US Food and Drug Administration Regulation of Medical Devices and Radiation Oncology: Can Reform Improve Safety?

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Abstract

Although radiation therapy is highly safe and effective in treating cancer, recent reports of dangerous radiation-related errors have focused a national spotlight on the field of radiation oncology and, more specifically, on the rapidly evolving and complex nature of radiation devices and how they are regulated. The purpose of this review is to explore the issues involved in medical device regulation in radiation oncology. We start with a general review of federal medical device regulation, including explanations of the legal and regulatory framework, and then discuss

issues specific to radiation oncology with real-world examples. We also provide our thoughts on potential solutions and reforms to the current system, including better reporting of radiation-related errors in a centralized database, well-defined criteria for establishing substantial equivalence of a new device, and standard postmarket surveillance of radiation devices. Modern radiation therapy is a powerful tool that can help cure many patients' cancers and alleviate others' suffering with limited adverse effects. We must ensure that this promise is never compromised by avoidable mistakes.

Introduction

Radiation therapy is highly safe and effective in treating cancer. However, recent media reports^{1,2} on dangerous radiation overdoses and misadministrations have focused a national spotlight on the field of radiation oncology. More specifically, there has been a growing interest in the rapidly evolving and complex nature of radiation devices and how they are regulated.^{3,4}

Radiation treatment units, simulation, and treatment planning systems, along with other medical equipment, are regulated by the Center for Devices and Radiologic Health (CDRH). The CDRH is one of the six arms of the US Food and Drug Administration (FDA), established under the authority of the Medical Device Amendments to the Federal Food and Drugs Act, passed by Congress in 1976.⁵ Three medical device classes are defined based on the level of control required to ensure device safety and effectiveness, the level of risk the device poses to the patient, and the process required to obtain FDA clearance for marketing.⁶ Class I devices are the least controlled, including products like dental floss and tongue depressors.⁷ Class III devices support or sustain human life or present a potential, unreasonable risk of illness or injury if they malfunction; examples include artificial heart valves and defibrillators. This class generally requires premarket approval, a process of scientific review to ensure safety and effectiveness, much like the review process for new drugs. Class II devices include everything in between, including all radiation therapy systems.

Class I and II devices do not require premarket approval; instead, they are cleared through a process of premarket notification or 510(k).⁸ Manufacturers must demonstrate to the CDRH that the device is at least as safe and effective, or substantially equivalent, to a legally marketed device or predicate. A new device is considered substantially equivalent to a predicate if the FDA determines that it has either the same intended use and technologic characteristics or the same intended use but different technologic characteristics that do not raise questions

of safety or effectiveness. Decisions are handed down by the CDRH within 90 days after submission.

The major advantage of the premarket notification process is that it shortens the time and expense required to introduce new medical devices and changes in those already approved. Hence, this process encourages innovation and the continuous improvement of devices. However, the decision of the CDRH is based solely on data submitted by the manufacturer. Also, to speed up the process and reserve the scientific review resources of the FDA for higher-risk devices, the FDA Modernization Act of 1997 allows the CDRH to outsource many 510(k) reviews of class I and II devices to the private sector.⁹ These third parties often do not have appropriate expertise and may conduct inadequate analyses.¹⁰ The combination of a short review process and heavy workload can lead to mistakes. The FDA recently revoked 510(k) clearance of the Menaflex knee implant after internal investigations revealed that it is intended for a different purpose and is technologically dissimilar from predicate devices.¹¹ Finally, new 510(k) review is not required for modifications of already-approved devices unless the changes could "significantly affect its safety or effectiveness."¹² However, it is the manufacturer who decides whether this is the case.

An example of how the current 510(k) process may not adequately protect patients undergoing radiation therapy is the saga of the Trilogy Radiation Therapy System (Varian Medical Systems, Palo Alto, CA). Multiple hardware modifications and the addition of increasingly complex software systems that integrate treatment planning, electronic medical records, and treatment delivery have transformed the originally approved linear accelerator into a highly complex, multifaceted device. These modern devices are capable of performing radiation treatments not dreamed of in 1977, such as intensity-modulated radiation therapy, image-guided radiation therapy using onboard digital x-ray imaging, and stereotactic radiosurgery. Although each new model in this chain was deemed to be substantially equivalent to a predicate (Fig 1),¹³ over time these

Figure 1. Timeline from 1976 to the present, showing the genesis of the current Trilogy radiation therapy system through iterative 510(k) product clearances. After the Medical Device Amendment was passed in Congress in 1976, the first Clinac linear accelerator machine received 510(k) clearance in 1977, deemed to be substantially equivalent (SE) to predicate device in use before 1976. Over the next several decades, numerous iterations of US Food and Drug Administration (FDA) 510(k) clearances were obtained for successive models, as shown. Trilogy debuted in 2003 after it was determined to be SE to the prior Clinac model. Subsequent modifications to Trilogy include the most recent Trilogy system with full-function stereotactic radiosurgery (SRS) and RapidArc technologies, both of which were recently recalled. Three Varian systems that perform SRS (C-Series Clinac, Trilogy, Novalis TX) were recalled on January 18, 2011, because of a warning that the “product may deliver radiation treatment to areas larger than intended, to healthy tissue.”¹³ All data obtained through public FDA online database of 510(k) clearances and recalls.¹³ Trilogy, Clinac, Novalis, TrueBeam, and RapidArc are products of Varian Medical Systems (Palo Alto, CA). 3D-CRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; MV, megavolt; SRT, stereotactic radiotherapy.

new machines became significantly different than the original (referred to as predicate creep).^{14,15} Some of these changes, such as the use of multileaf collimators to shape fields, thus replacing handmade blocks, have reduced error rates.¹⁶ However, the evolution of a simple machine into a complex one introduces new potential sources of errors,¹⁷⁻¹⁹ particularly when it contains multiple subsystems that may interact in unexpected ways. Varian Medical Systems recalled three different linear accelerator systems in January 2011²⁰ after major treatment overdoses occurred because of treatment setup errors on linear accelerators retrofitted with stereotactic radiosurgery capability.²¹

Reporting of radiation errors is crucial in ensuring that other facilities and providers employ safeguards to avoid similar mistakes. Hospitals are required to report suspected device-related deaths to both the FDA and the manufacturer, but serious injuries need only be reported to the manufacturer.²² Health care professionals and patients can voluntarily report adverse events through the MedWatch system, an FDA reporting system that collects safety information on medical products and disseminates the information through safety alerts.²³ However, reporting is not mandatory, and the MedWatch system collects reports on everything from defective alcohol swabs to cosmetics to infant formula. No single agency collects and record errors in radiation administration, let alone notifies users in a timely and efficient manner. Furthermore, fear of litigation may no longer be an effective constraint on device manufacturers. The landmark eight-to-one US Supreme Court ruling in *Riegel v.*

Medtronic, Inc., in 2008 declared that a device maker may not be sued in state courts over the safety or effectiveness of a medical device to which the FDA has given detailed class III pre-market approval.²⁴ Thus, even an inadequate FDA review provides immunity for the device manufacturer on class III devices. (This federal preemption does not apply to class II devices, nor is this true for medications. In *Wyeth v. Levine*, the Supreme Court ruled in 2009 that FDA approval of a medication does not shield the manufacturer from liability under state law.²⁵)

The existing 510(k) system must be reformed to ensure patient safety but still encourage device innovation in radiation oncology. The CDRH recently released results of an internal evaluation, which proposed increasing transparency and consistency and requiring submission of more complete safety and effectiveness information in determining substantial equivalence.²⁶ The Institute of Medicine also reviewed the 510(k) clearance process and recently released a report calling for the design of a new medical device regulatory framework for class II devices.²⁷ We believe that considerable reforms to the current system are needed. Currently, any device with 510(k) clearance may be used as a predicate, regardless of whether it is still relevant to current practice. Stricter criteria should be applied on the degree of change acceptable to consider an older approved device as a predicate. Third-party reviewers should be appropriately trained and accredited and must be equipped with device-specific guidelines for reviewing 510(k) applications. Labeling

of devices, including precautions, warnings, and potential contraindications, should be thoroughly reviewed by the FDA before marketing by device manufacturers. Certainly such reforms may slow the pace of modifications to existing devices and the introduction of new technologies. However, more thorough vetting would help reduce the number of patients potentially harmed by problems not detected by the current system. This may also lead to fewer recalls of devices.

Even with better premarket scrutiny, the increasing complexity of medical devices makes it impossible to anticipate all potential problems. Therefore, the FDA should require post-market surveillance, or real-world clinical studies of potential device safety issues, after 510(k) clearance is granted to detect problems early on. The postmarket surveillance process should be organized by device manufacturers, working closely with clinics and hospitals in an ongoing process of review and risk assessment throughout the life of the device. Adverse event reports, recalls, and inspectional findings should be recorded in a mandatory centralized database of radiation-related errors. This system should disseminate alerts to users immediately when errors occur, whether resulting from faulty devices, software malfunction, personnel error, or systems mistakes. Access to such databases must be open to all users and regulatory authorities.

Finally, it is also the responsibility of radiation oncologists and users of these technologies both individually and collectively to use channels like MedWatch and to work with the FDA to help protect patients. The American Society for Radiation Oncology, the largest radiation oncology society in the world, has committed to improve patient safety by promoting the use of national standards and consensus treatment guidelines, supporting stronger federal rules for error reporting, more training of radiation health care providers, enhanced accreditation of radiation facilities, and better use of health information technology.²⁸ Modern radiation therapy is a powerful tool that can help cure many patients' cancers and alleviate others' suf-

fering with limited adverse effects. We must ensure that this promise is never compromised by avoidable mistakes.

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