Radiological Medical Device Innovation: Approvals via the Premarket Approval Pathway From 2000 to 2015

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Abstract

Purpose: The aim of this study was to critically assess the clinical evidence leading to radiologic medical device approvals via the premarket approval pathway from 2000 to 2015.

Methods: This study used the publically available FDA premarket database for radiologic device approvals over the past 15 years (September 1, 2000, to August 31, 2015). Approval characteristics were collected for each device, and statistical analysis was performed on the data for each pivotal trial. Additionally, methodological quality of the pivotal trial was determined using the Quality Assessment of Diagnostic Accuracy Studies tool.

Results: Twenty-three class III radiologic device approvals were identified, with breast imaging accounting for 16 (70%) and computer-aided detection software accounting for 9 (39%) approvals. The median premarket approval time was 475 days (range, 180-1,116). Twenty-one devices were approved on the basis of multireader, multicenter studies, one on the basis of a randomized controlled trial, and one on the basis of a preclinical technical equivalence trial. The median number of patients per pivotal trial was 201 (range, 25-3,946). Twenty-six of the 34 pivotal trials (76%) had at least one methodologic bias. Breast imaging devices had a greater number of patients per pivotal trial ($P = .009$) and more prospective studies. With regard to all modalities, increased time to device approval correlated with weaker trial quality ($r = 0.600$, $P < .001$).

Conclusions: Radiologic devices are largely approved by multireader, multicenter studies, the recommended standard for assessing diagnostic technologies. Given that radiologic devices play a key role in modern medicine, further efforts should be made to increase transparency of clinical data leading to approval.

Key Words: Medical device innovation, FDA, patient safety, health policy, medical device regulation, innovation, 21st Century Cures Act, National Evaluation System for Health Technology

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INTRODUCTION

Medical devices remain a central component of the practice of radiology: the global radiologic device market is expected to reach $35.4 billion by 2019 [1]. Prior rankings of the impact of medical innovations have identified diagnostic imaging systems (MRI, CT, mammography) as three of the top five most transformative medical innovations in modern medicine [2]. Recent legislation in the form of the 21st Century Cures Act proposes to increase research funding for the National Institutes of Health by $8.75 billion over the course of 3 years; however, the bill also contains provisions that affect medical device regulation. Such provisions allow device approval on the basis of evidence from case reports rather than promoting clinical trials. Additionally, the act allows manufacturers to make changes to already existing medical devices under the regulation of third-party organizations rather than submitting applications to the FDA [3]. As of April

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2016, the Senate has passed 19 companion bills to the 21st Century Cures Act [4]. To assess the implications of the proposed legislation for radiology, it is essential to understand the current state of device regulation. Previous work has shown that although major radiologic device recalls are rare, the impact of a single recall can reverberate across thousands of imaging systems [5]. Currently, limited literature is available on the strength of clinical studies, leading to high-risk device approval in the field of radiology.

The FDA approves devices on the basis of three classes of risk. Class I devices are considered the lowest risk and generally must follow only general controls before marketing. Examples include bandages and tongue depressors. Class II devices, which are moderate risk, include the majority of radiologic devices as well as a broad range of other technologies, such as infusion pumps and mobile phone–based PACS applications. Specific examples of class II radiologic devices include ultrasound, fluoroscopic x-ray, MRI, CT, and nuclear medicine scanners and a portion of breast imaging devices. Clearance of class II devices occurs via the 510(k) pathway, which typically does not require manufacturers to submit additional clinical evidence when substantial equivalence to an existing medical device can be established [6]. The highest risk devices are designated as class III. These technologies include cardiac implants, devices intended to sustain or support life, and novel devices without predicates. Examples include implantable cardiac defibrillators and cochlear implants [7]. Before approval, class III devices typically undergo premarket approval (PMA). The PMA pathway represents the most rigorous regulatory process for medical devices in the United States and requires the submission of independent safety and effectiveness data [8].

The goal of this study is to provide an overview of radiologic device innovation along the PMA pathway from 2000 to 2015 and a critical appraisal of the clinical evidence leading to each approval. It is important for radiologists and policymakers to understand recent high-risk device innovation within the field to formulate potential improvements that will ensure patient safety and enable future device innovation.

METHODS

The FDA PMA public online database was mined for radiologic device committee approvals along the PMA pathway across a recent 15-year time span (September 1, 2000, to August 31, 2015). Radiologic device approvals were defined by using the parameters advisory committee = "radiology" and supplement type = "originals only" [9]. Our inclusion criteria included any device under the direct purview of the Radiology Devices Advisory Committee, which included both diagnostic and therapeutic modalities. Furthermore, all other advisory committees (eg, general surgery, ophthalmic, cardiovascular, gastroenterology, urology, orthopedic, pathology, and obstetrics and gynecology) were surveyed for additional imaging or software devices. This search did not yield additional devices that met our inclusion criteria. A time interval spanning the past 15 years was used to adequately assess the recent developmental life cycle of approved devices. The FDA provides a summary of safety and effectiveness data (SSED) for approved devices, which details the preclinical, pivotal, and supplemental trials used as evidence leading to approval. One device, the Syngo Lung Computer Aided Detection Software, did not have a publically available SSED, and analysis was instead completed using published clinical trial data [10]. Pivotal studies are defined as conclusive trials that provide evidence to support the safety and effectiveness of a medical device for its intended use. Evidence from multiple pivotal studies may be used to determine the overall safety and effectiveness of medical devices for the purposes of FDA approval.

For each approval, the pivotal study type was determined and the following data were extracted: duration of study, patient accrual, number of patients studied, number of readers, and primary end points. Patients were accrued prospectively or retrospectively. In prospective accrual, patient recruitment depends on signs and symptoms, whereas in retrospective accrual, patient pathology is already known. Retrospective accrual generally allows a decreased sample size [11]. For each device, the following data were extracted: median time to approval, device modality, manufacturer, indication, number of supplements, and postmarket requirements. Supplements are required applications submitted to the FDA for manufacturer device or labeling alterations not significant enough to warrant another PMA. The median time to approval was determined by the number of days between the submission date and the FDA approval date.

Statistical analysis was performed on data for each trial (device modality, duration of study, number of patients enrolled per trial, median time to approval, number of supplements). Two-tailed, two-sample t tests were performed to compare mean values for mammographic