DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Medical Devices; Radiology Devices; Classification of Blood Irradiators

Docket No. FDA-2025-N-5996

Preliminary Regulatory Impact Analysis
Initial Regulatory Flexibility Analysis
Unfunded Mandates Reform Act Analysis

Economics Staff
Office of Economics and Analysis
Office of Policy, Legislation, and International Affairs
Office of the Commissioner

Table of Contents

List of Tables

Executive Summary

The proposed rule, if finalized, would classify blood irradiator devices (unclassified, preamendments devices) into two classes based on intended use. It would classify blood irradiator devices intended to irradiate blood or blood products to prevent transfusion-associated graft versus host disease (blood irradiators intended to prevent TA-GVHD) into class II (special controls) and blood irradiator devices intended to irradiate intra-operatively salvaged blood in cancer patients undergoing surgery to prevent metastasis (blood irradiators intended to prevent metastasis) into class III (premarket approval). Separately, FDA also is issuing a proposed order requiring the filing of a premarket approval application (PMA) for blood irradiators intended to prevent metastasis. Quantified benefits of the proposed rule, if finalized, would consist of cost savings to industry and FDA from a reduction in the quantity and time burden of informal inquiries related to blood irradiators intended to prevent TA-GVHD. We also estimate cost savings to industry and FDA from a reduction in the number of premarket notification (510(k)) submissions necessitating requests for additional information from FDA before and during review. Industry and FDA could incur costs associated with premarket approval for current and future blood irradiators intended to prevent metastasis. We additionally quantify one-time costs to industry to read and understand the proposed rule and the proposed order requiring the filing of a PMA, as well as one-time costs to industry to revise labeling. We estimate that the annualized benefits over 10 years would range from $84 to $180,268 at a 7 percent discount rate, with a primary estimate of $90,176, and from $86 to $184,271 at a 3 percent discount rate, with a primary estimate of $92,178. The annualized costs would range from $0.68 million to $1.51 million at a 7 percent discount rate, with a primary estimate of $1.07 million, and from $0.66 million to $1.53 million at a 3 percent discount rate, with a primary estimate of $1.07 million.

I. Introduction and Summary

A. Introduction

We have examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, Executive Order 14192, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4).

Executive Orders 12866 and 13563 direct us to assess all benefits and costs of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits. Rules are economically significant under Executive Order 12866 if they have an annual effect on the economy of $100 million or more; or adversely affect in a material way the economy, a sector of the economy, productivity, competition, jobs, the environment, public health or safety, or State, local, or tribal governments or communities. The Office of Information and Regulatory Affairs has determined that this proposed rule is not a significant regulatory action under Executive Order 12866.

Executive Order 14192 requires that any new incremental costs associated with certain significant regulatory actions "shall, to the extent permitted by law, be offset by the elimination of existing costs associated with at least 10 prior regulations." This proposed rule, if finalized as proposed, is not expected to be an Executive Order 14192 regulatory action because this rule is not significant under Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because net annualized compliance costs of the proposed rule are more than 1 percent of average annual revenues and unquantified effects are uncertain, we find that the proposed rule will have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (Section 202(a)) requires us to prepare a written statement, which includes estimates of anticipated impacts, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any 1 year." The current threshold after adjustment for inflation is $187 million, using the most current (2024) Implicit Price Deflator for the Gross Domestic Product. This proposed rule would not result in an expenditure in any year that meets or exceeds this amount.

B. Overview of Benefits and Costs

The proposed rule, if finalized, would classify blood irradiator devices (unclassified, preamendments devices) into two classes based on intended use. It would classify blood irradiator devices intended to irradiate blood or blood products to prevent transfusion-associated graft versus host disease (blood irradiators intended to prevent TA-GVHD) into class II (special controls) and blood irradiator devices intended to irradiate intra-operatively salvaged blood in cancer patients undergoing surgery to prevent metastasis (blood irradiators intended to prevent metastasis) into class III (premarket approval).[1] The proposed special controls for blood

[1] Blood irradiators intended to prevent metastasis are not intended to be used for cancer treatment or therapy.

irradiators intended to prevent TA-GVHD are already generally practiced by manufacturers of currently cleared devices, with the primary change consisting of the labeling special controls. FDA believes that the proposed special controls, together with the general controls in the Federal Food, Drug, and Cosmetic Act (FD&C Act), would provide reasonable assurance of the safety and effectiveness of these devices and help ensure that all new devices meet the same standards as the currently marketed devices. FDA has determined that general controls and special controls together are insufficient to provide reasonable assurance of safety and effectiveness for blood irradiators intended to prevent metastasis, and that these devices present a potential unreasonable risk of illness or injury. Separately, FDA also is issuing a proposed order requiring the filing of a premarket approval application (PMA) for blood irradiators intended to prevent metastasis.

Quantified benefits of the proposed rule, if finalized, would consist of cost savings to industry and FDA from a reduction in the quantity and time burden of informal inquiries related to blood irradiators intended to prevent TA-GVHD. We also estimate cost savings to industry and FDA from a reduction in the number of premarket notification (510(k)) submissions necessitating requests for additional information from FDA before and during review. Industry and FDA could incur costs associated with premarket approval for current and future blood irradiators intended to prevent metastasis. Industry would incur costs to prepare and submit PMAs and annual and supplemental reports and costs to undergo facility inspections. In turn, FDA would incur costs to review and respond to PMAs and annual and supplemental reports, and costs to inspect facilities. We quantify the associated user fees for these PMAs and annual and supplemental reports as transfers from industry to FDA.[2] We additionally quantify one-time costs to industry to read and understand the proposed rule and the proposed order requiring the filing of a PMA, as well as one-time costs to industry to revise labeling.

We summarize the quantified benefits and costs of the proposed rule, if finalized, in Table 1. We estimate that the annualized benefits over 10 years would range from $84 to $180,268 at a 7 percent discount rate, with a primary estimate of $90,176, and from $86 to $184,271 at a 3 percent discount rate, with a primary estimate of $92,178. The annualized costs would range from $0.68 million to $1.51 million at a 7 percent discount rate, with a primary estimate of $1.07 million, and from $0.66 million to $1.53 million at a 3 percent discount rate, with a primary estimate of $1.07 million.

We estimate that the present value of total benefits over 10 years would range from $0.001 million to $1.35 million at a 7 percent discount rate, with a primary estimate of $0.68 million, and from $0.001 million to $1.62 million at a 3 percent discount rate, with a primary estimate of $0.81 million. The present value of total costs would range from $5.09 million to $11.38 million at a 7 percent discount rate, with a primary estimate of $8.06 million, and from $5.80 million to $13.41 million at a 3 percent discount rate, with a primary estimate of $9.39 million.

[2] Transfers are monetary payments between persons or groups that do not affect the total resources available to society (Ref. [8]).

Table 1. Summary of Benefits, Costs, and Distributional Effects of the Proposed Rule (millions of 2024 dollars)

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits	Annualized Monetized ($m/year)	$0.09	$0.0001	$0.18	2024	7%	10 years	Estimated benefits are cost savings
		$0.09	$0.0001	$0.18	2024	3%	10 years	
	Annualized Quantified							
	Qualitative							
Costs	Annualized Monetized ($m/year)	$1.07	$0.68	$1.51	2024	7%	10 years	
		$1.07	$0.66	$1.53	2024	3%	10 years	
	Annualized Quantified							
	Qualitative							
Transfers	Federal Annualized Monetized ($m/year)	$0.05	$0.03	$0.07	2024	7%	10 years	User fee payments associated with premarket approval for class III blood irradiator devices
		$0.05	$0.03	$0.07	2024	3%	10 years	
		From: Blood irradiator device industry			To: FDA			
	Other Annualized Monetized ($m/year)							
Effects	State, Local, or Tribal Government: None							
	Small Business: Quantified effects of more than 1 percent of average annual revenues and uncertain unquantified effects							
	Wages: None							
	Growth: None							

In line with Executive Order 14192, in Table 2 we estimate present and annualized values of costs, cost savings, and net costs over a perpetual time horizon. We estimate that this proposed rule would generate $570,338 in annualized net costs at a 7 percent discount rate, discounted relative to year 2024, over a perpetual time horizon.

Table 2. Executive Order 14192 Summary Table (millions of 2024 dollars, discounted over a perpetual time horizon relative to year at a 7 percent discount rate)

	Primary Estimate	Low Estimate	High Estimate
Present Value of Costs	$9.21	$4.59	$14.54
Present Value of Cost Savings	$1.06	$0.001	$2.12
Present Value of Net Costs	$8.15	$4.59	$12.42
Annualized Costs	$0.64	$0.32	$1.02
Annualized Cost Savings	$0.07	$0.0001	$0.15
Annualized Net Costs	$0.57	$0.32	$0.87

Note: Due to uncertainty regarding future impacts of the proposed rule, if finalized, we assume that undiscounted costs and cost savings in years 10 through infinity would equal costs and cost savings in year 9. We assume that costs and cost savings would begin to accrue in 2028 (year 0).

II. Preliminary Economic Analysis of Impacts

A. Background

Blood irradiator devices are prescription devices that deliver a controlled radiation dose to blood or blood products and may include an x-ray tube or a radionuclide sealed radiation source (e.g., Cobalt-60 or Cesium-137). The radiation dose from blood irradiators intended to prevent TA-GVHD is intended to inactivate viable leukocytes, including lymphocytes, prior to transfusion. The radiation dose from blood irradiators intended to prevent metastasis is intended to result in damage and the resulting death and removal of tumor cells in intra-operatively salvaged blood irradiated *ex vivo* for cancer patients undergoing surgery. In the following sections, we describe the regulatory history of blood irradiators and associated health risks, adverse events, and recalls.

1. Regulatory History

The Medical Device Amendments of 1976 amended the FD&C Act to define and create a risk-based classification system for medical devices. Under this system, FDA classifies medical devices into class I (low to moderate risk), class II (moderate to high risk), or class III (high risk). FDA refers to devices that were in commercial distribution prior to May 28, 1976, the date of enactment of the Medical Device Amendments of 1976, as "preamendments devices." Section 513(d)(1) of the FD&C Act allows FDA to classify preamendments devices once we: (1) receive a recommendation from a device classification panel (an FDA advisory committee); (2) publish the panel's recommendation for comment, along with a proposed regulation classifying the device; and (3) review and respond to comments and publish a final regulation classifying the device. FDA is following these procedures to classify blood irradiators. FDA currently regulates blood irradiators as unclassified, preamendments devices requiring premarket notification with the product code[3] "MOT."[4]

Based on recommendations from the Radiological Devices Advisory Panel (serving as a device classification panel) convened on April 12, 2012, and FDA's experience with blood irradiators intended to prevent TA-GVHD, FDA is proposing to classify blood irradiators intended to prevent TA-GVHD into class II (special controls) (Ref. [1]). Based on recommendations from the Radiological Devices Advisory Panel convened on November 7, 2023, and uncertainties about the associated risks and the effective radiation dose for blood irradiators intended to prevent metastasis, FDA is proposing to classify blood irradiators intended to prevent metastasis into class III (premarket approval) (Ref. [2]).

[3] "Classification product codes are a method of internally classifying and tracking medical devices. CDRH and a subset of CBER regulated medical device product codes consist of a [three] letter combination which associates a device's type with a product classification designated for the application. Classification product codes and information associated with these devices, such as names and attributes, are assigned by CDRH to support their regulation" (Ref. [14], p. 4).

[4] This product code (MOT) currently includes blood irradiators intended to prevent TA-GVHD and blood irradiators intended to prevent metastasis. FDA intends to create a separate product code for blood irradiators intended to prevent metastasis upon finalization of the proposed rule.

2. Health Risks, Adverse Events, and Recalls

FDA believes that the proposed special controls, in addition to general controls in the FD&C Act, are sufficient to mitigate health risks associated with the use of blood irradiators intended to prevent TA-GVHD. These potential health risks include delivery of an improper radiation dose; damage to red blood cells from radiation; unintended radiation exposure to the operator or public; electrical shock or burns from insufficient or malfunctioning safety controls or interlocks; and mechanical or crush injury. Failure to deliver the proper radiation dose to blood or a blood component can result in TA-GVHD in the recipient. TA-GVHD occurs when viable lymphocytes in transfused blood or blood products attack the recipient's own tissues, resulting in the recipient's death in most cases (Ref. [3]).

Blood irradiators intended to prevent metastasis share similar health risks related to the device hardware and software with blood irradiators intended to prevent TA-GVHD. Unique health risks for blood irradiators intended to prevent metastasis include the presence of proliferative malignant cells in re-transfused blood due to an incorrect dose or improper dose of radiation delivered; worsened control of oncologic disease or patient prognosis; delayed or lack of re-transfusion of irradiated blood or blood components; induction of a new cancer due to irradiation of the blood or blood components; and risks associated with usability, including irradiating the salvaged blood outside the operating room and the potential for blood to be incorrectly labeled or misidentified. Long-term health risks, such as impacts on cancer outcome, patient recovery, and survival, are uncertain based on available information.

Since 1984, FDA has received three substantive medical device reports (MDRs) for blood irradiators reporting device malfunction. Two MDRs were received in 2010, and one MDR was received in 2024.[5] The events reported in the three MDRs are within the scope of the proposed special controls for blood irradiators intended to prevent TA-GVHD. There have been two recalls of blood irradiators, occurring in 2004 and 2016. The first recall was to complete a cooling system retrofit to preclude overheating and failure of the device.[6] The second recall was for non-compliance with FDA's performance standard for cabinet x-ray devices.[7]

B. Need for Federal Regulatory Action

After the enactment of the Medical Device Amendments of 1976, FDA began to identify and classify all preamendments devices. FDA has determined that the unclassified blood irradiators intended to prevent TA-GVHD should be classified into class II (special controls), and the unclassified blood irradiators intended to prevent metastasis should be classified into class III (premarket approval). The proposed rule is in line with FDA's efforts to classify all preamendments devices. Thus, regulatory action is necessary to classify blood irradiators intended to prevent TA-GVHD as class II devices and blood irradiators intended to prevent metastasis as class III devices.

[5] We base this estimate on internal data from FDA's Center for Devices and Radiological Health (CDRH). We exclude two MDRs for blood irradiators containing no information, one MDR related to an accessory film used with blood irradiators, and one MDR that was a suggestion for device improvements.
[6] See: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm?id=28970.
[7] See 21 CFR 1020.40 and https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm?id=148078.

The proposed rule would also address information asymmetries in the market for blood irradiators. All blood irradiators intended to prevent TA-GVHD cleared by FDA are following most of the proposed special controls. However, the labeling special controls would help ensure the safe use of these devices, which have the potential for malfunctions that may cause adverse health consequences, by operators. Additionally, without the rule, industry may be uncertain about the requirements for blood irradiators and subsequently submit information requests and incomplete 510(k) submissions to FDA that they would not need to submit with more information.

C. Purpose of the Proposed Rule

The proposed rule, if finalized, would classify blood irradiators intended to prevent TA-GVHD into class II (special controls) and blood irradiators intended to prevent metastasis into class III (premarket approval).

The proposed special controls for blood irradiators intended to prevent TA-GVHD include nonclinical performance testing that demonstrates that the device performs as intended, software verification and validation, electrical safety and electromagnetic compatibility testing, and labeling information, such as a procedure to verify minimum dose delivery during each use, a summary of performance testing, information about safety features, a recommended schedule of maintenance and a quality assurance program, warning statements, and a statement specifying that the device is intended to prevent TA-GVHD.[8] These special controls are already generally practiced by manufacturers of currently cleared devices, with the primary change consisting of the labeling special controls.

The proposed rule would also give notice that FDA does not intend to exempt blood irradiators intended to prevent TA-GVHD from premarket notification requirements and would identify blood irradiators intended to prevent TA-GVHD and blood irradiators intended to prevent metastasis as intended for prescription use. Because this is currently the status quo for these devices, we do not consider any costs or benefits of these provisions.

In addition to the classification of blood irradiators for the prevention of metastasis into class III in the proposed rule, FDA also is issuing a proposed order requiring the filing of a PMA for blood irradiators intended to prevent metastasis.[9] In our analysis, we quantify potential costs associated with premarket approval. While these PMA-related costs are attributable to the proposed order, rather than this proposed rule, we include them here because this rulemaking is required prior to issuing the proposed order.

The proposed rule would become effective 30 days after publication of the final rule, and FDA would require manufacturers of blood irradiators intended to prevent TA-GVHD legally marketed prior to the effective date to comply with the rule within 12 months of the effective date. If FDA finalizes the proposed order at the same time as the proposed rule, as anticipated, the proposed order would permit blood irradiators intended to prevent metastasis to remain in

[8] See the proposed rule for a detailed description of the proposed special controls.

[9] The manufacturer of a preamendments class III device may comply with a call for PMAs by filing a PMA or a notice of completion of a product development protocol (PDP). In practice, manufacturers have rarely used the option of filing a notice of completion of a PDP. We therefore assume in our analysis that manufacturers would comply by filing a PMA.

commercial distribution without a PMA for 30 months after the classification of the device into class III, at which time the filing of a PMA would be required.

D. Baseline Conditions

We estimate the impact of the rule relative to the baseline, which is the state of the world in absence of regulatory action. Since the passage of the Medical Device Amendments in 1976, FDA has cleared 16 MOT devices: three in the 1980s, five in the 1990s, four in the 2000s, and four since 2010. However, some of these devices are not currently listed in FDA's Establishment Registration and Device Listing database as in commercial distribution, and some of the applicants that submitted the 510(k)s for these devices are not currently registered with FDA as establishments that are involved in the production and distribution of medical devices intended for commercial distribution in the United States. We assume that the proposed rule, if finalized, would impact only those establishments currently involved in the manufacture of blood irradiators intended for commercial distribution in the United States.

Therefore, to establish the baseline market, we determine the number of MOT devices and manufacturing establishments listing MOT devices, and their owner-operator firms, actively registered with FDA's Establishment Registration and Device Listing database as of September 2024. We identified six currently marketed MOT devices and three manufacturing establishments listing these devices. A unique firm owns and operates each of these manufacturers. Four devices have an indication solely for the intended prevention of TA-GVHD, and two devices have a dual indication for the intended prevention of TA-GVHD and the intended prevention of metastasis. A single firm currently manufactures both devices with the dual indication.

E. Benefits of the Proposed Rule

In this section, we quantify benefits to industry and FDA in the form of cost savings from a reduction in the quantity and time burden of informal inquiries related to blood irradiators intended to prevent TA-GVHD. We also estimate cost savings to industry and FDA from a reduction in the number of 510(k)s for blood irradiators intended to prevent TA-GVHD necessitating requests for additional information from FDA before and during review. We do not quantify public health benefits associated with the classification of blood irradiators intended to prevent TA-GVHD because the proposed rule, if finalized, would require the adoption of practices that manufacturers of currently marketed devices already generally follow and would not change the use of the devices. We do not quantify public health benefits associated with blood irradiators intended to prevent metastasis because long-term health risks of these devices are uncertain based on available information. Presented estimates are rounded to the nearest dollar unless otherwise specified. Values may not be exact due to rounding.

1. Public Health Benefits

In 1993, CBER published the memorandum "Recommendations Regarding License Amendments and Procedures for Gamma Irradiation of Blood Products" for facilities irradiating blood products to be shipped in interstate commerce (Ref. [4]). In 2012, the Radiological Devices Advisory Panel agreed that the memorandum, although intended for blood establishments manufacturing irradiated blood products, provided a good resource for

developing special controls for blood irradiators intended to prevent TA-GVHD (Ref. [1]). Since the publication of the CBER memorandum, blood irradiators have been associated with few published problems and adverse events.

Since 1984, FDA has received three MDRs for blood irradiators that are within the scope of the proposed special controls. Two of the MDRs, both received in 2010, involved the detection of low radiation output at points within the device cannister. The third MDR, received in 2024, reported component failures and burn injuries resulting from malfunctioning safety interlocks. It is possible that labeling requirements in the proposed special controls for blood irradiators intended to prevent TA-GVHD could prevent similar adverse events from happening in the future.[10] However, due to the infrequency of such events, any public health benefits would likely be small.

This proposed rule, if finalized, would provide reasonable assurance of safety and effectiveness of blood irradiators, and help ensure that all new 510(k) submissions for blood irradiators intended to prevent TA-GVHD meet the same standards as the currently marketed devices. These devices provide important public health benefits through the prevention of TA-GVHD. The proposed rule would provide additional assurance that the current level of public health protection is maintained.

2. Cost Savings from a Reduction in the Quantity and Time Burden of Informal Inquiries for Blood Irradiators Intended to Prevent TA-GVHD

While there are no quantifiable public health benefits, the rule would benefit current and potential manufacturers of new blood irradiators intended to prevent TA-GVHD by clarifying important information about the devices. These clarifications would generate cost savings by reducing the time it takes to inquire about a cleared device or developing a new device. We additionally assume that the time needed by FDA to respond to inquiries would decrease.

To estimate the magnitude of these cost savings to industry and FDA, we first estimate the baseline annual costs for inquires related to blood irradiators intended to prevent TA-GVHD. Since FDA's Center for Devices and Radiological Health (CDRH) has not received any formal inquiries (Q-Submissions [Q-Subs] or Q-Sub supplements) for blood irradiators, we focus our analysis on informal inquiries. We estimate that CDRH currently receives between 1 and 2 informal inquiries related to blood irradiators per year and that the labor burden for each inquiry ranges from 1 to 24 hours for both industry and FDA.[11]

[10] The inclusion of a recommended schedule of maintenance and a quality assurance program in the labeling special controls for blood irradiators intended to prevent TA-GVHD, as well a detailed procedure allowing the device operator to verify that the device is delivering a minimum of at least 15 Gy of radiation to all contents at any other point within the container and at least 25 Gy of radiation targeted to the central portion of the container, could prevent such adverse events in the future.

[11] A "Q-Sub" is a mechanism "available to submitters through which they can request feedback in writing or during a meeting with [FDA] regarding potential or planned medical device" applications (Ref. [15], p. 1). A "Pre-Submission" (Pre-Sub), one type of Q-Sub, "includes a formal written request from a submitter for feedback from FDA that is provided in the form of a formal written response or, if the submitter chooses, formal written feedback followed by a meeting" (p. 3). A "Q-Sub supplement" is "any new request for feedback and/or a meeting about the same device with the same or similar indications for use as an original Q-Sub that already exists" (p. 15).

To value the time for industry to informally inquire about blood irradiators intended to prevent TA-GVHD, we rely on the Bureau of Labor Statistics' (BLS) National Industry-Specific Occupational Employment and Wage Statistics (OEWS) for the Navigational, Measuring, Electromedical, and Control Instruments Manufacturing industry (North American Industry Classification System [NAICS] code 334500) in May 2024 (Ref. [5]). We select this industry because wage estimates are not available for the more detailed Irradiation Apparatus Manufacturing industry (NAICS code 334517). The mean hourly wage for managers (occupation code 11-0000) in the Navigational, Measuring, Electromedical, and Control Instruments Manufacturing industry is $87.95. We double this wage to account for employee benefits and overhead, yielding a fully-loaded hourly wage of $175.90. To estimate the time burden to FDA to respond to informal inquiries, we use 2024 data on FDA fully-loaded Full Time Equivalent (FTE) costs. The fully-loaded mean hourly wage for CDRH employees is $174.17.[12]

We multiply the lower and upper burden per exchange by the fully-loaded hourly wage for managers to obtain the cost to industry per informal inquiry ($176 to $4,222). We multiply the lower and upper burden per exchange by the fully-loaded mean hourly wage for CDRH employees to obtain the cost to FDA per informal inquiry ($174 to $4,180). We multiply the lower bound per inquiry costs by 1 inquiry and the upper bound per inquiry costs by 2 inquiries to determine that the baseline costs for informal inquiries related to blood irradiators intended to prevent TA-GVHD would range from $176 to $8,443 per year for industry and from $174 to $8,360 per year for FDA.

We assume that the proposed rule, if finalized, would reduce the number of informal inquiries related to blood irradiators intended to prevent TA-GVHD that current and potential manufacturers submit to FDA each year by 15 percent. We also assume that it would reduce the labor burden per inquiry by between 15 percent and 20 percent. We request comment on the extent to which the proposed rule, if finalized, would reduce the quantity and labor burden of informal inquiries related to blood irradiators intended to prevent TA-GVHD. Based on these assumptions, CDRH would receive between 0.85 and 1.70[13] informal inquiries related to these devices per year, and the labor burden for each inquiry would range from 0.85 to 19.20[14] hours for both industry and FDA. Thus, if the proposed rule is finalized, costs for informal inquiries related to blood irradiators intended to prevent TA-GVHD would range from $127 to $5,741[15] per year for industry and $126 to $5,685[16] per year for FDA.

To calculate cost savings from a reduction in the quantity and time burden of informal inquiries related to blood irradiators intended to prevent TA-GVHD, we subtract the costs to industry and FDA under the proposed rule, if finalized, from the baseline costs. Annual cost savings to industry would range from $49 to $2,702, and annual cost savings to FDA would range from $48 to $2,675. We assume that these cost savings would begin to accrue in year 1. We summarize these estimates in Table 3.

---

[12] For this estimate, we assume that each FTE employee works 2,080 hours annually.
[13] These values equal 1 inquiry × (1 – 0.15) and 2 inquiries × (1 – 0.15), respectively.
[14] These values equal 1 hour × (1 − 0.15) and 24 hours × (1 − 0.20), respectively.
[15] These values equal 0.85 inquiries × 0.85 hours per inquiry × $175.90 and 1.70 inquiries × 19.20 hours per inquiry × $175.90, respectively.
[16] These values equal 0.85 inquiries × 0.85 hours per inquiry × $174.17 and 1.70 inquiries × 19.20 hours per inquiry × $174.17, respectively.

Table 3. Annual Cost Savings to Industry and FDA from a Reduction in the Quantity and Time Burden of Informal Inquiries Related to Blood Irradiators Intended to Prevent TA-GVHD

Value	Industry or FDA	Low Estimate	Primary Estimate[a]	High Estimate
Baseline Annual Costs	Industry	$176	$4,310	$8,443
	FDA	$174	$4,267	$8,360
	Total	$350	$8,577	$16,803
Annual Costs Under Proposed Rule	Industry	$127	$2,934	$5,741
	FDA	$126	$2,905	$5,685
	Total	$253	$5,840	$11,426
Annual Cost Savings	Industry	$49	$1,375	$2,702
	FDA	$48	$1,362	$2,675
	Total	$97	$2,737	$5,377

[a] We calculate each primary estimate as the average of the low and high estimate.

3. Cost Savings from a Reduction in the Quantity of 510(k) Submissions Requiring Additional Information

Due to a lack of clear guidelines, such as a defined regulatory classification and published special controls, applicants may submit a 510(k) submission for a blood irradiator intended to prevent TA-GVHD that is lacking information required for the submission's review or includes excessive information that exceeds the utility of the 510(k) pathway, necessitating requests for additional information by CDRH. Cost savings from a reduction in the quantity of 510(k) submissions requiring additional information reflect fewer resubmissions from applicants and reduced review time for CDRH employees. We estimate the annual cost savings to industry and FDA by multiplying the reduction in the quantity of submissions requiring additional information each year by the average cost to prepare and submit a 510(k) and the average cost to review a 510(k), respectively.

FDA estimates that the majority of the 510(k) submissions it receives for blood irradiators intended to prevent TA-GVHD require additional information before FDA clears the device. In the past 10 years, the number of submissions FDA received in a given year ranged from 0 to 1. We therefore estimate that FDA receives between 0 submissions and 1 submission requiring additional information each year. FDA estimates the number of submissions requiring additional information would be reduced by 70 percent with the rule, or a reduction of between 0 and 0.70 submissions per year on average.[17] We request comment on this assumption.

We base our estimated costs to industry for preparing and submitting 510(k)s and costs to FDA for reviewing and responding to 510(k)s on reports from Eastern Research Group, Inc. (ERG) (2012) and Geiger (2005), respectively (Refs. [6], [7]). In 2024 dollars, ERG estimates industry costs ranging from $67,201 to $268,805, while Geiger estimates FDA costs of $20,566.[18] To calculate the annual cost savings to industry from a reduction in the quantity of 510(k) submissions requiring additional information, we multiply the average preparation and submission cost by the annual reduction in the number of submissions requiring additional information. To calculate the annual cost savings to FDA, we multiply the average 510(k) review

[17] These values equal 0 submissions × 0.70 and 1 submission × 0.70, respectively.

[18] ERG estimates a cost to industry ranging from $50,000 to $200,000 while Geiger (2005) estimates a cost to FDA of $13,391 ($107.7 million ÷ $8,043). We assume these estimates are in 2012 and 2005 dollars, respectively, prior to adjustment to 2024 dollars using the Bureau of Economic Analysis GDP deflator.

and response cost by the same reduction. Annual cost savings to industry would range from $0 to $188,164,[19] and annual cost savings to FDA would range from $0 to $14,396.[20] We assume that these cost savings would begin to accrue in year 1. We summarize these estimates in Table 4.

Table 4. Annual Cost Savings to Industry and FDA from a Reduction in the Quantity of 510(k) Submissions Requiring Additional Information

Industry or FDA	Low Estimate	Primary Estimate[a]	High Estimate
Industry	$0	$94,082	$188,164
FDA	$0	$7,198	$14,396
Total	$0	$101,280	$202,560

[a] We calculate each primary estimate as the average of the low and high estimate.

4. Other Potential Benefits

Reductions in the quantity and time burden of informal inquiries and the quantity of submitted 510(k)s for blood irradiators intended to prevent TA-GVHD requiring additional information before and during review as a result of the proposed rule, if finalized, could in turn benefit consumers if manufacturers are able to clear and market their new devices sooner. Given that there have been no new 510(k) submissions for MOT devices in several years, this is unlikely to be a significant source of benefits. We request comment on the likelihood and magnitude of such benefits.

F. Costs of the Proposed Rule

As a result of the proposed rule, if finalized, industry would incur one-time costs to read and understand the rule and the order requiring the filing of a PMA for blood irradiators intended to prevent metastasis, and one-time costs to revise labeling. Industry and FDA additionally could incur costs associated with premarket approval for current and future blood irradiators intended to prevent metastasis. We quantify these costs in this section. Presented estimates are rounded to the nearest dollar unless otherwise specified. Values may not be exact due to rounding.

1. Costs to Read and Understand the Rule

We expect that the 3 manufacturers we identify in section II.D would incur a one-time cost to read and understand the proposed rule, if finalized, in year 0. We assume that 1 to 3 employees at each manufacturer would read the rule's preamble and codified language, which contain approximately 15,000 words in total. We also assume that each reviewer would read at the average adult reading speed of 200 words to 250 words per minute (Ref. [8]). Based on these assumptions, it would take each reviewer between 60 minutes and 75 minutes to read the rule. Given the simplicity of the codified language, we do not expect that reviewers would need additional time to understand the rule.

To value the time for manufacturers to read and understand the rule, we assume a reviewer mix for each manufacturer of 50 percent managers (occupation code 11-0000) and 50 percent lawyers (occupation code 23-1011). Using BLS OEWS wages for the Navigational, Measuring, Electromedical, and Control Instruments Manufacturing industry in May 2024, this

[19] These values equal $67,201 × 0 submissions and $268,805 × 0.70 submissions, respectively.
[20] These values equal $20,566 × 0 submissions and $20,566 × 0.70 submissions, respectively.

mix yields a composite wage of $102.91.[21] We double this wage to account for employee benefits and overhead, yielding a fully-loaded hourly wage of $205.82 per reviewer.

We estimate that the cost per reviewer to read and understand the proposed rule, if finalized, would range from $206 to $257[22] and that total review costs per manufacturer would range from $206 to $772.[23] Therefore, we estimate that the total costs for reading and understanding the rule would range from $617 to $2,315 in year 0.[24]

2. Costs to Read and Understand the Order Requiring the Filing of a PMA

We expect that 1 manufacturer would incur a one-time cost to read and understand the proposed order requiring the filing of a PMA for blood irradiators intended to prevent metastasis, if finalized, in year 0. This corresponds to the number of manufacturers of currently marketed blood irradiators with an indication for the intended prevention of metastasis, which we identify in section II.D. We assume that 1 to 3 employees would read the order, which contains approximately 7,000 words, at the average adult reading speed of 200 words to 250 words per minute (Ref. [8]). Based on these assumptions, it would take each reviewer between 28 minutes and 35 minutes to read the order. We do not expect that reviewers would need additional time to understand the order.

Adopting the fully-loaded hourly wage of $205.82 per reviewer from the previous section, we estimate that the cost per reviewer to read and understand the proposed order, if finalized, would range from $96 to $120.[25] Therefore, we estimate that the total costs for reading and understanding the order would range from $96 to $360 in year 0.[26]

3. Costs to Revise Labeling

We assume that all manufacturers of currently marketed blood irradiators would incur costs to revise labeling if the proposed rule is finalized. To estimate the cost to revise labeling per device, we use the FDA Labeling Cost Model developed by RTI International (Ref. [9]). This model uses data provided by FDA to estimate the cost of a labeling change for specific types of products, minor to extensive labeling changes, and different compliance periods.

Since the model is limited to consumer products, it does not include blood irradiators. Instead, we use the average cost of a minor labeling change[27] for included products in the Surgical and Medical Instrument Manufacturing industry[28] (NAICS code 339112) as a proxy for the cost of a minor labeling change for a blood irradiator. We request comment on this approach. We estimate that the one-time cost to revise labeling per device would range from $616 to

[21] The mean hourly wage for managers is $87.95, and the mean hourly wage for lawyers is $117.87.
[22] These values equal $205.82 × (60 minutes ÷ 60 minutes) and $205.82 × (75 minutes ÷ 60 minutes), respectively.
[23] These values equal $205.82 × 1 reviewer and $257.28 × 3 reviewers, respectively.
[24] These values equal $205.82 × 3 manufacturers and $771.83 × 3 manufacturers, respectively.
[25] These values equal $205.82 × (28 minutes ÷ 60 minutes) and $205.82 × (35 minutes ÷ 60 minutes), respectively.
[26] These values equal $96.05 × 1 reviewer and $120.06 × 3 reviewers, respectively.
[27] A minor labeling change has a specific definition in this model. A minor change is a change that only affects one color and does not require redesign of labeling.
[28] In this industry, the FDA Labeling Cost Model includes costs for blood pressure kits and accessories, first aid thermometers, and insulin syringes.

$3,168, with a primary estimate of $1,674.[29] Therefore, we estimate that total costs to revise labeling for all 6 currently marketed MOT devices in year 1 would range from $3,696 to $19,008, with a primary estimate of $10,044.[30]

4. Costs Associated with Blood Irradiators Intended to Prevent Metastasis

Manufacturers of blood irradiators for the intended prevention of metastasis would incur additional costs due to the proposed rule, if finalized. These costs accrue to manufacturers of products designated as class III, thus requiring a PMA. This would affect both currently marketed devices and any future devices that firms seek to market as class III. For industry, costs include resources necessary to prepare and submit PMAs and annual and supplemental reports, and labor burdens related to facility inspections. For FDA, costs include resources to review and respond to PMAs and annual and supplemental reports and to inspect facilities.

We expect two currently marketed blood irradiators to be classified as class III as a result of the proposed rule, if finalized. As we state in section II.D, both of these devices have an additional indication for the intended prevention of TA-GVHD and are manufactured by a single manufacturing firm. It is possible that, after weighing the costs we describe in this section, the firm would choose to remove the intended prevention of metastasis indication from these devices and continue to market them for the intended prevention of TA-GVHD only. In this case, the firm would incur costs to comply with the special controls for class II devices but would not incur any costs specific to devices in the class III category. In this main analysis, we assume that the firm would maintain the intended prevention of metastasis indication for both devices and incur the associated costs, since this assumption results in the highest cost estimates. We request comment on this assumption. We estimate costs assuming that the firm would maintain the intended prevention of metastasis indication for fewer than two devices in an uncertainty and sensitivity analysis in section II.K.1.

For our analysis, we assume that the PMA-related costs quantified in this section associated with currently marketed blood irradiators intended to prevent metastasis would begin in year 3. If the proposed rule and order finalize simultaneously, we expect manufacturers would defer filing a PMA until the end of the 30-month compliance period, since this would allow them to continue commercial distribution in the interim while minimizing these costs. We assume that the PMA-related costs quantified in this section associated with future blood irradiators intended to prevent metastasis would begin in year 1, given the greater uncertainty around when manufacturers of future devices would choose to file their PMA and potential incentives to file sooner to minimize time to market. We request comment on these assumptions.

It is likely that prior to preparing and submitting a PMA, industry may incur additional costs associated with earlier phases of device development, which could be significant. We discuss these costs as part of our uncertainty and sensitivity analysis in section II.K.2.

[29] These estimates include costs of labor and materials associated with a labeling change. We assume that manufacturers would coordinate their labeling revisions in response to the proposed rule with a planned labeling change.

[30] To calculate these costs, we multiple the per device costs by the 6 currently marketed MOT devices.

a. Costs to Industry to Prepare and Submit PMAs

FDA previously estimated that the cost to industry to prepare and submit a PMA was $1 million (Ref. [10]). This equals approximately $1.34 million when adjusted from 2012 dollars to 2024 dollars using the Bureau of Economic Analysis (BEA) GDP deflator. More recent data suggests that PMA submission costs could be higher, approximately $2.33 million in 2024 dollars (Ref. [11]). We take the average of these two estimates as our primary estimate of $1.84 million. We expect 2 currently marketed blood irradiators to be classified as class III as a result of the proposed rule, if finalized. Therefore, we estimate that total costs to industry to prepare and submit PMAs for currently marketed devices would range from $2.69 million to $4.65 million in year 3.[31]

Manufacturers of future blood irradiators intended to prevent metastasis would also incur incremental costs to prepare and submit PMAs. These manufacturers would submit a 510(k) to market their device in absence of the rule. Consequently, the incremental cost to prepare and submit a PMA for future devices would equal the cost to prepare and submit a PMA less the cost to prepare and submit a 510(k). Using our primary estimate of 510(k) preparation and submission costs from section II.E.3 ($134,403, the average of $67,201 and $268,805), we estimate that this incremental cost would range from $1.21 million to $2.19 million per device.[32]

Since the passage of the Medical Device Amendments, FDA has cleared 2 blood irradiators for the intended prevention of metastasis. This amounts to approximately 0.04 devices per year between 1976 and 2024, or about one device every 24 years.[33] We therefore assume that the number of future class III submissions for blood irradiators would range from 0 to 0.04 per year, with a primary (average) estimate of 0.02, resulting in costs ranging from $0 to $91,322 per year.[34] We assume that these annual costs to industry to prepare and submit PMAs for future class III devices would begin in year 1.

b. Costs to Industry to Prepare and Submit Annual Reports

Firms marketing a class III product must also comply with annual reporting requirements. To maintain marketing approval, these reports require the manufacturer to submit information summarizing changes to the product, results of unpublished investigations and studies, and reports in the scientific literature regarding the device. Lacking direct evidence of the cost to prepare and submit annual reports, we assume that the ratio of user fee to preparation cost is the same for annual reports as for the PMA itself. The fiscal year 2024 standard user fees for a PMA and an annual report are $483,560 and $16,925, respectively (Ref. [12]). Our primary estimate of the cost to prepare and submit a PMA from section II.F.4.a is $1.84 million. This yields a user fee to cost ratio of 0.26.[35] The cost to industry to prepare and submit an annual report must equal $64,229 to yield a user fee to cost ratio of 0.26 for annual reports.[36] We therefore estimate that

[31] These values equal $1,344,026 × 2 devices and $2,326,121 × 2 devices, respectively.
[32] These values equal $1,344,026 − $134,403 and $2,326,121 − $134,403, respectively.
[33] This value equals 2 devices ÷ 48 years.
[34] These values equal $1,209,624 × 0 devices and $2,191,718 × 0.04 devices, respectively
[35] This equals $483,560 ÷ $1,835,074.
[36] To estimate the cost to industry to prepare and submit an annual report ($64,229), we divide $16,925 by 0.26.

annual costs to prepare and submit annual reports for currently marketed devices would equal $128,458 beginning in year 3.[37]

We also account for annual reports for future devices in the class III category. To calculate the total number of future devices requiring annual reports in each year, we add the expected number of new devices in the class III category in each year to the number of devices from the previous year. In section II.F.4.a, we assume that that the number of future class III submissions for blood irradiators would range from 0 to 0.04 per year beginning in year 1, with a primary estimate of 0.02. We likewise adopt this range for the number of future class III approvals per year. To calculate costs to prepare and submit annual reports for future devices in each year, we then multiply by the cost to industry per annual report ($64,229), since we assume industry would submit one annual report per device per year. For example, our high estimate of industry costs in year 2 equals $5,352 (0.08 devices × $64,229). We present these estimates in Table 5.

Table 5. Costs to Industry to Prepare and Submit Annual Reports for Future Class III Devices

Year	Number of Devices (Low Estimate)	Number of Devices (Primary Estimate)	Number of Devices (High Estimate)	Costs (Low Estimate)	Costs (Primary Estimate)	Costs (High Estimate)
0	0	0	0	$0	$0	$0
1	0	0.02	0.04	$0	$1,338	$2,676
2	0	0.04	0.08	$0	$2,676	$5,352
3	0	0.06	0.13	$0	$4,014	$8,029
4	0	0.08	0.17	$0	$5,352	$10,705
5	0	0.10	0.21	$0	$6,691	$13,381
6	0	0.13	0.25	$0	$8,029	$16,057
7	0	0.15	0.29	$0	$9,367	$18,733
8	0	0.17	0.33	$0	$10,705	$21,410
9	0	0.19	0.38	$0	$12,043	$24,086

The annualized costs to industry to prepare and submit annual reports for future class III devices over 10 years would range from $0 to $10,561 at a 7 percent discount rate, with a primary estimate of $5,280. At a 3 percent discount rate, these annualized costs would range from $0 to $11,391, with a primary estimate of $5,696.

c. Costs to Industry to Prepare and Submit Supplemental Reports

Manufacturers of class III products may also incur costs to prepare and submit supplemental reports. FDA requires a supplement to an existing PMA whenever a firm wishes to make a change that affects the safety or effectiveness of the device. Such changes may include new indications for use, labeling changes, or changes to packaging. Based on data internal to the agency, we estimate that each PMA receives between 0 and 3 supplements per year.[38] We use these values as our low and high estimates of the number of supplemental reports submitted per

[37] This equals $64,229 × 2 devices.

[38] This is based on PMAs receiving favorable decisions between fiscal year 2020 and fiscal year 2024. We limit our sample to devices with the product code "OTE" (digital breast tomosynthesis), the closest technological surrogate to blood irradiators in the Office of Radiological Health for which FDA requires premarket approval.

device annually. We assume that the primary estimate is 1.5 supplemental reports per device annually, the average of this range. We request comment on these assumptions.

As with annual reports, we lack information of the cost to prepare and submit a supplemental report. Consequently, we assume that the ratio of user fee to preparation cost is the same for supplemental reports as it is for the PMA. We estimate the user fee for a supplemental report as the average of the 2024 standard user fees for each type of supplemental report weighted by the distribution of total supplements by type between 2014 and 2023. We consider the 180-day, 30-day notice, panel-track, and real-time supplement types. We estimate the distribution of total supplements by type based on publicly available data on releasable PMAs.[39] This yields a weighted average user fee of $24,018.[40]

In section II.F.4.b, we estimate a user fee to cost ratio of 0.26 for PMAs. The cost to industry to prepare and submit a supplemental report must equal $91,148 to yield a user fee to cost ratio of 0.26 for supplemental reports.[41] We therefore estimate that annual costs to prepare and submit supplemental reports for currently marketed devices would range from $0 to $546,890 beginning in year 3.[42]

We also account for supplemental reports submitted by manufacturers for future class III devices. To calculate the total number of supplemental reports for future devices in each year, we multiply the estimated number of devices in each year from Table 5 by 0 reports (low estimates), 1.5 reports (primary estimates), and 3 reports (high estimates). To calculate costs to prepare and submit supplemental reports for future devices in each year, we then multiply by the cost to industry per supplemental report ($91,148). For example, our high estimate of industry costs in year 2 equals $22,787 (0.08 devices × 3 supplemental reports × $91,148). We present these estimates in Table 6.

[39] See: https://www.fda.gov/medical-devices/device-approvals-and-clearances/pma-approvals.
[40] The 2024 standard user fees are $72,534 for 180-day supplements, $7,737 for 30-day notices, $386,848 for panel-track supplements, and $33,849 for real-time supplements. We estimate that between 2014 and 2023, 14.12 percent of supplements were 180-day supplements, 71.64 percent were 30-day notices, 0.97 percent were panel-track supplements, and 13.28 were real-time supplements.
[41] To estimate the cost to industry to prepare and submit a supplemental report ($91,148), we divide $24,018 by 0.26.
[42] These values equal $91,148 × 0 reports per device × 2 devices and $91,148 × 3 reports per device × 2 devices, respectively.

Table 6. Costs to Industry to Prepare and Submit Supplemental Reports for Future Class III Devices

Year	Number of Reports (Low Estimate)	Number of Reports (Primary Estimate)	Number of Reports (High Estimate)	Costs (Low Estimate)	Costs (Primary Estimate)	Costs (High Estimate)
0	0	0	0	$0	$0	$0
1	0	0.03	0.13	$0	$2,848	$11,394
2	0	0.06	0.25	$0	$5,697	$22,787
3	0	0.09	0.38	$0	$8,545	$34,181
4	0	0.13	0.50	$0	$11,394	$45,574
5	0	0.16	0.63	$0	$14,242	$56,968
6	0	0.19	0.75	$0	$17,090	$68,361
7	0	0.22	0.88	$0	$19,939	$79,755
8	0	0.25	1.00	$0	$22,787	$91,148
9	0	0.28	1.13	$0	$25,635	$102,542

The annualized costs to industry to prepare and submit supplemental reports for future class III devices over 10 years would range from $0 to $44,960 at a 7 percent discount rate, with a primary estimate of $11,240. At a 3 percent discount rate, these annualized costs would range from $0 to $48,497, with a primary estimate of $12,124.

d. Costs to FDA to Review and Respond to PMAs

FDA would also experience additional PMA-related costs because of the proposed rule, if finalized. We estimate that it would cost FDA approximately $864,688 to review and respond to each PMA submission from industry. This is based on a 2005 estimate of $562,992, which we adjust to 2024 dollars using the BEA GDP deflator (Ref. [7]). Because FDA expects 2 currently marketed blood irradiators to be classified as class III, total costs to FDA to review and respond to PMAs for currently marketed devices would equal $1.73 million in year 3.[43]

We estimate that the incremental cost to FDA to review and respond to a PMA for future devices would equal the cost to review and respond to a PMA less the cost to review and respond to a 510(k). Using our primary estimate of 510(k) review and response costs from section II.E.3 ($20,566), we estimate that this incremental cost would equal $844,122 per device.[44] If FDA receives between 0 and 0.04 PMA submissions for future devices per year, with a primary estimate of 0.02, as we assume in section II.F.4.a, then annual costs to FDA to review and respond to these submissions would range from $0 to $35,172, with a primary estimate of $17,586.[45] We assume that these costs would begin to accrue in year 1.

e. Costs to FDA to Review and Respond to Annual and Supplemental Reports

FDA must also review and respond to annual and supplemental reports submitted by industry. Our estimate of the cost to review and respond to an annual or supplemental report is

[43] This equals $864,688 × 2 devices.
[44] This value equals $864,688 − $20,566.
[45] The low cost estimate equals 0 devices × $844,122, the primary cost estimate equals 0.02 devices × $844,122, and the high cost estimate equals 0.04 devices × $844,122.

$22,604. This value is based on a 2005 estimate of $14,717, which we adjust to 2024 dollars using the BEA GDP deflator (Ref. [7]). Based on these assumptions, annual costs to review and respond to annual reports for the 2 currently marketed devices to be classified as class III would equal $45,208 beginning in year 3.[46]

In section II.F.4.c we assume that the number of supplemental reports submitted per device annually would range from 0 to 3. Therefore, we estimate that annual costs to review and respond to supplemental reports for currently marketed devices would range from $0 to $135,624 beginning in year 3.[47]

To estimate costs to FDA to review and respond to annual and supplemental reports for future class III devices, we refer to Table 5 and Table 6. For costs to review and respond to annual reports, we multiply the number of devices in each year from Table 5 by the cost to FDA per annual report ($22,604), since we assume FDA would receive one annual report per device per year. For costs to review and respond to supplemental reports, we multiply the number of supplemental reports in each year from Table 6 by the cost to FDA per supplemental report ($22,604). We summarize these costs to FDA in Table 7.

Table 7. Costs to FDA to Review and Respond to Annual and Supplemental Reports for Future Class III Devices

Year	Annual Report Costs (Low Estimate)	Annual Report Costs (Primary Estimate)	Annual Report Costs (High Estimate)	Supplemental Report Costs (Low Estimate)	Supplemental Report Costs (Primary Estimate)	Supplemental Report Costs (High Estimate)
0	$0	$0	$0	$0	$0	$0
1	$0	$471	$942	$0	$706	$2,825
2	$0	$942	$1,884	$0	$1,413	$5,651
3	$0	$1,413	$2,825	$0	$2,119	$8,476
4	$0	$1,884	$3,767	$0	$2,825	$11,302
5	$0	$2,355	$4,709	$0	$3,532	$14,127
6	$0	$2,825	$5,651	$0	$4,238	$16,953
7	$0	$3,296	$6,593	$0	$4,945	$19,778
8	$0	$3,767	$7,535	$0	$5,651	$22,604
9	$0	$4,238	$8,476	$0	$6,357	$25,429

We estimate that the annualized costs to review and respond to annual reports for future class III devices would range from $0 to $3,717 at a 7 percent discount rate, with a primary estimate of $1,858, and from $0 to $4,009 at a 3 percent discount rate, with a primary estimate of $2,004. The annualized costs to review and respond to supplemental reports for future class III devices would range from $0 to $11,150 at a 7 percent discount rate, with a primary estimate of $2,787, and from $0 to $12,027 at a 3 percent discount rate, with a primary estimate of $3,007.

[46] This equals $22,604 × 2 devices.

[47] These values equal $22,604 × 0 reports per device × 2 devices and $22,604 × 3 reports per device × 2 devices, respectively.

f. Costs to Industry and FDA for Facility Inspections

As part of the PMA process, FDA field personnel may inspect the manufacturing facilities belonging to the manufacturer. These inspections are costly for both industry and FDA. We assume that cost of a facility inspection to FDA is $134,403 ($100,000 adjusted from 2012 to 2024 dollars using the BEA GDP deflator) (Ref. [6]). Firms must prepare for the inspection and perform practice runs, as well as host the inspection itself. Therefore, we assume that the cost of a facility inspection to industry is twice as large as the FDA cost at $268,805. We therefore estimate that total costs to industry to undergo facility inspections for currently marketed devices would equal $537,611 in year 3.[48] Total costs to FDA to conduct these inspections would equal $268,805 in year 3.[49]

In section II.F.4.a, we assume that that the number of future class III submissions for blood irradiators would range from 0 to 0.04 per year, with a primary estimate of 0.02. To calculate costs to industry and FDA associated with facility inspections for future class III devices, we multiply these values by the cost to industry per inspection ($268,805) and the cost to FDA per inspection ($134,403), respectively. The annual costs to industry would range from $0 to $11,200, with a primary estimate of $5,600.[50] The annual costs to FDA would range from $0 to $5,600, with a primary estimate of $2,800.[51] We assume that these costs would begin to accrue in year 1.

G. Summary of Benefits and Costs

In Table 8, we summarize the stream of total benefits and costs of the proposed rule over 10 years. Quantified benefits include annual cost savings to industry and FDA from a reduction in the quantity and time burden of informal inquiries and a reduction in the quantity of 510(k) submissions requiring additional information for blood irradiators intended to prevent TA-GVHD. Quantified costs include one-time costs to industry to read and understand the rule and the order requiring the filing of a PMA for blood irradiators intended to prevent metastasis, one-time costs to industry to revise labeling, and costs to industry and FDA associated with premarket approval for blood irradiators intended to prevent metastasis.

[48] This equals $268,805 × 2 devices.
[49] This equals $134,403 × 2 devices.
[50] The low estimate equals 0 devices × $268,805, the primary estimate equals 0.02 devices × $268,805, and the high estimate equals 0.04 devices × $268,805.
[51] The low estimate equals 0 devices × $134,403, the primary estimate equals 0.02 devices × $134,403, and the high estimate equals 0.04 devices × $134,403.

Table 8. Stream of Total Benefits and Costs of the Proposed Rule over 10 Years

Year	Total Benefits (Low Estimate)	Total Benefits (High Estimate)	Total Costs (Low Estimate)	Total Costs (High Estimate)
0	$0	$0	$714	$2,676
1	$97	$207,937	$3,696	$180,139
2	$97	$207,937	$0	$178,968
3	$97	$207,937	$5,397,511	$8,241,018
4	$97	$207,937	$173,666	$1,070,822
5	$97	$207,937	$173,666	$1,088,659
6	$97	$207,937	$173,666	$1,106,496
7	$97	$207,937	$173,666	$1,124,333
8	$97	$207,937	$173,666	$1,142,170
9	$97	$207,937	$173,666	$1,160,007

The annualized benefits over 10 years would range from $84 to $180,268 at a 7 percent discount rate, with a primary estimate of $90,176, and from $86 to $184,271 at a 3 percent discount rate, with a primary estimate of $92,178. The annualized costs would range from $0.68 million to $1.51 million at a 7 percent discount rate, with a primary estimate of $1.07 million, and from $0.66 million to $1.53 million at a 3 percent discount rate, with a primary estimate of $1.07 million.

H. Distributional Effects

We do not expect any distributional effects from the proposed rule, if finalized, across varying income, ethnic, geographic, gender, or age groups. This is primarily because we only estimate benefits and costs accruing to industry and FDA. However, patients receiving medical care with blood irradiators covered by the proposed rule could be affected. These effects could come in the form of improved transparency in product labeling leading to more informed treatments and associated reductions in morbidity and medical spending. In this way, the proposed rule could better align the use of blood irradiators with their social costs.

I. Transfers Caused by the Proposed Rule

The proposed rule, if finalized, would generate transfers in the form of user fee payments from industry to FDA. These transfers are the result of covered devices receiving the class III designation and associated PMAs. This includes fees for the PMA itself, as well as any associated annual and supplemental reports, which would be paid by manufacturers.

First, we estimate user fees for the PMA. Small businesses certified through FDA's Small Business Determination (SBD) program with gross receipts or sales of $100 million or less are eligible for reduced (small business) user fees.[52] Based on proprietary sales data from Dun & Bradstreet, most MOT device manufacturers have annual sales less than $100 million, including the single manufacturer of blood irradiators intended to prevent metastasis. We therefore assume that current and future manufacturers of blood irradiators intended to prevent metastasis would pay small business user fees. We vary this assumption in an uncertainty and sensitivity analysis in section II.K.3.

[52] See: https://www.fda.gov/industry/fda-user-fee-programs/medical-device-user-fee-amendments-mdufa.

The fiscal year 2024 small business user fees for a PMA and a 510(k) are $120,890 and $5,440, respectively. We adopt $120,890 as the incremental PMA user fee for the two currently marketed blood irradiators intended to prevent metastasis. For future devices in the class III category, we adopt an incremental PMA user fee equal to the PMA small business user fee less the 510(k) small business user fee ($115,450). This is because these manufacturers would submit a 510(k) to market their device in absence of the rule. We continue to assume that the number of future class III submissions for blood irradiators would range from 0 to 0.04 per year beginning in year 1, with a primary estimate of 0.02. Based on these assumptions, PMA user fees for currently marketed devices would equal $241,780 in year 3.[53] Annual PMA user fees for future devices in the class III category would range from $0 to $4,810 beginning in year 1, with a primary estimate of $2,405.[54]

Next, we estimate user fees for annual reports. The fiscal year 2024 small business user fee for an annual report submission equals $4,231. Assuming that FDA would receive one annual report per device per year, industry would incur $8,462 in annual reporting user fees for the two currently marketed devices beginning in year 3. For future devices in the class III category, we multiply the number of devices in each year from Table 5 by $4,231. We estimate that the annualized value of annual reporting user fees associated with future devices over 10 years would range from $0 to $696 at a 7 percent discount rate, with a primary estimate of $348, and from $0 to $750 at a 3 percent discount rate, with a primary estimate of $375.

Finally, we estimate user fees for supplemental reports. Similar to section II.F.4.c, we estimate the small business user fee for a supplemental report as the average of the 2024 small business user fees for each type of supplemental report weighted by the distribution of total supplements by type between 2014 and 2023. This yields a weighted average small business user fee of $7,391.[55] We assume that FDA would receive between 0 and 3 supplemental reports per device per year, with a primary estimate of 1.5. Then, supplemental reporting user fees for the two currently marketed devices would range from $0 to $44,344 beginning in year 3, with a primary estimate of $22,172.[56]

For future devices in the class III category, we multiply the number of supplemental reports in each year from Table 6 by $7,391. We estimate that the annualized value of supplemental reporting user fees associated with future devices over 10 years would range from $0 to $3,646 at a 7 percent discount rate, with a primary estimate of $911, and from $0 to $3,932 at a 3 percent discount rate, with a primary estimate of $983.

In Table 9, we summarize the stream of total transfers caused by the proposed rule over 10 years. The annualized total transfers from industry to FDA would range from $31,562 to $67,849 at a 7 percent discount rate, with a primary estimate of $48,794, and from $30,839 to $69,425 at a 3 percent discount rate, with a primary estimate of $49,149.

---

[53] This value equals 2 devices × $120,890.

[54] The low estimate equals 0 devices × $115,450, the primary estimate equals 0.02 devices × $115,450, and the high estimate equals 0.04 devices × $115,450.

[55] The 2024 small business user fees are $18,134 for 180-day supplements, $3,869 for 30-day notices, $96,712 for panel-track supplements, and $8,462 for real-time supplements.

[56] The low estimate equals 2 devices × 0 reports per device × $7,391, the primary estimate equals 2 devices × 1.5 report per device × $7,391, and the high estimate equals 2 devices × 3 reports per device × $7,391.

Table 9. Stream of Total Transfers Caused by the Proposed Rule over 10 Years

Year	Low Estimate	Primary Estimate	High Estimate
0	$0	$0	$0
1	$0	$2,724	$5,911
2	$0	$3,043	$7,011
3	$250,242	$275,777	$302,697
4	$8,462	$34,316	$62,017
5	$8,462	$34,635	$63,117
6	$8,462	$34,954	$64,217
7	$8,462	$35,273	$65,318
8	$8,462	$35,592	$66,418
9	$8,462	$35,911	$67,518

J. International Effects

We do not expect any significant international effects from the proposed rule, if finalized. We assume that the proposed rule would affect all establishments involved in the manufacture of blood irradiators intended to prevent TA-GVHD and blood irradiators intended to prevent metastasis that are intended for commercial distribution in the United States, currently or in the future, no matter where the manufacturers are located. Our analysis estimates the impacts of the proposed rule on all such manufacturers.

K. Uncertainty and Sensitivity Analysis

Due to uncertainty regarding current and expected firm behavior and incomplete data, we must make certain assumptions, including our baseline, in order to estimate the potential effects of the proposed rule, if finalized. We have built sensitivity analyses into this benefit-cost analysis by using a range of inputs for many estimates. In this section, we address additional uncertainties and sensitivities regarding the number of currently marketed blood irradiators that would maintain the intended prevention of metastasis indication, PMA costs and user fees, and future blood irradiators intended to prevent metastasis.

1. Number of Currently Marketed Devices Maintaining Intended Prevention of Metastasis Indication

In section II.F.4, we assume that industry would maintain the intended prevention of metastasis indication for the two currently marketed devices with a second indication for the intended prevention of TA-GVHD. Due to uncertainty regarding this assumption, in this section we present costs under alternative assumptions that industry would maintain the intended prevention of metastasis indication for either one or zero devices.

If the intended prevention of metastasis indication is maintained for only one currently marketed device, we estimate that the annualized costs of the proposed rule over 10 years would range from $338,648 to $855,849 at a 7 percent discount rate, with a primary estimate of $574,177, and from $330,581 to $865,793 at a 3 percent discount rate, with a primary estimate of $573,836. If the intended prevention of metastasis indication is maintained for zero devices, the annualized costs would range from $555 to $197,333 at a 7 percent discount rate, with a primary estimate of $75,873, and from $490 to $205,313 at a 3 percent discount rate, with a primary

estimate of $78,550. We compare these annualized cost estimates under uncertainty to our main cost estimates in Table 10. We request comment on the likelihood of these alternative scenarios.

Table 10. Annualized Costs of the Proposed Rule over 10 Years Based on the Number of Currently Marketed Devices Maintaining Intended Prevention of Metastasis Indication

Number of Devices	Low Estimate (7%)	Primary Estimate (7%)	High Estimate (7%)	Low Estimate (3%)	Primary Estimate (3%)	High Estimate (3%)
0	$555	$75,873	$197,333	$490	$78,550	$205,313
1	$338,648	$574,177	$855,849	$330,581	$573,836	$865,793
2 (Main Analysis)	$676,741	$1,072,482	$1,514,365	$660,672	$1,069,122	$1,526,274

As we state in section II.D, a single firm manufactures the two currently marketed devices that are indicated for the intended prevention of metastasis. This firm could choose to bundle the devices in a single PMA submission. If the firm maintains the intended prevention of metastasis indication for both devices and bundles the devices in a single PMA submission, we assume that the annualized costs of the proposed rule over 10 years would range from $338,648 to $855,849 at a 7 percent discount rate, with a primary estimate of $574,177, and from $330,581 to $865,793 at a 3 percent discount rate, with a primary estimate of $573,836. These estimated costs are equivalent to the costs under the scenario in which the intended prevention of metastasis indication is maintained for only one currently marketed device.

2. Additional Costs for PMAs

In section II.F.4.a, we assume that the cost to industry to prepare and submit a PMA for a blood irradiator would range from $1.34 million to $2.33 million. It is likely that prior to preparing and submitting a PMA, manufacturers of blood irradiators intended to prevent metastasis would additionally incur costs associated with the nonclinical and clinical phases of device development that they did not incur for the original 510(k). These costs to industry could be significant. One recent study on the cost of therapeutic complex medical device development estimates average costs of $24.49 million for the nonclinical phase and $39.30 million for the clinical phase of device development, when converted from 2018 to 2024 dollars (Ref. [11]).

We request comment on the likelihood that manufacturers of current and future blood irradiators for the intended prevention of metastasis would incur nonclinical and clinical phase costs, and other costs, prior to the submission of a PMA, as well as the magnitude of any such costs and how they would be distributed over time.

In section II.E.2, we assume that industry and FDA would realize cost savings from a reduction in the quantity and time burden of informal inquiries related to blood irradiators intended to prevent TA-GVHD, which we would classify into class II under the proposed rule, if finalized. We assume the proposed special controls would clarify important information about submissions for these unclassified devices, for which a 510(k) is already required. However, the proposed rule would classify blood irradiators intended to prevent metastasis into class III. Classifying blood irradiators intended to prevent metastasis into class III could increase the quantity or time burden of informal and formal inquiries (Q-Submissions) manufacturers submit

to FDA for these devices, since the filing of a PMA would represent a new requirement. An increase in the quantity or time burden of informal and formal inquiries for class III blood irradiators could, in turn, increase associated costs to industry and FDA.

However, we would only attribute inquiry costs to the proposed rule, if finalized, if they exceed the costs manufacturers would normally incur in the absence of the rule. For example, a manufacturer developing a new blood irradiator intended to prevent metastasis would likely contact FDA during development regardless of its classification status. We would only consider inquiry costs above baseline levels to be attributable to the proposed rule. We request comment on the likelihood and magnitude of increases in the quantity and time burden of inquiries submitted to FDA for blood irradiators intended to prevent metastasis.

3. Eligibility for Small Business User Fees and User Fee Waivers

For our estimates of user fee transfers in section II.I, we assume that manufacturers of blood irradiators intended to prevent metastasis that are on the market or would enter the market in the future would pay small business user fees. For manufacturers of future devices, we base our assumption on the current market; most manufacturers of currently marketed blood irradiators have annual sales less than $100 million, the small business user fee eligibility threshold, based on proprietary sales data from Dun & Bradstreet.[57] If manufacturers of future blood irradiators intended to prevent metastasis are not eligible for small business user fees, and pay standard user fees, then the annualized total transfers from industry to FDA over 10 years would equal up to $90,649 at a 7 percent discount rate and up to $93,312 at a 3 percent discount rate.

Small businesses certified through FDA's SBD program with gross receipts or sales of $30 million or less are eligible for a user fee waiver on their first PMA. We observe that annual sales for manufacturers of currently marketed blood irradiators are mostly below $30 million. If any manufacturers of current or future blood irradiators intended to prevent metastasis would receive a PMA user fee waiver, we likely overestimate the corresponding user fee transfers in section II.I.

4. Uncertainties Associated with Future Blood Irradiators Intended to Prevent Metastasis

In our main analysis, we estimate costs to industry to prepare and submit PMAs for future blood irradiators intended to prevent metastasis (section II.F.4.a) and costs to FDA to review and respond to these PMAs (section II.F.4.d). We assume that the incremental cost to industry to prepare and submit a PMA for future devices would equal the cost to prepare and submit a PMA less the cost to prepare and submit a 510(k). Similarly, we assume that the incremental cost to FDA to review and respond to a PMA for future devices would equal the cost to review and respond to a PMA less the cost to review and respond to a 510(k). These incremental costs are uncertain due to several factors.

As we state in section II.D, there are two currently marketed MOT devices with an indication for the intended prevention of metastasis. Both devices have a second indication for the intended prevention of TA-GVHD. During the premarket notification stage, manufacturers

[57] All manufacturing firms with non-missing Dun & Bradstreet data on annual sales have annual sales less than $100 million.

chose to submit a single 510(k) covering both indications, rather than a separate 510(k) for each indication. If the proposed rule is finalized with the split classification, manufacturers of future blood irradiators with both indications would need to submit a 510(k) for the intended prevention of TA-GVHD indication and a PMA for the intended prevention of metastasis indication. In absence of the rule, we assume that all manufacturers of blood irradiators marketed for both indications would choose to submit a single 510(k), as they have done previously. Thus, the incremental cost to these manufacturers if the proposed rule is finalized would equal the cost to prepare and submit a 510(k) for the intended prevention of TA-GVHD indication plus the cost to prepare and submit a PMA for the intended prevention of metastasis indication less the cost to prepare and submit a 510(k) including both indications.

The magnitude of this incremental cost would depend on the difference between the cost to prepare and submit a 510(k) including one indication and the cost to prepare and submit a 510(k) including two indications (i.e., the extent of efficiency gains from including two indications in a single 510(k)). At one extreme, if the cost to prepare and submit a 510(k) including two indications is twice the cost to prepare and submit a 510(k) including one indication, our main estimates in section II.F.4.a likely reasonably approximate the incremental cost. At the other extreme, if the cost to prepare and submit a 510(k) including two indications equals the cost to prepare and submit a 510(k) including one indication, our main estimates likely underestimate the incremental cost. Similar reasoning applies to the incremental FDA cost to review and respond to a PMA for the intended prevention of metastasis.

The proposed split classification is also associated with uncertainty regarding the magnitude of user fee transfers from industry to FDA. In absence of the rule, manufacturers of dually indicated blood irradiators would incur one 510(k) fee, compared to a 510(k) fee for the intended prevention of TA-GVHD indication and a PMA fee for the intended prevention of metastasis indication with the rule. Thus, the incremental transfer associated with submitting a new dually indicated blood irradiator would equal the PMA fee (one 510(k) fee and one PMA fee with the rule less one 510(k) fee in absence of the rule), or approximately $120,890. In section II.I, we assume that this incremental transfer would equal $115,450. Thus, if manufacturers choose to include the intended prevention of TA-GVHD indication for future blood irradiators for the intended prevention of metastasis, we likely underestimate transfers in our main analysis. We do not consider the impact of the proposed split classification on future dually indicated blood irradiators in our main analysis due to uncertainties regarding (1) the percentage of future blood irradiators for the intended prevention of metastasis that would include a second indication for the intended prevention of TA-GVHD and (2) the difference in cost to industry (FDA) to prepare and submit (review and respond to) a 510(k) for a blood irradiator including two indications compared to one indication. In addition, the impact of this decision on the magnitude of costs and transfers is small.

If all future blood irradiators include both indications and the cost to industry (FDA) to prepare and submit (review and respond to) a 510(k) for a blood irradiator including two indications equals the cost for one indication, which would result in the highest costs and transfers, then:

1) Annual costs to industry to prepare and submit PMAs for future class III devices would equal up to $96,922 beginning in year 1, compared to our high estimate of $91,322 from our main analysis;

2) Annual costs to FDA to review and respond to PMAs for future class III devices would equal up to $36,029, compared to our high estimate of $35,172 from our main analysis; and
3) The annualized total transfers from industry to FDA would equal up to $68,045 at a 7 percent discount rate and up to $69,625 at a 3 percent discount rate, compared to our high estimates of $67,849 and $69,425, respectively, from our main analysis.

We request comment on our approach, the likelihood that future blood irradiators would include both indications, and the difference in cost to industry (FDA) to prepare and submit (review and respond to) a 510(k) for a blood irradiator including two indications compared to one indication.

L. Analysis of Regulatory Alternatives to the Proposed Rule

We identify five regulatory alternatives to the proposed rule. The first alternative is to continue regulating blood irradiators intended to prevent TA-GVHD and blood irradiators intended to prevent metastasis as unclassified devices. However, this alternative would not provide reasonable assurance of the safety and effectiveness of these devices and would not address the existing information asymmetries in the market for blood irradiators that we discuss in section II.B. There would be no costs and benefits associated with this alternative, as it would be the same as the baseline.

The second alternative is to regulate blood irradiators intended to prevent TA-GVHD as class I devices (general controls). Under this alternative, blood irradiators would not be subject to the special controls in the proposed rule, if finalized. In absence of these special controls, manufacturers may not know how to safely and effectively market blood irradiators. This may decrease the clarification value of the rule and therefore decrease cost savings. This alternative would also eliminate the need for labeling revisions and decrease the time burden of reading the rule for this blood irradiator device type. Therefore, this alternative would reduce both cost savings and costs and likely would result in lower net benefits than the proposed rule, if finalized. General controls alone are not sufficient for the potential risks of blood irradiators intended to prevent TA-GVHD and would not provide reasonable assurance of the safety and effectiveness of these devices; therefore, FDA did not choose this option.

The third alternative is to regulate blood irradiators intended to prevent TA-GVHD as class III devices (premarket approval). This alternative would provide the same cost savings by providing important clarifying information to industry. However, it would also increase costs to existing manufacturers of this blood irradiator device type by requiring them to meet a higher regulatory standard without increased assurance of safety and effectiveness. Furthermore, this alternative may cause some firms to leave the market or keep new firms from entering the market due to the greater costs. Overall, we expect this alternative to result in lower net benefits than the proposed rule, if finalized. Sufficient information exists to determine that special controls would provide reasonable assurance of the safety and effectiveness of blood irradiators intended to prevent TA-GVHD. Based on their risk profile, the 2012 Radiological Devices Advisory Panel recommended classifying these devices into class II (Ref. [1]).

The fourth alternative is to regulate blood irradiators intended to prevent metastasis as a class II device (special controls). This scenario would eliminate costs related to PMAs and

associated reporting requirements for class III devices. Our primary estimates of these annualized costs over 10 years are $1.071 million at a 7 percent discount rate and $1.068 million at a 3 percent discount rate.[58] However, manufacturers of currently cleared devices would still incur costs to read and understand the rule and comply with any special controls they do not already practice. The overall impact on net benefits is uncertain since insufficient information exists to determine that general and special controls are sufficient provide reasonable assurance of the safety and effectiveness of these devices. Based on their risk profile, the 2023 Radiological Devices Advisory Panel recommended classifying blood irradiators intended to prevent metastasis into class III (Ref. [2]).

A final alternative is to delay the implementation of the final rule by one year. We assume that this alternative would not impact the timing of costs to industry to read and understand the rule or the order requiring the filing of a PMA for blood irradiators intended to prevent metastasis, or cost savings to industry and FDA. However, manufacturers would have an additional year to comply with the rule. Manufacturers would incur costs to revise labeling in year 2 instead of in year 1. Under this scenario, we additionally assume that costs and user fee transfers related to PMAs for class III blood irradiators would begin in year 4 instead of year 3 for currently marketed devices and year 2 instead of year 1 for future devices. If we delay the implementation of the final rule by one year, the primary estimates of the annualized costs over 10 years would equal $960,083 at a 7 percent discount rate and $985,089 at a 3 percent discount rate (compared to $1.072 million and $1.069 million, respectively, without delayed implementation). However, this alternative also would delay any public health benefits resulting from the rule, which we cannot quantify.

III. Initial Small Entity Analysis

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because quantified effects of the proposed rule are estimated to be more than 1 percent of average annual revenues and unquantified effects are uncertain, we find that the proposed rule will have a significant economic impact on a substantial number of small entities. This analysis, as well as other sections in this document, serves as the Initial Regulatory Flexibility Analysis, as required under the Regulatory Flexibility Act.

A. Description and Number of Affected Small Entities

In this section, we describe the number of affected small entities. The FDA Establishment Registration & Device Listing database indicates that there are three manufacturing establishments with listings for currently marketed MOT devices. A unique firm owns and operates each of these manufacturers. Of these three firms, two operate domestically (67 percent). The Small Business Administration (SBA) defines entities classified in the Irradiation Apparatus Manufacturing industry (NAICS code 334517) to be small if they employ fewer than 1,200 workers (Ref. [13]). Using information from Dun & Bradstreet, we estimate that both domestic firms are small. These small domestic firms manufacture five MOT devices in total. Of

[58] Our primary estimates of the total annualized costs of the proposed rule, if finalized, are $1,072,482 at a 7 percent discount rate and $1,069,122 at a 3 percent discount rate. Nearly 100 percent of these costs ($1,071,019 annualized at 7 percent and $1,067,829 annualized at 3 percent) are costs related to PMAs and associated reporting requirements for class III devices.

these devices, three would be classified into class II as a result of the proposed rule, if finalized. The other two devices have a dual indication and thus would be classified into class II as a blood irradiator intended to prevent TA-GVHD and class III as a blood irradiator intended to prevent metastasis as a result of the proposed rule, if finalized.

Using data from the U.S. Census Bureau's 2022 Statistics of U.S. Businesses (SUSB), we estimate that 98 firms in the Irradiation Apparatus Manufacturing industry with employees have fewer than 1,200 employees.[59] These data also show that there are 113 firms in this industry in total. Using this information, we estimate that approximately 87 percent of Irradiation Apparatus Manufacturing firms are small. We present these estimates in Table 11.

Table 11. Domestic Firms in Irradiation Apparatus Manufacturing Industry

Employment Size Category	Number of Firms	Percentage of Firms
0 to 4	25	22%
5 to 9	19	17%
10 to 19	17	15%
20 to 99	25	22%
100 to 499	11	10%
500 to 1,199[a]	1	1%
1,200+[a]	15	13%
Total Small	98	87%
Total	113	100%

[b] Data for these employment size categories are not available from the SUSB for this industry. We estimate the number of firms for these size categories based on available data for other size categories. We assume a uniform distribution of firms by size.

B. Description of the Potential Impacts of the Rule on Small Entities

In this section, we describe the potential impacts of the rule on small entities. We assume that manufacturers of currently marketed devices would each have an upfront cost in year 0 to read and understand the rule and to revise labeling. Manufacturers of devices that would be classified into class III additionally would experience a one-time cost to read and understand the order requiring the filing of a premarket approval application (PMA) in year 0; one-time costs to prepare and submit PMAs and undergo inspections in year 3; recurring costs to prepare and submit annual and supplemental reports beginning in year 3; and associated user fee transfers to FDA.

In our analysis, we also estimate time cost savings to industry related to informal inquiries and 510(k) submissions for blood irradiators intended to prevent TA-GVHD, as well as costs and user fees associated with PMAs for future class III devices that may be covered by this rule. For analytical simplicity, we allocate all of these economic impacts to the manufacturers of currently marketed devices, while acknowledging that new market entrants could also experience these effects. We assume that domestic firms would realize 67 percent of the total impacts, which reflects the observed percentage of firms with currently marketed devices that operate domestically.

[59] We use SUSB data from 2022 because it is the most recent year for which receipts (revenue) data are available from the Statistics of U.S. Businesses.

Given these assumptions, we estimate that the total annualized net value of these compliance costs to small domestic manufacturers would equal up to $1.05 million.[60] Based on proprietary sales data from Dun & Bradstreet, the total revenue for the 2 domestic firms with currently marketed devices was $62.73 million as of September 2024. Thus, our high estimate of annualized net compliance costs would correspond to 1.67 percent of total revenue for small domestic manufacturers of currently marketed devices.

In addition to these quantified costs, nonclinical and clinical phase costs to manufacturers of blood irradiators intended to prevent metastasis prior to the submission of a PMA, which we are unable to quantify due to uncertainty, could be significant. Therefore, we find that the proposed rule will have a significant economic impact on a substantial number of small entities. We request comment on our determination.

C. Alternatives to Minimize the Burden on Small Entities

In section II.L, we discuss five alternative policies. All domestic firms with currently marketed MOT devices are small and 87 percent of firms in the United States Irradiation Apparatus Manufacturing industry are small, as defined by the SBA. Therefore, those alternatives that minimize the burden on the industry as a whole would also minimize the burden on the subset of small entities. Specifically, continuing to regulate blood irradiators as unclassified devices; regulating blood irradiators intended to prevent TA-GVHD as class I devices (general controls); regulating blood irradiators intended to prevent metastasis as class II devices (special controls); or delaying the implementation of the final rule by one year would reduce the burden on small entities.

Based on available information and following recommendations from the Radiological Devices Advisory Panels convened in 2012 and 2023, FDA is proposing to classify blood irradiators intended to prevent TA-GVHD into class II (special controls) and blood irradiators intended to prevent metastasis into class III (premarket approval) (Refs. [1], [2]).

If we delay the implementation of the final rule by one year, we estimate that the total annualized net value of compliance costs to small entities would equal up to $946,592, corresponding to 1.51 percent of total revenue for these manufacturers.[61] We request comment on additional alternatives to the proposed rule that may reduce the burden on small entities.

IV. References

[1] U.S. Food and Drug Administration, "Center for Devices and Radiological Health Medical Devices Advisory Committee: Radiological Devices Panel," 12 April 2012. [Online]. Available:

[60] This ($1,050,210) equals the high estimate of total annualized net compliance costs to small domestic manufacturers of currently marketed blood irradiators discounted at 7 percent.

[61] Under this alternative, $946,592 equals the high estimate of total annualized net compliance costs to small domestic manufacturers of currently marketed blood irradiators discounted at 7 percent.

https://web.archive.org/web/20170509064443/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/RadiologicalDevicesPanel/UCM303363.pdf. [Accessed 25 April 2024].

[2] U.S. Food and Drug Administration, "Center for Devices and Radiological Health: Radiological Devices Panel of the Medical Devices Advisory Committee," 3 November 2023. [Online]. Available: https://www.fda.gov/media/174427/download. [Accessed 25 April 2024].

[3] D. M. Dwyre and P. V. Holland, "Transfusion-associated graft-versus-host disease," *Vox Sanguinis,* vol. 95, pp. 85-93, 2008.

[4] U.S. Food and Drug Administration, "Recommendations Regarding License Amendments and Procedures for Gamma Irradiation of Blood Products," 22 July 1993. [Online]. Available: https://www.fda.gov/media/70934/download. [Accessed 5 April 2023].

[5] U.S. Department of Labor, "Occupational Employment and Wage Statistics, OEWS Data, May 2024 National Industry-Specific Occupational Employment and Wage Estimates, NAICS 334500 - Navigational, Measuring, Electromedical, and Control Instruments Manufacturing," Bureau of Labor Statistics, 2 April 2025. [Online]. Available: https://data.bls.gov/oes/#/industry/334500. [Accessed 9 April 2025].

[6] Eastern Research Group, Inc., "Economic Analysis of CDRH Submission Requirements," 2012.

[7] D. R. Geiger, "FY 2003 and FY 2004 Unit Costs for the Process of Medical Device Review," 2005.

[8] U.S. Department of Health and Human Services, "Guidelines for Regulatory Impact Analysis," 2016. [Online]. Available: https://aspe.hhs.gov/sites/default/files/migrated_legacy_files//171981/HHS_RIAGuidance.pdf. [Accessed 19 July 2023].

[9] RTI International, "2014 FDA Labeling Cost Model," 2015.

[10] U.S. Food and Drug Administration, "Devices: General Hospital and Personal Use Devices; Reclassification of Medical Device Data System (Proposed Rule, 73 FR 7498)," 8 February 2008. [Online]. Available: https://www.govinfo.gov/content/pkg/FR-2008-02-08/pdf/E8-2325.pdf. [Accessed 25 April 2024].

[11] A. Sertkaya, R. DeVries, A. Jessup and T. Beleche, "Estimated Cost of Developing a Therapeutic Complex Medical Device in the US," *JAMA Network Open,* vol. 5, no. 9, pp. 1-10, 2022.

[12] U.S. Food and Drug Administration, "Medical Device User Fee Rates for Fiscal Year 2024 (Notice, 88 FR 48870)," 28 July 2023. [Online]. Available:

https://www.govinfo.gov/content/pkg/FR-2023-07-28/pdf/2023-15919.pdf. [Accessed 9 April 2025].

[13] U.S. Small Business Administration, "Table of Small Business Size Standards Matched to North American Industry Classification System Code," 17 March 2023. [Online]. Available: https://www.sba.gov/sites/sbagov/files/2023-03/Table%20of%20Size%20Standards_Effective%20March%2017%2C%202023%20%281%29%20%281%29_0.pdf. [Accessed 9 August 2023].

[14] U.S. Food and Drug Administration, "Medical Device Classification Product Codes (Guidance for Industry and Food and Drug Administration Staff)," 11 April 2013. [Online]. Available: https://www.fda.gov/media/82781/download. [Accessed 3 June 2024].

[15] U.S. Food and Drug Administration, "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program (Guidance for Industry and Food and Drug Administration Staff)," 2 June 2023. [Online]. Available: https://www.fda.gov/media/114034/download. [Accessed 27 July 2023].