this could be a primary tumor resection or a metastasectomy, so these are primary tumor cells. These are not necessarily circulating tumor cells, so that's probably the major concern is that these don't behave like circulating tumor cells. We know that they're circulating tumor cells in patient's bodies, but there's really a lot that's not known about what is the implications then of taking actual primary tumor cells and circulating that, but in terms of the dose, I think that's something that could be studied on a trial too. But there's a lot of experience with irradiating blood for other purposes. And 25 to 50 gray is generally the dose that's been used.

Dr. Carrino: Thanks. Anybody else? Okay. Andy Chen.

Dr. Chen: Hi. Thank you. I was curious if the FDA has looked or if there's any data out there on the incidence of secondary malignancies after radiation in this setting. When blood irradiators are used for transfusion-associated graft versus host disease, you do have the patient host

immune system to mop up any white cells that have been irradiated from the donor that could have survived the radiation process. But we know that irradiation can cause secondary malignancies, and if you're getting host cells returned, white cells, there is going to be no host defense system against that. So the concern of secondary malignancies from this type of treatment.

Dr. Sullivan: So thank you for that question. Based on the literature search that we did, those 10 articles that are part of the executive summary, is what we found in total. And so the risk of secondary malignancies is something that could come out in a well-designed randomized controlled trial, but we don't have any evidence or information about that currently based on our literature search for this panel.

Dr. Carrino: Okay. Next is Jorge Nieva.

Dr. Nieva: So in listening to the discussion and the fact that the alternative to these machines is that the blood leaves the cell saver in the operating room, goes to the blood bank, gets irradiated, and comes back, I'm having trouble understanding why these shouldn't be Class II devices rather than Class III. It seems like all this really is, is bringing together the radiation that would be normally delivered in the blood bank and bringing it closer to the patient in the operating room. And while I recognize that the benefits of doing this are entirely unclear, the fact that it's occurring anyway may be something that should affect the decision making in terms of regulatory classification. I'd love to hear from the FDA on that.

Dr. Sullivan: So when we classify our devices, we look into the amount of evidence that is present to classify into Class I, II, or III and whether there's a probable safety and effectiveness based on valid scientific evidence. So, as you note, there is a lack of evidence out there that this leads to better outcomes in patients. And so we're unclear that there's any evidence of safety or effectiveness for this device right now, which is why we are looking at the classification. And I

just want to clarify something. You noted that this would be moving the devices from the blood bank into the operating room. These would be the same devices that are currently used in the blood bank, and so it wouldn't be looking to necessarily move them. They could be moved if someone decided they wanted to use them in this manner and wanted to have them closer, but that wouldn't be a given.

Dr. Nieva: So in terms of Class II devices, endpoints such as radiation time, operating room time, other surrogate endpoints of benefit, you're really looking at very hard endpoints for a Class III device where you're going to have to ask for a metastasis free survival endpoint or something along those lines once it's a Class III device?

Dr. Sullivan: For both classifications, we can ask for the appropriate scientific evidence that we need. Class II what we're really saying is that we understand the risks for this device, and they are at a level that we feel we can write these special controls to get at those risks. And some of those are based on performance testing, they may be things like special labeling, they may be validation of certain processes like sterilization processes, which wouldn't be part of this type of a device. But a Class III device, it's basically that we are unable to write those special controls because we are unable to identify all the risks associated with the use of the device for that indication.

Dr. Nieva: Yeah. I'm just still struggling with how you make that distinction because obviously every device could have risks, right? I guess I'll let others ask questions.

Dr. Sullivan: Just to clarify, are you thinking about the device as the hardware itself, or are you also incorporating this specific indication for prevention of metastasis into the thought process?

Dr. Nieva: I'm thinking mostly about the device. Obviously, the indication is problematic, but the device itself seems to be substantially equivalent to what already exists. And all it's being done is combined in one location.

Dr. Sullivan: Yes. So when we were thinking of the hardware and identifying risks based on the blood irradiator hardware itself, or even the software used with the hardware, the device itself we felt that we could come up with those risks and potentially propose special controls based on those risks. However, when you add in the specific indication that it's meant to be used for, to assist in the prevention of metastasis, that's where we're finding the lack of evidence of safety and effectiveness that we would be comfortable relying on to move to a Class II indication.

So, for example, the 2012 blood irradiator panel recommended a Class II indication for transfusion associated graft versus host disease, and that was partially predicated on the fact that there was a lot of scientific evidence showing the use of that device for transfusionassociated graft versus host disease was effective and was safe. It was based on sort of the knowledge base prior to 1976 up to the classification. And so that panel focused on the device itself instead of looking at the full indication.

Dr. Nieva: So I guess what I'm getting at is if somebody brought one of these devices to market and said it's an interoperative blood irradiator for the purpose of avoiding need for transportation for blood irradiation, that would then be a Class II device?

Dr. Sullivan: Avoiding transportation? So just meaning that you could put the device in the operating room?

Dr. Nieva: Yeah, to avoid the need for radiation to be done outside of the operating room in the blood bank for avoiding transport to the blood bank for blood irradiation. That would then be a Class II device?

Dr. Sullivan: We'd have to think about what the actual indication for that would be. I think we would look at that as a feature of a device, whether you wanted to think of one that was on wheels. Maybe it can be moved. Although I don't know how that would affect the QC process to ensure the device was working. I'm not sure right now that the devices couldn't be put in the

operating room, the devices that are out there. I think it's depending on the weight of the device that there may be special needs to ensure the floors can hold that weight, or you can imagine if there's one of these devices in an operating room, maybe that would preclude it from being used by others. And so someone that works in the blood banks could speak to that more, but, as of right now, there's nothing stopping a device from being in an operating room.

Dr. Carrino: Okay. So just getting back to the process here. Edward Snyder.

Dr. Snyder: Thanks. Yeah. Just one or two more comments. I'm wondering if, as was pointed out the percent, assuming that you don't consider the Guinness Book of Record amounts of blood that has been mentioned to be irradiated, 125 liters, which is incredible, normally it's just one or two units be 300 or 400 or 500 mL. Since the amount of blood that would be irradiated would be so small compared to the total blood volume, what concern is there about the surgical manipulation of the site during the procedure that would shed and release and spread metastatic potential tumors so that we're basically locking up the front door by irradiating a small amount of blood with multiple devices or procedures, but metaphorically leaving the back door open, so that you were not doing anything about, nor could you probably, and we need a surgeon to comment on that. If you're doing a surgical procedure and you're shedding all kinds of tumor cells, you're probably not going to be capturing a lot of that. So are we really just looking at one small aspect of it, but there's still the procedure which is really spreading, and how do you determine the impact of that upon the efficacy of your radiation process? It's really, the more you look at it, the more curiouser it gets, so to speak.

Dr. Carrino: I'm not sure if FDA wanted to respond to any of that or move on.

Dr. Sullivan: I was following along, but I'm not sure if there was a specific question that you were asking?

Dr. Snyder: No, there wasn't a question. It was just pointing out that we're looking at one aspect of it, which is to irradiate blood that's salvaged. But the majority of the blood is still circulating. And with the manipulation of the surgical site, I don't know how much of an impact you're spreading or impact you're having on the spread of malignant cells just by doing the procedure.

Dr. Carrino: Right. I think those are maybe considerations for a study design if they come for PMA. Stephen Solomon.

Dr. Snyder: Correct.

Dr. Solomon: Yeah. Hi. Just a very similar comment. Given that we already know that they're circulating tumor cells, even in the early stage cancers, and we know surgery can move it around, I'm not sure, again, why irradiating this small volume is going to impact the whole thing. It raises the questions that make FDA justified in requiring some kind of clinical trial to prove the indication that's desired.

Dr. Carrino: Thank you. Yeah, I think I was along the lines as previous comment. Karen Rue.

Ms. Rue: Let me ask one quick question. I'm sorry for a second opportunity at this, but on this, the 10 studies that were utilized, what is the sample size of the participants in the studies? Are we talking 10 people? 1,000 people? Do we know?

Dr. Sullivan: I have those numbers in my document, but, from what I remember, I believe the most was somewhere between 50 and 100 patients. These were not tens of thousands of patients or even thousands of patients. And there were very few studies. I want to say one to two studies that actually re-transfused the irradiated blood back into patients and looked for a metastasis outcome.

Dr. Carrino: Thank you. Next is Natalie Compagni-Portis.

Dr. Compagni-Portis: Yes. Thank you. I have a question for my colleagues on the panel. I mean, clearly we don't have solid data about benefit or risk, but I wonder if the clinicians on the panel, if anyone sees potential benefit or has an enthusiasm for the potential here for this process, being able to prevent metastases.

Dr. Song: I'll take a stab at that. I mean, I think it still appears to be evolving data about what impact there is of surgery upon metastatic cells disseminating in the blood. I did see some data about minimally invasive surgeries or laparoscopic robotic surgeries potentially decreasing the number of circulating tumor cells found at the time of surgery compared to open standard procedures, but there are a lot of steps for metastasis to occur. And it's, I think, overly simplified to think it's just related to the number of circulating tumor cells. I mean, there's some data suggesting circulating tumor cells, like the higher the number, certainly a prognostic, and someone with theoretically, right, most of these patients are going to have localized disease, that those cancer cells need to evolve many different mechanisms in order to establish themselves in a cytometastasis. So it's just one factor in the equation, so I'm personally pessimistic.

And, as alluded to in prior comments, if you're only treating one to two liters maybe, then you're only watering down the percentage of cells by whatever, you know, relationship that is to the total volume of blood. And so I think there's a lot of questions. To me it seems like there seem to be definite risks in terms of the time, additional time under anesthesia. And I think the effect on the immune cells is definite, in terms of the T-cells are very sensitive. Lymphocytes are highly sensitive to radiation, much more sensitive than the tumor cells would be. And what effect that will have, I think, is questionable, but now that we understand that the immune system does have a role in controlling cancers, you may be having a negative impact from doing this. That would be my perspective.

Dr. Compagni-Potis: Thank you. That's helpful.

Dr. Carrino: Next is John Jaeckle.

Dr. Jaeckle: I have a question for FDA. Regarding the risks identified, two of them in specific, about that the irradiated blood may cause an immune response and that it may cause damage to red blood cells, have the sponsors of the 510(k)s for the graft versus host devices provided any evidence or data, I should say, regarding those two?

Dr. Sullivan: So we don't speak to what's in our submissions. I could only speak to what's in the 510(k) summaries. And since this panel wasn't focused on transfusion-associated graft versus host disease, I admit to not looking closely at those submissions. But based on scientific literature and also in the 1993 CBER guidance, there is a note that red blood cells are damaged, the membranes of red blood cells would be damaged by radiation exposure, which is why there's some limits on blood storage, red blood cell storage, for transfusions. And then, as far as the immune response, sort of what Dr. Song was speaking about, we know that there is an impact on the lymphocytes. That's what it's used for in prevention of graft versus host disease. And so we do know that there's an effect on the immune response.

Dr. Carrino: Thanks. Daniel Bourland.

Dr. Bourland: I'll try to be very brief. It's a very interesting challenge because think of it as sort of like here's a vessel, and there's a mixture of tumor and normal cells sort of distributed, and you want to give a dose that kills off the bad stuff and not the good stuff. And it's how those radio sensitivities align. And, fortunately, the white blood cells are very on the low end. This is why it works for graft host disease at 25 gray. So I think there are some interesting aspects about this. And I'm summarizing in my own head that, as a radiation device, operated, et cetera, that technology is simple and easy. The question is, I think here, the practice side. What doses would be appropriate that would work both well for, you know, tumor cells and still have in functioning

blood. And then, again, we're thinking about the ratios relative to the remaining amount of blood pool as well. Anyway, those are some thoughts.

Dr. Carrino: Okay. Thank you. I do not see any other clarifying questions or panelists that want clarifying questions. So at this point we have a break scheduled. So as a matter of process, Jarrod, we still have 10 minutes for the break?

Mr. Collier: Yes. That's correct.

Dr. Carrino: Okay. So I have 10:53. How about 11:05? So 10 plus? That still keeps us on time, so let's do 11:05. Thank you. And, panel members, please do not discuss the meeting topic during the break amongst yourselves or with anyone attending virtually. We will resume here at 11:05 as per the Zoom clock or the Navy atomic clock, whatever you're using

Break

Dr. Carrino: Okay. So, it's now after 11:05 and I'd like to call this meeting back to order. At this time, we're going to focus our discussion on panel questions and deliberations. Panel members, copies of the questions have been sent to you electronically and posted online for the public. I would ask each panel member to identify him or herself each time he or she speaks to facilitate the transcription. And now we'll turn it over to Dr. Justina Tam to read the FDA questions to the panel.

Panel Question 1A & 1B

Dr. Tam: Questions to panel. Question one. According to 21 C.F.R 860.7(d)(1), there is reasonable assurance that a device is safe when it can be determined based on 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 the device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device or its intended uses and conditions of use.

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.

Question 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 intraoperatively 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. 1. 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. However, given the limited reported clinical use of these devices in intraoperative blood salvage procedures, this list may not be exhaustive. The risks include the presence of proliferative malignant cells in retransfused blood due to incorrect dose or improper dose of radiation delivered, worsened control of oncologic disease for patient prognosis, damage to blood components from radiation, unintended radiation exposure to the operator in public, electrical shock or burn, delayed or lack of retransfusion of irradiated blood or blood components, 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 discuss risk 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, remote recurrence or invasiveness or surgical recovery. Given the limited reported clinical use of blood irradiators or 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 radiators 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. 2. 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. 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. Carrino: Okay, this is John Carrino. So, I understand we can display the questions to get the panelists' input. So, each question, two questions, but multiple parts and subparts. So, can we

go to the first subpart? Okay. And, all right, and let me get my, okay, so I see Elizabeth Krupinski.

Dr. Krupinski: Can you actually go to the question itself?

Dr. Carrino: The previous one? Yeah, sure.

Dr. Krupinski: Yeah, there was a summary statement of it at the end, though, of the two different questions. No, that. Yeah. Okay. I definitely agree with the inclusion of all those identified risks. That may not be exhaustive. I think potentially some of the ones during our discussion, yeah, it should be added. I honestly don't think that there's a lot of evidence, getting to question number two, that this is an effective device. From what I heard it doesn't sound to me at all that we have enough evidence.

Dr. Carrino: Okay. And Jorge Nieva?

Dr. Nieva: Yeah, I would just advocate for operating room time to be added as a risk. I don't think extension of operating room time is non-trivial and I'd like to see that included. As for the other questions, obviously, there's no evidence that this works for the indication. My concern, of course, is that the horse is out of the barn and people are doing this anyway without the use of these devices. But I do think that certainly nothing should be labeled with this benefit. Given everything we know about how tumor cells circulate and the incomplete information about immunologic effects. Thank you.

Dr. Carrino: And next Natalie Compagni-Portis.

Dr. Compagni-Portis: Yes, thank you. I appreciate the comments from the panel. I agree with the list of risks. I also agree with the comments that we don't know what the other risks are. And I

appreciate Dr. Nieva's comment about the horse out of the barn. I think part of what we're trying to do is see if we can contain this horse. And I really want to implore the panel and FDA to really utilize the precautionary principle, especially because of that, let's not let this get even further without having the data we need about, not only safety, but effectiveness. I think too often we haven't utilized the controls we have to keep patients safe and we've used or even exploited the vulnerability of patients and their hope for a cure and longer life to use them as guinea pigs in this regard with devices and drugs where we don't know the risks and treatments and the benefits are unproven. And I really agree with Diana Zuckermann's comments in the beginning that we all share the same goal. We want patient safety and that we really need to utilize the controls we have to make sure that we're either giving people longer life or the ability to live better. And we don't know that. So, thank you for letting me make that long comment.

Dr. Carrino: Next is Margarita Zuley.

Dr. Zuley: Thank you. I agree with all of the risks that the FDA has put forth here on this question and would like to suggest three additional that my colleagues mentioned during our panel discussion. The first being induction of a new cancer from irradiating the cells. The second being induction of some mutation of cells that inadvertently are irradiated twice. And the last being the potential risk of billing for a procedure that has not been shown to be safe and effective which was mentioned earlier. I do not feel that the safety and effectiveness of this device for this indication has been shown. Thank you.

Dr. Carrino: Thank you for that. And just to separate those two, so I understand it. So, summarizing it, in addition to the identified risks would think of a risk of potential for induction of cancer within the irradiated blood product and induction of mutation. I think the safety and effectiveness part is what companies come for the FDA process. And so, that part would then

play into deciding to go with the class III, but those other two we would want to add to this list. Is that, did I summarize that accurately? Okay. Thank you.

Dr. Zuley: Thank you.

Dr. Carrino: And next is Daniel Bourland.

Dr. Bourland: I wanted to comment on the risk here. I do agree that these are identified risk, especially the last one, which is where it says not exhaustive. And then wanted to make one clarification, perhaps that the effects on blood and blood products are not unknown. There is a large amount of experience at 25 gray, but this is not blood from the individual undergoing surgery, of course. So, there is some literature out there about effect on blood, at least at 25 gray. There are other studies that show what happens to nuclei, et cetera, with radiation and blood. But I agree that at higher doses, we may not know when the performance of that blood to be transfused back into the patient.

The additional risk, I think it's one, I think Dr. Nieva stated is the logistics. How's the thing going to work? Where does the blood go? Is it going to be misidentified or not? And I think these are some of the steps, at least for the current devices. If there were some other device that was made brand new, that was in the line of everything, filtration and all that would be a little different. There would still be risk there. But I do think there is some risk of logistics. How would it process, what would be the workflow to ensure safety in the use of the device in the clinic?

Dr. Carrino: Gotcha. Yeah, so I understand to summarize, you state that there's a certain dose limit. We will certainly want to know what amount of radiation is going to be applied and the vendor has support for use of that dose. I wanted to ask the FDA about the separating workflow

from safety and effectiveness, right? So, FDA is focused on safety and effectiveness of the devices. Does the workflow or embodiment of that device and how it's used play into that or what can the panel comment on that or use some of that for the answering the questions?

Dr. Sullivan: Yes, I believe that would be relevant. So, what we would be looking for we do evaluate usability and human factors in our review. So can the device be used by the potential user in the correct manner.

Dr. Carrino: Okay, so we would put that under a big umbrella of usability I think that's been a good theme from the panel members. Okay, and Grace Kim.

Dr. Kim: Yes, just short comments that to understand more how it works into our human body, dose ranging study will be important. Not just one prime dose, what's the escalation dose or de-escalation of dose of proper design, understanding safety regarding dose.

Dr. Carrino: So, just to flesh that out a little bit more, if the vendors looking at using main multiple doses or multiple levels of radiation, how that might affect the product?

Dr. Kim: Yes, 25 milligray would be lower or higher. How much they can escalate? What is those dose toxicity level with the patient? And that means the cancer patient in this population.

Dr. Carrino: Right. So, if they come in with a proposal, they would want to provide a range or a number that ensure that the device is going to deliver that amount. So, I think that's another consideration we've mentioned. Did I capture that correctly?

Dr. Kim: Yes.

Dr. Carrino: Great. Elizabeth Krupinski.

Dr. Krupinski: Yeah, just to follow up on what Grace just said. It's not just the overall dose. It gets back to what I talked about before, which is it going to differ as a function of the type of cancer? And I didn't mention it before, but the stage of the cancer, because that's going to potentially affect the number of circulating cells. So, we need more data on that as well.

Dr. Carrino: Cancer, type, and stage. All right. So, that is for the rest of question one. Let's make sure we go through the rest of the slides to see the rest of question one. Okay. Okay. And good. So, should we do a summary of question one from the panel? So, based on this one here so I think to summarize the panel's sentiment on this or the panel's feeling is that there is no reasonable assurance of effectiveness of blood irradiators for the prevention of metastasis. And then we can go to the next one, where Dr. Sullivan, do you want to do each part separately for is this adequate or not?

Dr. Sullivan: I think it would be probably easiest to do each section since there's so many parts.

Panel Question 1A Summary

Dr. Carrino: Sounds good to me. Okay. So, for this part so the panel summary is that there is not a reasonable assurance of effectiveness for blood irradiators currently with the data for the prevention of metastasis. Is this adequate?

Dr. Sullivan: Yes, this is adequate.

Dr. Carrino: Okay. All right. Let's go to the next part.

AV technician (Jim Veizis): Sorry. Do you want us to move on to question two or another part of section one?

Dr. Carrino: Part of section one.

AV technician (Jim Veizis): Okay, so we'll go back. Let's go back to the beginning of one and then we can just go to slide 29. So, you can just tell us where to move to.

Dr. Carrino: Gotcha. Yeah, so we can go to the next slide.

AV technician (Jim Veizis): Go to 30.

Dr. Carrino: Go back. So, there's part 1A. Okay, and the next slide. Okay, so if focusing on the bolded comments here so please comment on whether you agree with the inclusion of these identified risks in the overall risk assessment of blood irradiators for the prevention of metastasis. The panel agrees that these should all be included. There were some additional risks that were mentioned, so we'd also think it'd be important to include the risks of potentially what would be 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? And then I think with risks, we do want to get to usability, the risk of handling the blood product, transferring it from the OR to another facility would be included. And so, those would be the things that panel would endorse adding. So, Dr. Sullivan, is that adequate?

Dr. Sullivan: That is. Thank you.

Dr. Carrino: Okay. So, we did 1A. We did 1B. We miss any subparts?

Dr. Bourland: I was going to ask if we could just go to 1B.

Dr. Carrino: Yes.

Unknown Speaker: Because we didn't have any hands raised for it that I saw.

Dr. Carrino: Oh, gotcha.

Dr. Bourland: But I wasn't sure. But maybe that was what we just was that the earlier...

Dr. Carrino: Yeah, I think I synthesized that from everybody's previous comments, but certainly not to make sure we've captured everything does anybody wanna say anything in addition about the effectiveness?

Dr. Bourland: I guess I would say more information is needed.

Dr. Carrino: Right. So, we agree there's not reasonable assurance of effectiveness or there's not enough data supporting effectiveness of this.

Dr. Bourland: Okay. Thank you.

Dr. Carrino: Sure. And I see Andy Chen.

Dr. Chen: I would just want to emphasize that these are often used for curative intent therapy. And so, the bar for curative intent treatment of cancer, the standard of evidence should be significantly higher than what we often do in relapse refractory disease where we use less robust measurements of then overall survival. So, I would want to emphasize that this is often used in the curative intent setting.

Dr. Carrino: So, to summarize, you're going to surgery – the surgery is meant to be curative, then the effectiveness of this device for irradiating the blood should be in line with that same treatment goal. And that may be important for the study design or the type of evidence and data that the company would bring to the FDA. Does that capture it correctly, Andy?

Dr. Chen: Yes, more elegantly said.

Panel Question 1B Summary

Dr. Carrino: I had a little more time to think about it. So, I think the same thing, Dr. Sullivan, we said panel feels that there is not a reasonable assurance of effectiveness for the blood irradiators and certainly with consideration of potential for PMA, we'd want a rigorous study design with the same goals as surgery that is curative.

Dr. Sullivan: I see Dr. Kim has her hand up.

Dr. Carrino: Oh, okay. Great.

Dr. Kim: So, editorial comment. So, go back to the cancer type and stage, because based on the cancer type definition of the metastasis is different and the measurement they use. So, by cancer type and stage.

Dr. Carrino: Right. So, the safety and effectiveness would be determined based on the cancer type and the cancer stage. So, if a company is coming to market a product and let's say they tested on, lung cancer, it would then be for that particular lung cancer. There would be different, potentially for different stages, there that are in certain stages, we get the surgical treatment that should be included in their application. All right. And Margarita Zuley.

Dr. Zuley: Thank you. I would add, to what was just said, that types of cancers such as breast cancer, for example, are not all the same. And so, I think that there would need to be even more detailed evaluation. For example, a low-grade luminal A breast cancer is going to have a very different outcome than a triple negative breast cancer. And so, I think that there would have to be subset evaluation of this to really show effectiveness in any particular cohort. Thank you.

Dr. Carrino: Thanks. And could that be put within the framework of oncological society goals or what typical understanding is for prognosis for that particular cancer?

Dr. Zuley: Yes, I think so, but I would defer to my medical oncology colleagues to...

Dr. Carrino: No, exactly. So, if they're looking at cancer X, stage Y, and this is what's known about the typical prognosis. It's not that it's not that this device is going to make it better, but it's not going to impact it or adversely affect that that prognosis or something like that. Okay, so I think that was very good. Thanks everybody for their input. I think we answered all the parts to question one. If not, let's see if there's any other subparts to answer. Good.

Dr. Sullivan: Just to clarify, the panel believes there is not a reasonable assurance of effectiveness based on the evidence out there at this time.

Dr. Carrino: That is correct.

Dr. Sullivan: Thank you.

Dr. Carrino: So, with that, we'll go to question two.

Panel Question 2A

Dr. Tam: Question two to panel. Section 513A 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 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 the device is not purported or represented to be for 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. 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. 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 in all surgical procedures. Therefore, the risk of injury is unreasonable given the lack of probable benefit. One, do you agree with this assessment? If not, please explain why.

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.

One, 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.

Two. 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. Thank you. This is the end of the panel questions.

Dr. Carrino: Thank you. To facilitate the discussion, let's go to slide 40. So, there's question 2. There's parts A and part B. A is relatively straightforward. B has many subparts, which gets into some of the details and weeds that I think the panel members already dove into a little bit. So, I see Daniel Song would you like to comment on this part of the question? I think you're still on mute, Daniel...

Dr. Song: I believe my comment was on the next part.

Dr. Carrino: Oh, okay. Is it okay if we…

Dr. Song: Sure, go ahead.

Dr. Carrino: Do 2A and then have you come back just to keep me sane. Thank you. So, I think for 2A the risk of injury is unreasonable given the lack of probable benefit. And do people agree with this assessment or how would they like to comment on it? I see Elizabeth Krupinski.

Dr. Krupinski: Yeah, I was just going to say, I think given what we said before, if you combine it with all this, it nicely summarizes and I would agree.

Dr. Carrino: Okay. Thank you. Daniel Bourland.

Dr. Bourland: I agree with this statement. It's really based on the last part of it: the lack of probable benefit. That's where I would say the great unknown exists. So therefore, don't do something. The risk, I think actually depending on dose could be small, but that's just the radiation risk, that’s not all the logistics and everything else we talked about. But I think it's that last part lack of probable benefit. So, I agree.

Dr. Carrino: Yeah, I think that's the emphasis. Whether there's risk of injury certainly needs to be taken into consideration, but there is this lack of probable benefit. So, if there's no other panel's comments for this question, I would say that the panel agrees with this assessment and we've explained why. Dr. Sullivan, is that suitable for question 2A?

Dr. Sullivan: Dr. Song, I saw you start looking like you were raising your hand. Did you have something to add?

Dr. Song: Sorry, I realized that I did have a comment on this one.

Dr. Carrino: Oh, sure.

Dr. Song: It's just that the statement that towards the bottom says it is unclear what dose of radiation could effectively be used. It's wordsmithing in a way, but you could theoretically give just a high enough dose to clear all metastases, but I'd really maybe change the wording to just ideally or, most effectively be used to prevent injury while preventing metastases. I'm not sure of the exact wording, one can interpret that and say we know what dose would work.

Dr. Carrino: So, the principle is the trade-off between getting rid of the cancer, but not damaging, the native or the cells that you want to preserve, is that kind of the idea?

Dr. Song: Exactly.

Dr. Carrino: Yeah. So, Dr. Sullivan, when we're saying we're agreeing with this assessment, do we need to update the words if we want to state that we agree with it.

Dr. Sullivan: I think if there is something specific that you find incorrect and would need to be updated to agree with the statement, we would want to know what that is exactly. But if it's pointing out that you don't agree for this particular reason, that's what we would want to know. And it could be a minor clarification.

Dr. Carrino: Okay, just looking at it again.

Dr. Song: I mean, you could change "could" to "should." I don't think it's worth holding up if you have to, go through a whole other process.

Dr. Carrino: Okay, but I think the point is well taken and understood. Jorge Nieva, can you comment on this?

Dr. Nieva: Yeah, the phrase active malignancy is considered a relative contraindication for the use of intraoperative blood salvage is one I have questions of. There have been meta-analyses

done on this and it's really not clear that it should be a contraindication, and I worry about the FDA promoting that message,

Dr. Carrino: So, you would suggest we…

Dr. Nieva: I think that statement active malignancy is considered a relative contraindication should be struck from—

Panel Question 2A Summary

Dr. Carrino: Yeah. Remove that sentence. So that would be our suggestion 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. I think it keeps the rest of it intact and we can remove it.

Dr. Song: I would agree with that.

Dr. Carrino: Thank you. And then Daniel Bourland.

Dr. Bourland: I'm agreeing with Dr. Song's recommendation for changing could to should.

Dr. Carrino: Okay, since we cut out one sentence, we can add a should or change a could to a should. Okay, without any other panelists' hands, so with the two modifications that we just mentioned, we would agree with this assessment.

Dr. Sullivan: Okay, can I ask one clarifying question, please, on the change from could to should? Is it that it is unclear for each different cancer type what dose should be used? Or is it stating that you could theoretically give some very high dose that would be shown in some way to kill all potential cancer cells, but then having to look at the effects on the blood that would be

retransfused into the patient. So, is it thought that there is a sort of maximum dose you could give that would kill everything?

Dr. Bourland: That latter.

Dr. Sullivan: Thank you.

Dr. Carrino: Okay. So, with that, then, Dr. Sullivan, is this adequate?

Dr. Sullivan: Yes. It's adequate. Thank you.

Panel Question 2B

Dr. Carrino: Okay. Now on to 2B. Slide 41. Okay. So, we have 2B1 and 2B2. So, with 2B1 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 of risk to health associated with these devices. And do you agree with this assessment? And now we can start adding some type of details here and I see a number of people already. So, Margarita Zuley.

Dr. Zuley: Apologies. I wasn't quick enough with my hand. I wanted to go back and add in the last paragraph something about volume of Gray—

Dr. Carrino: To 2A? Back to 2A?

Dr. Zuley: Yes. I'm sorry. We're speaking about the dose, but I think we also need to say something about the amount and the volume of the blood treated.

Dr. Carrino: Yeah.

Dr. Zuley: Thank you.

Dr. Carrino: Do you think it requires some additional verbiage in there?

Dr. Zuley: Yes.

Dr. Carrino: So, we can go back to slide 40, please.

Dr. Zuley: So, I'm speaking about the sentence, it is unclear what dose of radiation should effectively be used to irradiate intraoperatively salvaged blood.

Dr. Carrino: Yes. And what volume would be, what volume would be safe?

Dr. Zuley: Yes.

Dr. Carrino: Something like that. Yeah. Okay. So that's our third edit. I know FDA is diligently capturing our edits. Or is that my job?

Dr. Sullivan: We're capturing it. Thank you.

Dr. Carrino: Okay, so now with those three edits, is that suitable? Dr. Sullivan, is it adequate?

Dr. Sullivan: Yes.

Dr. Carrino: Great. Okay, slide 41, 2B, question 1 and I see Natalie Compagni-Portis.

Dr. Compagni-Portis: Thank you. So, I agree with the assessment, and I think we really would need performance data around, especially overall survival, as was mentioned, that we need to have randomized controlled studies to analyze and assess the benefit and the risks. And that we have long term data on risk that really reflects the comments before in the prior FDA statement and the additional named risks that the panel has brought up. And that hopefully we have the results of these studies before patients would be exposed to the risks and that we're not doing this before we know if there truly is a benefit that outweighs the risk.

Dr. Carrino: Okay. And then Elizabeth Krupinski.

Dr. Krupinski: And just add what we've talked about before which is the different types of cancers and stages.

Dr. Carrino: Right. So, then we would state that we agree that...we don't believe that special controls can be established, generally to mitigate the risks to health associated with these devices. And then the types of performance data would be the outcome of randomized trials. Looking at the two groups, how one does with the irradiated blood and potentially another without. Then, the clinical information, so has been emphasized is the type of cancer, the stage, and what the typical prognosis would be are additional data elements. And I see more hands up now so Natalie Compagni-Portis.

Dr. Compagni-Portis: No, my apologies. I just didn't put my hand down in time.

Dr. Carrino: Okay. All right. Edward Snyder.

Dr. Snyder: Yeah, I was just wondering the idea of blood volume, there might be some benefit to listing it as a percentage of total blood volume. And then I started thinking if you have a very large individual compared to someone as much smaller physical stature, and that led me to the concept of pediatrics. It hasn't been mentioned at all about pediatrics. There used to be some comments about the age or something, or is that not appropriate at this time?

Dr. Carrino: I think I would rely on the other clinicians as well. The device could potentially be used across pediatric and adult and if it's done as a proportion of the volume, I guess that would mitigate the size issue as opposed to an absolute number. And Daniel Bourland.

Dr. Bourland: Thank you. I had one contrary comment on this, and I thought of, would there ever be a special control? What if you said you could never do above 25 gray, for whatever it was you were doing? Then as well would it be effective for this? We don't know one way or the other. Could someone choose to use it as a matter of practice? Professional practice? I don't know. Maybe yes, but the answer would never be there. Whether it would, there would actually be any in, of any effectiveness, I think the safety aspect might be there, but not effectiveness. So, it's a contrary thing, but, in general, I agree that there is limited information available on the effectiveness for metastasis.

Safety, I guess, I just think because we have a 25 gray point, we know certain aspects, but that's ex vivo blood and that's a little different from coming from this patient. So, in the long run, I'll agree with letter “i", that I agree with that assessment. But I do think potentially it'd be like the governor on the old motor scooter, you can't go above 30 miles per hour. Of course, the first thing people do is adjust them so you can go faster.

Dr. Carrino: Yeah, understood. So, I think the idea there is it can be challenging to design a trial to show that a blood irradiator really improves outcomes overall given all the other events that occur in cancer treatment, but, obviously, if there was a rate of increased metastasis in that group that had the autologous blood given back that would be a safety issue. Or even an effectiveness issue that would bear out, potentially, that it's worse outcome.

Dr. Bourland: I end up thinking about this in the context of radiation oncology, which has only developed since the 1940s. So, think of all the work that has gone into that to find our dose fractionation schedules and our techniques, et cetera. Substantial work and it's like okay, how do you bring all that to here? It's the same questions. And I think it's a great upward slope for this particular indication.

Dr. Carrino: Gotcha. Yeah. Yeah. The in vivo part makes it more complex. Next is Marjan Boerma.

Dr. Boerma: Yes. Thank you. So, I also agree with "i", with this assessment that we've been discussing, and I wanted to come back to these long-term health risks that were just mentioned and thinking of the risk of secondary cancers that were mentioned before, as we were having our panel discussions. Because to actually get to that risks, but we need to remember is that these clinical studies would have to be long term. And we would have to be following patients for several years after this procedure to really get to the answer of long-term health risks and secondary cancer risk.

Dr. Carrino: Yeah, or follow up studies. And then Victor van Berkel.

Dr. van Berkel: Yeah, so I, formally, I guess I would agree with statement one here that there's not enough information and this should be a class III device. I feel like we may be getting a little bit into the weeds on something that is perhaps not necessarily relevant to what we're talking about today. I don't think, practically speaking, that there is going to be a pre-market evalue... application for any of these devices. I can't imagine that someone is going to design a trial to try to look at these things in such a small-use patient population.

But given that this part A here seems to be saying like, okay, if someone was going to design a trial, what are the things that we want to worry about. From the FDA's perspective, I would imagine what we want to say here is something along the lines of we would like a very clearly delineated clinical profile of the patients that would fit into this circumstance, and we would want both short-term and long-term oncologic data suggesting benefit and leave it at that. Because if we get into the weeds of okay, we want to know exactly what the blood volume is and

all this sort of stuff, if they hit those things, but then miss something that we didn't think of today, then they're going to think that they've hit all of the requirements to achieve an application success. So, I think all of the points that people have brought up are excellent points. Hopefully, if a company decides that they wanted to go for this application, they would work through all these different things. But I don't know that we necessarily need to design the trial for them here.

Dr. Carrino: I think that was a good point. I think it was a nice way you put it all under that umbrella of the clinical profile. And Andy Chen.

Dr. Chen: Yes. This is more of a question to the FDA is that would they 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 use in for prevention of metastasis to, given the comments of this panel, to discourage off-label use of that unless it's part of if an investigator wants to design a study for that's fine, but I was wondering what the FDA thought of that.

Dr. Sullivan: Thanks for the feedback. I think we'd have to take this internally and see what we could do regarding asking for some sort of limitation of an indication within, for the devices that were, for example, having this indication removed.

Dr. Carrino: Thank you. Daniel Bourland

Dr. Bourland: I wanted to comment briefly on Dr. van Berkel's comments. I think those are important. For instance, what if a company had a very selected disease to work on? It might be effective. I don't know if lymphoma post-surgery or during surgery or not, but anyway, something like that you can imagine. There should be the opportunity for this to be investigated and put forward for that purpose, provided the company shows that it would be effective and safe.

Dr. Carrino: Okay. And Margarita Zuley.

Dr. Zuley: Thank you. I agree with (b)(i)i(A). I would suggest consideration of performance data that would look at near and midterm complications such as additional therapies required due to injuries or hospitalizations or other such things. Overall survival is a long-term endpoint. Maybe disease-free interval could be something. So, just to suggest a few additional types of performance data to consider. Thanks.

Panel Question 2B Summary

Dr. Carrino: Thank you. And yeah, I think with answering this question, we've heard lots of good comments from the panelists. I think Victor van Berkel put it under this nice umbrella of getting the clinical profile but we're not going to specify all the exact data elements right here. So, I think to answer this question, we agree that this, given the limited information available on the safety and effectiveness we do not believe that special controls can be established. And so, that answers a question 2(b)(i). We provided some examples and then also some framework for the clinical information. And so, answering it that way, then I think two is not applicable since we don't disagree. So, with all that Dr. Sullivan, is this adequate for a question 2b?

Dr. Sullivan: Yes, this is adequate. Thank you.

Dr. Carrino: And I think with that, we have done all of our questions. So, at this time the panel will hear summations comments or clarifications from the FDA.

FDA Summary

Dr. Sullivan: So, from the first part of the session, we note that there are concerns about the risks of delay during the procedure and potential logistical errors that could occur from the use of

this device, including radiation into surgery. The panel's consensus was: that it was unclear that the clinical benefit of the indication of metastasis or unclear what the clinical benefit of the indication for prevention of metastasis is; that clinical trials would need to be performed to explore parameters such as dose, type of cancer, and blood volume as well as secondary malignancies. We heard that there is no reasonable assurance of effectiveness. The panel agreed with the risks identified by FDA and they also noted that they could not be sure that all the risks could be exhaustively identified. They did include additional risks. These included cancer or mutation in the irradiated blood volume. Are there dose effects and usability issues?

And then, for question 2A, the summary was that there seemed to be a risk of injury that was unreasonable given the lack of probable benefit, but the panel did not agree with the language that was written. They did want to strike a phrase about the contraindication of the use of irradiated blood in cancer surgeries or the contraindication for the use of interoperative blood salvage in cancer surgery. There was some discussion about what dose of the radiation could be used. Theoretically, you could give a large dose of radiation that would kill every type of tumor, but there was also the balance of managing the risk to the blood product that would be returned to the patient and would that be actually a functional re-transfusion. And there was a note that we wanted to add something about the volume of blood treated in order to agree with the language about risk of injury being unreasonable.

For question 2b, the panel agreed that in general, there's a limited amount of information available on effectiveness. Agreed there was the nice summary from Dr. Van Berkel about there needs to be a clearly delineated clinical profile for patients that fit into the circumstances and short- and long- term outcomes would be related to the type of evidence that we would want to see for safety and effectiveness, or it was recommended that FDA look into that type of

information to show safety and effectiveness. I believe that's what I heard. Is there anything else that I've missed? Hearing nothing...

Adjournment

Dr. Carrino: I don't see any other hands up. I think that does that does summarize it. And I think at this point we can go toward adjournment. Last chance for any comments from anybody. Okay. So, with that I would really like to thank the panel members I know there was a lot of material to digest, for some of us, it's on the periphery of what we do, but obviously this is very important for patient care. I want to thank the FDA particularly for their detail-oriented organization, pulling the panel together and the presenters for being succinct and articulate with their information content and everybody's contribution to the panel meeting today. This meeting of the radiological devices panel is now adjourned.