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FDA Premarket Approval Supplements and Medical Device Safety and Effectiveness

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Abstract

Background: The Food and Drug Administration (FDA) evaluates high-risk medical devices, such as cardiac implantable electronic devices (CIEDs), via the pre-market approval (PMA) process, during which manufacturers submit data demonstrating safety and effectiveness. Subsequent changes to approved high-risk devices are implemented via “supplements,” which may not require additional clinical testing.

Objective: To characterize the prevalence and characteristics of changes to CIEDs made through the PMA supplement process.

Methods: Using the FDA’s PMA database, we reviewed all CIEDs approved as original PMAs or supplements from 1979-2012. For each supplement, we collected the date approved, type of supplement (panel-track, 180-day, real-time, special, and 30-day notice), and the nature of the changes. We calculated the number of supplements approved per PMA and analyzed trends relating to different supplement regulatory categories over time. For supplements approved via the 180-day regulatory pathway, which often involve significant design changes, from 2010-2012, we identified how often additional clinical data were collected.

Results: From 1979-2012, the FDA approved 77 original and 5,829 supplement PMA applications for CIEDs, with a median of 50 supplements per original (interquartile range [IQR]: 23-87). Excluding manufacturing changes that do not alter device design, the number of supplements approved each year was stable around a mean of 2.6 supplements (standard deviation 0.9) per PMA per year. PMAs remained active via successive supplements over a median period of 15 years (IQR: 8-20), and 79% of the 77 original PMAs approved during our study period were the subject of at least one supplement in 2012. Thirty-seven percent of

approved supplements involved a change to the device's design. Among 180-day supplements approved from 2010-2012, 23% (15 out of 64) included new clinical data to support safety and effectiveness.

Conclusions: Many CIED models currently used by clinicians were approved via the PMA supplement process, not as original PMAs. Most new device models are deemed safe and effective without requiring new clinical data, reinforcing the importance of rigorous post-approval surveillance of these devices.

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Glossary

CIED	Cardiac implantable electronic device
CRT	Cardiac resynchronization therapy
FDA	Food and Drug Administration
FDAMA	Food and Drug Administration Modernization Act
ICD	Implantable cardioverter defibrillator
PMA	Premarket approval
SSED	Summary of Safety and Effectiveness Data

Background

Introduction

In the US, the Food and Drug Administration (FDA) reviews high-risk medical devices – those that support human life, prevent illness, or present an unreasonable risk¹ – via the premarket approval (PMA) pathway, through which manufacturers collect preclinical and clinical data as necessary to provide “reasonable assurance” of the device’s safety and effectiveness.² The PMA process is generally regarded as the most rigorous medical device regulatory review process in the world,^{3–5} though recent studies examining the process have raised concerns about the quality of data that FDA experts consider when they review PMA applications.^{6–8}

Medical device regulation earned scrutiny in recent years following several device recalls. Zuckerman et al. found that from 2005-2009, the FDA issued 21 high-risk safety recalls for PMA-approved devices, over half of which were cardiovascular devices.⁹ Among these recalls were the Medtronic Sprint Fidelis and St. Jude Medical Riata implantable cardioverter defibrillator (ICD) leads.^{10,11} However, these leads were not original PMA applications and were not tested clinically in human trials prior to approval. Rather, these ICD leads were design changes to prior-marketed devices and were “supplements” to PMA applications originally submitted almost a decade prior.¹²

PMA supplements are commonly used to approve changes to existing high-risk devices. A Government Accountability Office report found that from 2003-2007, the FDA authorized 170 PMA applications and 664 supplements for high-risk devices.¹³ Supplements allow patients to benefit from incremental innovation in device technology by providing efficient and

inexpensive FDA review pathways for smaller device changes. Supplements may include major or minor design changes as well as routine changes in labeling, materials, or packaging.¹⁴ By statute, the FDA must seek only the “least burdensome” supporting data necessary for review.¹⁵

Given the frequent use of PMA supplements for high-risk devices, we performed an in-depth review of the PMA supplement process. Specifically, we examined how the PMA supplements related to cardiac implantable electronic devices (CIEDs), including pacemakers, ICDs, and cardiac resynchronization therapy (CRT) devices. CIEDs provide a useful case study, since they have been the subject of substantial evolution over the past 30 years.¹⁶ We reviewed original and supplement PMAs for CIEDs approved 1979-2012 to identify the number of PMA supplements emerging from each original PMA, characterize the nature of the changes in each supplement, and understand the data supporting these changes.

History of Medical Device Regulation

The FDA first received statutory authority to regulate medical devices as part of the 1976 Medical Device Amendments to the federal Food, Drug, and Cosmetic Act.² Until that point, medical devices had no official premarket requirements and were subject to state-level oversight via consumer-protection statutes applicable to all commercial products. However, a public health crisis arose when the Dalkon Shield, an intrauterine device originally marketed in 1970 and used by millions of women in the US, was found to be associated with increased risk of pelvic inflammatory disease, sepsis, miscarriage, and death.¹⁷ As with all medical devices at the time, there was no premarket assessment of the Dalkon Shield’s safety or effectiveness.¹⁸

After the Dalkon Shield was ultimately withdrawn from the market in 1974, the episode inspired Congress to centralize medical device regulatory power in the FDA.^{17,18}

The Medical Device Amendments enumerated three different regulatory classes of devices based on their risk to patients. Low-risk, or Class I, devices (*e.g.*, bandages, stethoscopes) are generally exempt from FDA review, requiring only registration with the agency and adherence to basic FDA standards about good manufacturing practices. Medium-risk, or Class II, devices (*e.g.*, blood pressure cuffs, peripheral vascular catheters) most often gain clearance for widespread use based on a finding “substantial equivalence” to an existing marketed device.¹⁹ This process is commonly referred to as the 510(k) pathway after the applicable section of the Federal Code. A finding of “substantial equivalence” means that the device shares pertinent characteristics with another marketed device that has been safely used by patients and, therefore, does not require additional clinical testing to ensure its safety and effectiveness. The substantial equivalence standard for Class II devices has been criticized in recent years for failing to adequately assure device safety and effectiveness.^{17,20} The recent recall of metal-on-metal hip implants has served as an example of the danger in allowing new devices to gain 510(k) clearance based on similarity to previous versions, not based on evidence of safety and effectiveness.²⁰

High-risk, or Class III, devices — those which support or sustain human life, prevent impairment of human health, or present a potential, unreasonable risk of illness or injury — are generally reviewed via the premarket approval (PMA) process.¹ Historically, the FDA has permitted select categories of high-risk devices to gain clearance through the 510(k) pathway rather than requiring PMA approval, a practice that has been criticized in recent years.^{9,20} The

FDA has been working to update device classifications to prevent high-risk devices from gaining approval via the substantial equivalence standard, so fewer such devices should be on the US market in the future.²¹

The Medical Device Amendments established the standard of evidence for PMA review, authorizing the FDA to require “reasonable assurance of safety and effectiveness” for new high-risk devices.² Similar to the FDA process for approving new drugs, the PMA process requires manufacturers to perform pre-clinical and clinical studies before a device can be marketed (Table 1). The FDA was granted permission to request from a device manufacturer any data it considered relevant to providing reasonable assurance of safety and effectiveness.

In the subsequent decades, Congress continued to amend the Food, Drug, and Cosmetic Act to address concerns that over-burdensome regulatory processes were inefficient and preventing new medical devices from reaching the market in a timely manner. For example, while all new high-risk devices were originally required to be reviewed by an independent panels of experts, Congress amended the law in 1990 to allow the FDA to internally review PMA applications in cases in which such panels were not deemed to be necessary.²²

In the 1997 FDA Modernization Act (FDAMA), Congress required the FDA to work with manufacturers to determine “the least burdensome appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in approval.”²³ The FDA released a guidance document in 2002 that described how it intended to implement this “least burdensome” approach while still assuring device safety and effectiveness prior to marketing.¹⁵ The FDA permitted the use of non-clinical data (bench or animal testing) in place of clinical data in limited circumstances, and, when clinical data was needed, urged manufacturers to consider

study designs other than randomized controlled trials and the use of surrogate endpoints to shorten study duration.¹⁵ The FDA also indicated that manufacturers could offer to formally collect safety and effectiveness data in the postmarket period to speed premarket review.¹⁵ Finally, the FDA recommended using “information that is available from earlier versions of the same device or from marketing experience with similar devices” as part of a PMA review.¹⁵

Changes to PMA devices: supplement pathways

After a high-risk device is approved via PMA, manufacturers may wish to make modifications to integral components of the design, such as improving battery life, upgrading software, or revising connectors to ensure compatibility with other devices. Unlike drugs, where any change to the active ingredient would create a new product requiring its own original FDA authorization, incremental alterations to device design are an accepted part of the product life cycle. The 1976 Medical Device Amendments provided no formal pathway for a device manufacturer to submit changes to a PMA-approved device. However, when the FDA published its first set of regulations related to PMA in 1986, it included the ability to supplement the design of existing devices to account for small technological innovations.²⁴ Congress then codified the PMA supplement process in FDAMA in 1997.²³

Supplements are permitted through five distinct pathways, with different data requirements for each type (Table 2).¹⁴ Manufacturers choose which pathway to use for a given device change, though the FDA maintains the right to override this decision if necessary. The most significant changes (so-called “panel-track” supplements) are reviewed by an independent panel of experts and, like original PMA applications, must be supported by new clinical data.

Changes requiring a panel-track supplement include new indications for an existing device, such as using a prosthetic heart valve approved for use in the aortic position to also be used in the mitral position.¹⁴ Major changes to a device's design are approved via a 180-day review pathway, in which preclinical testing is often sufficient to assure safety and effectiveness with "limited confirmatory clinical data" needed in some cases.¹⁴ Such major changes may include altered design (*e.g.*, a thinner, more flexible ICD lead) or new features (*e.g.*, wireless programming capabilities).¹⁴ Minor design changes, such as a circuitry modification to correct battery problems, may qualify for "real-time" review, in which the FDA meets with a manufacturer and issues a same-day decision.¹⁴ To qualify for real-time review, a change must not require any new clinical data to assure safety and effectiveness.²⁵

Changes to a device's manufacturing that do not alter the device itself (*e.g.*, converting a manual manufacturing process to an automated one) require notice to the FDA.¹⁴ The manufacturer may enact the manufacturing change 30 days after the FDA receives the notice, unless the FDA deems the notice inadequate and requests a more formal 135-day review. Finally, changes to a device's labeling to address a newly discovered safety concern (*e.g.*, adding a contraindication) can be approved via a "special supplement" process, during which the manufacturer may enact the change prior to formal FDA approval.¹⁴

Manufacturers may submit a single change that affects multiple devices approved under different PMAs (*e.g.*, a connector change that affects ICD, CRT, and pacemaker models). The change is bundled under a single review at FDA.³¹ The PMA database contains a unique entry for each affected device, regardless of whether the change was bundled with and reviewed at the same time as other applications.

User Fees

In 2002, Congress acted to increase FDA's resources by requiring manufacturers to pay user fees for each device approval.²⁶ The user fee provision, which expires every 5 years, was renewed in 2007 and again in 2012.²⁷ Currently, the FDA collects user fees for reviewing original PMAs and all supplement types except special supplements. For the 2014 fiscal year, an original PMA application costs \$258,502, a panel-track supplement costs \$193,890, and other supplement types cost \$38,778 or less (Figure 1).²⁸ Small business may qualify for reduced fees for PMA and supplement applications.²⁸

Past Studies of the PMA Process

Several investigators have studied how the FDA has implemented its charge to ensure safety and effectiveness of high-risk devices through the PMA pathway. Dhruva and colleagues found that for high-risk cardiovascular devices approved from 2000-2007, 27% of premarket studies were randomized and 52% included control groups.⁶ Over a similar time frame, Kramer and colleagues found that 60% of premarket studies for new cardiovascular devices had clearly defined safety outcomes, with important clinical comorbidities commonly unreported.⁸ Chen and colleagues examined devices across multiple specialties approved via PMA and similarly found that 36% were studied against an active control group.⁷

All of the above studies reviewed original PMA applications. To our knowledge, no previous studies have examined PMA supplement pathways for approval of changes to high-risk medical devices.

Methods

Data Sources

We searched for original PMA applications filed under CIED-related product codes (DSZ, DTB, DTD, DXY, KRG, LOT, LWO, LWP, LWS, LWW, MRM, NIK, NKE, NVN, NVY, NVZ, OJX, OSR) in the FDA's public PMA Database, which categorizes approved PMA applications by approval date, device type, and application type (original vs. supplement).^{12,29} The PMA Database links each PMA application to records of its supplements.

Data Extraction

For each PMA application for a CIED, we extracted the approval date, manufacturer, device type, and number of approved supplements (through December 2012). When available, we also downloaded the Summary of Safety and Effectiveness Data (SSED), which describes the device and supporting data. Using this information, two authors (BNR, DBK) classified each original PMA as a pacemaker, ICD, or CRT.

For each PMA supplement, we extracted the date of approval, type (panel-track, 180-day, real-time, special, or 30-day notice), and reason for the supplement. The supplement reason described in the database allowed us to identify those supplements that included a change to a device's design, compared with supplements for labeling or manufacturing changes. Since the mid-1990s, the FDA's database has included a short paragraph describing the change for most approved supplements. Starting in 2010, the FDA published longer "review memos" to accompany approval of 180-day supplements. Panel-track supplements are generally accompanied by SSED reports, similar to original PMA applications. We used these

descriptive paragraphs, review memos, and SSEs accompanying any supplement to determine nature of the approved changes.

Data Analysis

We calculated the median number of supplements per PMA. For each PMA, we calculated the time during which that PMA was active, defined as the amount of time (in years) between initial approval and the PMA's most recent supplement. For example, an original PMA approved in January 1985 and most recently supplemented in December 2000 was active for 16 years.

We then identified the number of PMA supplements approved in each of the five regulatory categories each year from 1979-2012. Since original PMAs for CIEDs were added over time, we divided the number of supplements approved in a given year by the number of active PMAs in that year.

Finally, we identified examples of changes made to CIEDs by 180-day and real-time supplements. According to FDA's industry guidance, these two categories are intended to encompass changes to a devices' design that are not reviewed by an independent panel of experts.¹⁴ We identified CIED device models advertised in July 2013 on the websites of the five manufacturers with the most approved PMA applications (Biotronik, Boston Scientific, Medtronic, Sorin Group, and St. Jude Medical), and we searched the PMA database to determine how and when each device model was approved. We also determined manufacturer-level trends in the number of 180-day vs. real-time supplements approved since

1997 (the year the real-time pathway was introduced) for the six device manufacturers that received the most supplement approvals for CIEDs.

Results

From 1979-2012, the FDA approved 77 PMA applications for CIEDs, including 46 pacemaker devices (32 pulse generators, 11 leads, and 3 combined systems), 19 ICDs (7 pulse generators, 3 leads, and 9 combined systems), and 12 CRT devices (1 CRT-D and 1 CRT-P pulse generator, 4 CRT-D and 3 CRT-P combined systems, and 3 left ventricular leads).

These PMAs were the subject of 5,829 PMA supplement applications. Nearly half (2,754, 47%) were approved as 30-day notice supplements for manufacturing changes. The FDA required a 135-day review for 13% (346) of these approved 30-day notice applications. The next-largest categories were 180-day supplements (1,538, 26%) and real-time supplements (1,312, 23%). Small fractions were panel-track supplements (15, 0.3%) or special supplements (108, 2%). Data were missing for 102 supplements (2%).

The number of supplements approved for each PMA ranged from 0 to 366, with a median of 50 (interquartile range [IQR]: 23-87). Excluding 30-day notice supplements, each PMA led to a median of 30 supplements (range 0 to 177; IQR 10-50).

Variations in Supplement Approval over Time

In the last decade, the number of supplements approved annually increased nearly ten-fold, from 77 to 704. Excluding 30-day notice supplements, which have increased markedly

since their introduction in 1997, there was still a 3-fold increase over the past decade, from 60 supplements to 194.

Figure 2 displays the number of supplements approved each year, adjusted for the number of active PMAs in that year. Excluding 30-day notice supplements, the number of supplements approved per active PMA has remained stable around a mean of 2.6 supplements per PMA per year (standard deviation 0.9; range 1.1-4.6). Before 1986, most PMA supplements were not explicitly classified. From 1986 to 1996, 93% were 180-day supplements. Starting in 1997, minor design changes previously classified as 180-day supplements were diverted into the real-time pathway.

PMA Lifespan

Figure 3 shows the active time period of each of the 77 PMAs (median 15 years, range 0-31, IQR 8-20). We found that 61 (79%) received at least one supplement in 2012. The most recent original PMA for any transvenous ICD system was approved in 2000, indicating that all ICD models released since then have been supplements to existing PMAs.

For example, the St. Jude Riata ICD lead was a real-time supplement to a PMA from May 1996 that led to 78 supplementary changes (including 45 non-30-day notice supplements) through October 2012. St. Jude originally marketed the PMA in 1996 as “TVL Lead System,” and subsequent models have been marketed under four additional names, including the now-recalled Riata and Riata ST lead models, which were introduced as real-time supplements in 2002 and 2005, respectively. Similarly, the Medtronic Sprint Fidelis lead, recalled in 2007, originated as a PMA for the Transvene Lead System in 1993. Through 2012, that PMA has been

successively supplemented 91 times (38, excluding 30-day notices), including the 180-day supplement that approved the Sprint Fidelis model.

We found that all ICD leads and pulse generators currently advertised on the websites of major CIED manufacturers were either 180-day or real-time supplements (Table 3). These devices were the culmination of successive iterations dating back to PMAs from 3.7 to 19.0 years prior.

Characteristics of 180-Day and Real-Time Supplements

Among 180-day and real-time supplements, 76% (2,155) represented a change to a device's design or materials; the remaining 24% were related to changes to labeling, manufacturing, and post-approval study protocols. Since the 1997 introduction of real-time review, the FDA has approved 542 (32%) 180-day supplements and 1,170 (68%) real-time supplements for changes to a device's design. The six manufacturers with the most 180-day and real-time supplements collectively accounted for 95% of such supplements. Among these six manufacturers, the use of real-time supplements for design changes ranged from 58% (Biotronik) to 85% (Boston Scientific). Medtronic utilized the real-time process to approve 67% of device design changes, while St. Jude used the real-time process 77% of the time.

Review memos were available for 157 of 223 (70%) 180-day supplements from 2010-2012. Changes to device design described in these memos included changes in lead insulation material, new software features, and new lead connections. Because proposed changes could affect more than one device, many of the review memos were duplicates; there were 64 unique review memos for the 157 cases, indicating that a single FDA review included changes to an

average of 2.5 devices. Among the 180-supplement review memos, 15 (23%) mentioned the collection of new clinical data supporting the altered device. Among the 15 review memos that included clinical data, 5 described the study design as prospective, multi-center, non-randomized clinical trials, and one memo described a retrospective analysis to support a labeling change. The remaining nine did not describe the study design. Seven memos with clinical data described the number of patients in the study (median 175, range 111-539).

Discussion

To our knowledge, this analysis is the first to characterize the PMA supplement process, as past studies of high-risk device approvals have focused exclusively on original PMA applications.^{7,8,32} Since the first CIED was approved via PMA in 1979, the FDA has authorized 5,829 supplements for 77 PMA applications, a median of 50 supplements per PMA. Over one-third (37%; 2,163) of supplements represented at least minor alterations to the device's design or materials. In the vast majority of these cases, the FDA deemed that new clinical data were not necessary for approval.

The PMA supplement process allows manufacturers to update devices via incremental innovations rather than waiting to release a package of more sweeping changes, a feature that has important implications for patients and physicians. For patients, this means that useful technological advances can be rapidly integrated into clinical care. The FDA reviews supplements in the context of the original application, previous supplements, and post-market device experiences. If a new device was approved in Europe before the US, the FDA can review European post-market data. In the review process, the FDA consults staff experts (including

clinicians) to make a determination as to what types of data are necessary for approval. In some cases, preclinical testing may be superior to clinical testing in assessing changes.³³ For example, mechanical testing of ICD leads can simulate years of clinical conditions relatively quickly, and animal studies may allow for repeated induction of arrhythmias that would be impossible in a human model.³³ Thus, our results should not be interpreted to indicate that the FDA is failing to review PMA supplement applications to determine safety and effectiveness.

However, clinicians and patients should also be aware of our finding that clinical data are rarely collected as part of PMA supplement applications prior to marketing. The recalled Medtronic Sprint Fidelis and St. Jude Riata ICD leads were both PMA supplements — Fidelis as a 180-day supplement and Riata as a real-time supplement. Neither lead was studied in human trials prior to FDA approval. The FDA's approval of many supplements without new human trials, as in the case of these recent ICD changes, highlights the importance of collecting rigorous post-approval performance data.

Awareness by physicians of how incremental device innovation is facilitated by the PMA supplement process may have implications for the rapid adoption of newly-approved CIED technologies. One study found that nearly two-thirds of ICDs implanted in the US are a manufacturer's most current model.³⁴ Physicians should weigh the potential benefits offered by new device models against possible harms in the context of established alternatives, particularly for life-saving or life-sustaining interventions. Indeed, greater attention to this issue by the clinical community may motivate manufacturers to conduct much-needed comparative effectiveness studies, since currently little prospective testing of this sort exists to guide physicians' decision making.

In contrast to the summary of safety and effectiveness data (SSED) reports provided with each original PMA, the evidence supporting PMA supplements has traditionally not been as accessible to clinicians or the public. Since 2010, the FDA has improved transparency by providing abbreviated review memos for approved 180-day supplements. For example, in the last few years, the FDA has approved novel four-pole connection systems for ICD leads and generators as 180-day supplements without requiring new clinical studies.¹⁰ Medtronic's four-pole ICD connection system was approved in January 2012, and the review memo published by the FDA outlines the preclinical testing performed, including a 6-month animal study.³⁵

We also found differences in how device manufacturers used 180-day and real-time PMA supplements to modify their devices. It is uncertain whether these differences reflect development and marketing strategies, with some companies releasing updated products that each offer smaller innovations over the previous generation more quickly than others. Alternatively, manufacturers may simply have varying thresholds for deciding which device changes should be submitted for real-time review instead of the normal 180-day process. Regulators and industry should ensure that standards for selecting PMA supplement pathways are consistently applied.

Our analysis of PMA supplements has several limitations. We relied on the FDA's PMA database, which may contain errors in classifying supplements and provides only limited information about the nature of changes to medical devices and the data used to support those changes. Some data pre-date the FDA's digital efforts, while other data may be considered proprietary. In the past three years, the FDA has started providing insight into the clinical data submitted to justify supplement approval, although greater transparency would be useful about

the rationale behind the approved study designs and the outcomes of any required post-market analyses. In addition, the PMA database contains an entry for each PMA supplement application, even if multiple applications were bundled together under a single review. Consequently, our results represent the number of applications, which is greater than the number of reviews performed by the FDA. However, bundled applications often include changes to more than one device, and so our analysis approximates the total number of altered device models even if similar changes are reviewed at the same time.

Our study excludes any CIEDs approved via FDA pathways other than PMA. For example, implantable pacemakers were in use before 1976, and until the mid-1990s the FDA continued to approve some new pacemakers via the 510(k) pathway as substantially equivalent to pre-amendment devices. We also limited our analysis to the pre-market device review process and did not consider post-approval studies that may be required for PMA supplement-approved devices, as these are uncommon and only evaluate safety and effectiveness after a device may have gained widespread clinical use. While PMA applications are used to regulate many types of high-risk devices, including some ophthalmologic, orthopedic, and urologic implants, our analysis was limited to cardiovascular devices, as has been done in other studies of the PMA pathway.^{8,32} Cardiovascular devices make up almost half of all PMA and PMA supplement applications.

While recent media and policymaking attention around medical devices has focused on the 510(k) process,^{9,17,20} we found that many high-risk cardiovascular devices, including those in widespread use today, are approved as PMA supplements. Many supplements involved minor design changes or changes to labeling, packaging, or manufacturing, and in these cases the

supplement process provides a speedy and inexpensive avenue for regulatory review. The long active life of CIED PMA approvals suggests that minor design changes may accumulate over time and in some cases may add up to substantial changes from the device approved in the original PMA application. To guard against this outcome, the FDA could mandate an expert panel review of each PMA every 5-7 years in which it is active to evaluate the extent to which clinical data from older models still apply to newer ones. Another possibility would be more widespread implementation of rigorous post-market studies to evaluate device performance once approved for clinical use. The rise of unique device identifiers and device registries may permit more comparative effectiveness research between older and newer versions of devices that emerge via the PMA supplement pathway.³⁶

The PMA process supporting FDA approval has long been considered the gold standard for rigorously establishing the safety and effectiveness of high-risk medical devices. Our findings demonstrate that the PMA supplement process provides a commonly-used review pathway for FDA authorization of changes to existing high-risk devices. Many of the pacemaker, implantable cardioverter-defibrillator, and cardiac resynchronization therapy models currently used by clinicians have come via the PMA supplement process. Most device models approved as PMA supplements are deemed safe and effective without requiring new clinical data, reinforcing the importance of post-approval surveillance of these devices. In making decisions about utilization of these high-risk devices, clinicians and patients should consider the strengths and limitations of the PMA supplement approval processes.

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Figure Legends:

Figure 1: Submission Fees for Premarket Approval Applications, Fiscal Year 2014

Each bar represents the FDA fee for reviewing an original or supplement premarket approval application for the 2014 fiscal year.

Figure 2: Trends in PMA Supplement Approvals, 1980-2012

Figure 2 shows the number of PMA supplements, by type, approved per active PMA each year from 1980-2012. The first supplement for a CIED device was approved in 1981. The secondary axis displays the number of active PMAs, which rose steadily to 61 in 2012.

Figure 3: Lifespan of 77 PMAs for CIED devices

The length of each horizontal bar represents the time between the date a PMA was approved and the date of its most recent supplement. The first original PMA for a CIED device was approved in 1979. Three original PMAs underwent zero supplements.

Table 1: Comparing FDA Authorization of Drugs and Devices

	Drugs	High-Risk Devices	Medium-Risk Devices
Year FDA Began Mandating Proof of Safety and Efficacy	1962	1976	N/A
Authorization Process	New Drug Application (NDA)	Premarket Approval (PMA)	510(k) clearance
Standard of Evidence	Substantial evidence that the drug will have the effect it purports or is represented to have*	Reasonable assurance of safety and effectiveness	Substantial equivalence to a predicate device
Supporting Data	Clinical trials and pre-clinical studies	Clinical trials and pre-clinical studies	Pre-clinical studies**
Process for Introducing Post-Authorization Changes	None***	PMA supplement pathways	New 510(k) clearance
Tort Liability Claims Against Manufacturer Mostly Preempted?	No	Yes	No

* Substantial evidence is defined as “adequate and well-controlled investigations, including clinical investigations”

** Clinical trials are rarely required as part of the 510(k) process

***Changes to the molecular structure of an active ingredient require their own New Drug Application. In some instances, the FDA may approve new formulations of an approved drug based on bioequivalence studies.

Table 2: FDA Regulatory Categories for PMA Supplements

Type of Supplement	Types of Changes to Device	Data Required	User Fee (FY2014)	Reviewer	Year Category Formally Introduced
Panel-Track	Significant design change; new indication	Clinical; Limited preclinical data in some cases	\$193,890	Panel of Subject Matter Experts and FDA staff	1990
180-Day	Significant design change; labeling change	Preclinical; Confirmatory clinical data in some cases	\$38,778	FDA staff	1986
Real-Time	Minor design change	Preclinical only	\$18,096	FDA staff	1997
Special*	Labeling change that enhances device safety	No specific data requirements	N/A	FDA staff	1986
30-Day Notice**	Manufacturing change	No specific data requirements	\$4,136	FDA staff	1997

* A manufacturer may temporarily enact the change before the FDA issues approval.

**A manufacturer may enact the change 30 days after the FDA files the notice if there is no FDA action. Alternatively, the FDA may request a 135-day review if 30-day notice is deemed insufficient

Table 3: Origins of Currently-Marketed ICD Systems

Manufacturer	Device Model(s)	PMA Number (Supplement Number)	Supplement Type	Date Approved	Age of PMA at approval (years)
Leads					
Biotronik	Linux Smart	P980023 (S038)	180-Day	9/17/2010	11.9
Boston Scientific	Endotak Reliance G 0174/0175/0176/0177	P910073 (S041)	180-Day	11/4/2003	10.2
Boston Scientific	Endotak Reliance G/SG 0180-0187	P910073 (S043)	Real-Time	3/2/2004	10.5
Medtronic	Sprint Quattro 6944	P920015 (S017)	180-Day	12/15/2000	7.0
Medtronic	Sprint Quattro 6947	P920015 (S024)	Real-Time	11/2/2001	7.9
Medtronic	Sprint Quattro 6935	P920015 (S039)	Real-Time	4/29/2008	14.4
Medtronic	Sprint Quarto 6947M	P920015 (S055)	180-Day	1/9/2012	18.1
Medtronic	Sprint Quattro 6935M	P920015 (S091)	Real-Time	7/2/2012	18.6
St. Jude Medical	Durata 7120/7121/7122	P950022 (S040)	Real-Time	9/6/2007	11.3
St. Jude Medical	Durata 7170/7171	P950022 (S041)	Real-Time	10/16/2007	11.4
St. Jude Medical	Durata 7120Q/7121Q/7122Q	P950022 (S042)	180-Day	1/13/2009	12.7
St. Jude Medical	Durata 7170Q/7171Q	P950022 (S060)	Real-Time	7/10/2009	13.2
Pulse Generators					
Biotronik	Lumax 300/340	P000009 (S020)	180-Day	12/7/2006	6.2
Biotronik	Lumax 540	P000009 (S026)	180-Day	11/4/2008	8.1
Biotronik	Lumax 700/740	P000009 (S047)	180-Day	5/4/2012	11.6
Biotronik	Lumax 540 VR-T DX	P050023 (S029)	Real-Time	4/30/2010	3.7
Biotronik	Lumax 740 VR-T DX	P050023 (S048)	180-Day	5/4/2012	5.7

Boston Scientific	Teligen E102/E110	P960040 (S155)	180-Day	5/8/2008	10.8
Boston Scientific	Energen, Incepta, Punctua	P960040 (S235)	180-Day	11/17/2011	14.3
Medtronic	Secura	P980016 (S114)	180-Day	3/17/2008	9.4
Medtronic	Protecta, Protecta XT	P980016 (S211)	180-Day	3/25/2011	12.5
Sorin Group	Paradym 8250/8550	P980049 (S050)	180-Day	4/7/2010	10.6
Sorin Group	Paradym RF 9250/9550	P980049 (S065)	180-Day	4/10/2012	12.6
St. Jude	Current+ CD1211-36Q	P910023 (S201)	Real-Time	4/8/2009	15.9
St. Jude	Fortify	P910023 (S226)	180-Day	5/7/2010	17.0
St. Jude	Ellipse, Fortify Assura	P910023 (S279)	180-Day	5/7/2012	19.0

Figure 1: Submission Fees for Premarket Approval Applications, Fiscal Year 2014

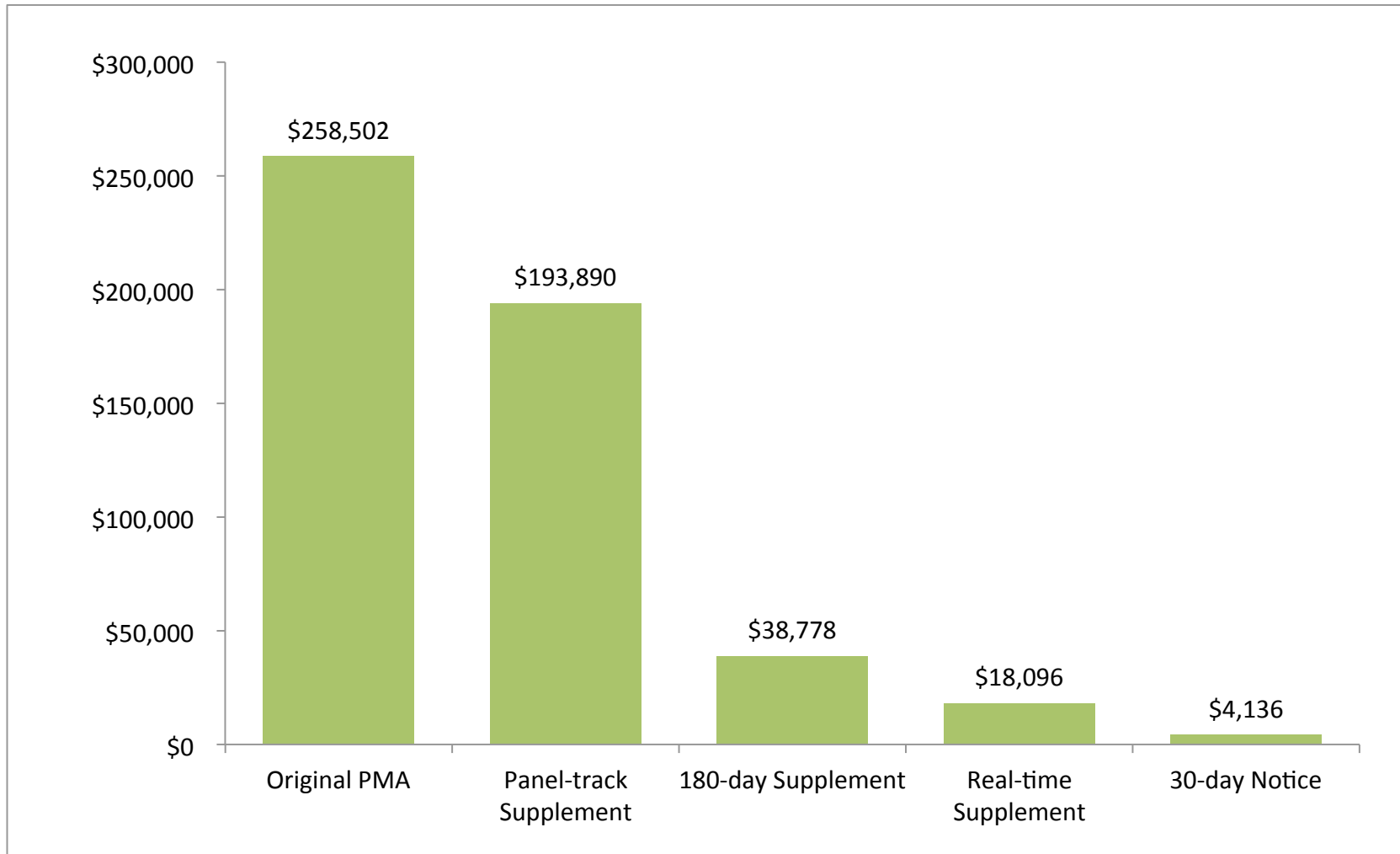


Figure 2: Trends in PMA Supplement Approvals, 1980-2012

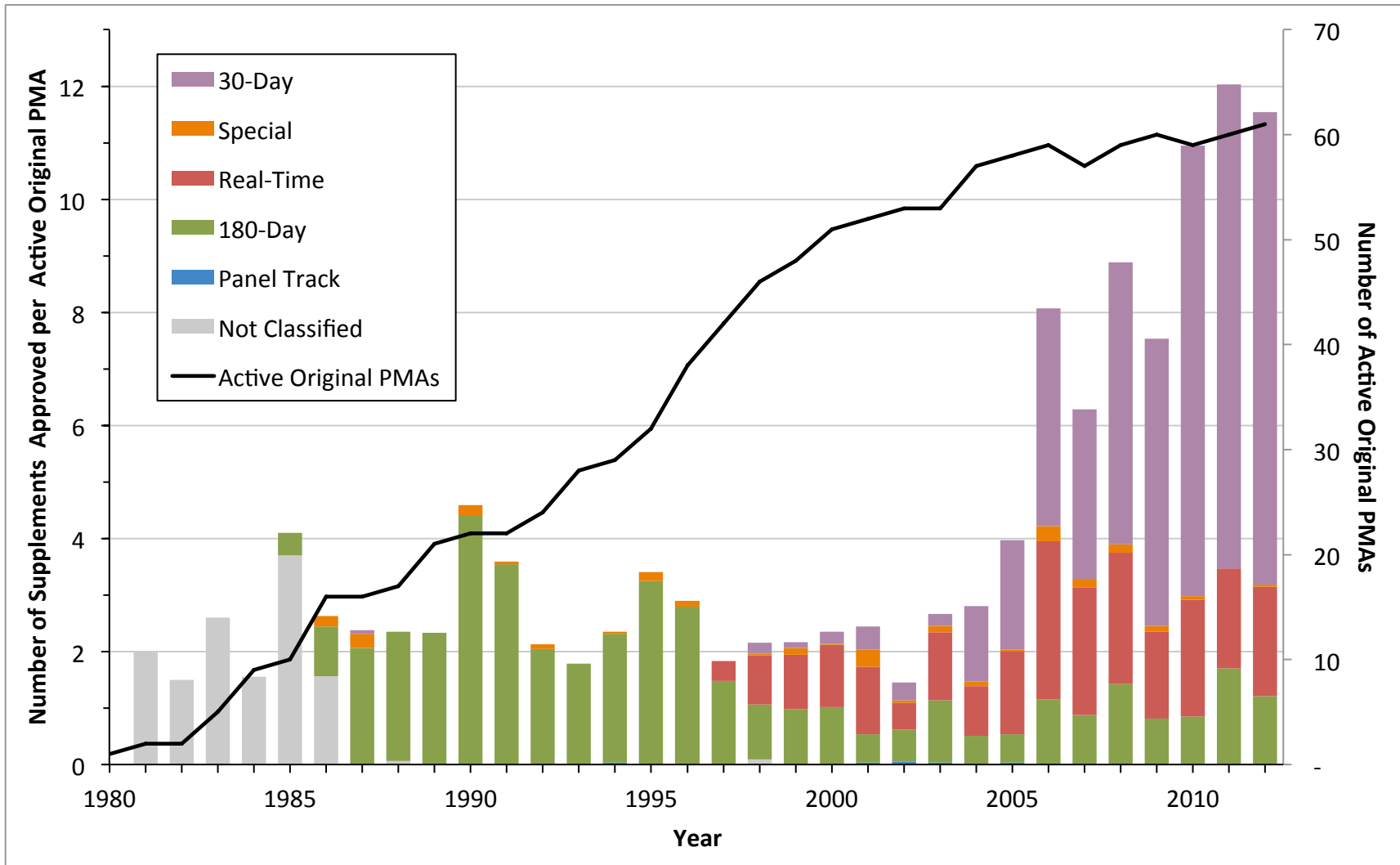


Figure 3: Lifespan of 77 PMAs for CIEDs, 1979-2012

