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CLINICAL RESEARCH

How do Orthopaedic Devices Change After Their Initial FDA Premarket Approval?

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Abstract

Background The FDA approves novel, high-risk medical devices through the premarket approval (PMA) process based on clinical evidence supporting device safety and effectiveness. Devices subsequently may undergo postmarket modifications that are approved via one of several PMA supplement review tracks, usually without additional supporting clinical data. While orthopaedic devices cleared via the less rigorous 510(k) pathway have been studied previously, devices cleared through the PMA pathway and those receiving postmarket PMA supplements warrant further investigation.

Questions/purposes We asked: What are (1) the types of original orthopaedic devices receiving FDA PMA approval, (2) the number and rate of postmarket device changes approved per device, (3) the types of PMA supplement review tracks used, (4) the types of device changes approved via the various review tracks, and (5) the number of device recalls and market withdrawals that have occurred for these devices?

Methods All original PMA-approved orthopaedic devices between January 1982 and December 2014 were identified in the publically available FDA PMA database. The number of postmarket device changes approved, the PMA supplement review track used, the types of postmarket changes, and any FDA recalls for each device were assessed.

Results Seventy original orthopaedic devices were approved via the FDA PMA pathway between 1982 and

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2014. These devices included 34 peripheral joint implants or prostheses, 18 spinal implants or prostheses, and 18 other devices or materials. These devices underwent a median 6.5 postmarket changes during their lifespan or 1.0 changes per device–year (interquartile range, 0.4–1.9). The rate of new postmarket device changes approved per active device, increased from less than 0.5 device changes per year in 1983 to just fewer than three device changes per year in 2014, or an increase of 0.05 device changes per device per year in linear regression analysis (95% CI, 0.04–0.07). Among the 765 total postmarket changes, 172 (22%) altered device design or components. The majority of the design changes were reviewed via either the real-time review track (n = 98; 57%), intended for minor design changes, or the 180-day review track (n = 71; 41%), intended for major design changes. Finally, a total of 12 devices had FDA recalls at some point during their lifespan, two being for hip prostheses with high revision rates.
Conclusions Relatively few orthopaedic devices undergo the FDA PMA process before reaching the market. Orthopaedic surgeons should be aware that high-risk medical devices cleared via the FDA's PMA pathway do undergo considerable postmarket device modification after reaching the market, with potential for design "drift," ie, shifting away from the initially tested and approved device designs.
Clinical Relevance As the ultimate end-users of these devices, orthopaedic surgeons should be aware that even among high-risk medical devices approved via the FDA's PMA pathway, considerable postmarket device modification occurs. Continued postmarket device monitoring will be essential to limit patient safety risks.

Introduction

According to the 1976 Medical Device Amendments Act [24], all novel "high-risk" medical devices must be approved by the U.S. FDA through the Premarket Approval (PMA) process [28]. These high-risk, or FDA Class III devices, include any that "support or sustain human life, are of substantial importance in preventing impairment of human health, or present a potential, unreasonable risk of illness or injury," [28] rather than Class I or Class II devices which pose less risk to patients (Table 1). Unlike the alternative 510(k) Premarket Notification pathway, which is designed to expedite clearance of low- and moderate-risk devices through the demonstration of "substantial equivalence" to existing predicate devices, the PMA pathway requires manufacturers to provide original clinical data that support device safety and effectiveness before device clearance [28].

However, several high-risk Class III devices have been cleared via the less-rigorous 510(k) pathway, owing to a legal provision in the Medical Device Amendments Act [24], allowing certain classes of high-risk devices to be exempt from the PMA process. As a result, these 510(k)-cleared devices may reach patients without prior clinical testing. In the field of orthopaedics this includes metal-on-metal hip prostheses, cement spacers, and spinal pedicle fixation systems. Owing to criticism of this regulatory loophole, Congress directed the FDA to either reclassify these exempt devices as Class I or Class II or retroactively require PMAs [4]. Although the process is still ongoing, in coming years we likely will see increased use of the PMA pathway for approval of high-risk orthopaedic devices.

Once a device is approved through the PMA pathway, PMA supplement applications can be submitted to the FDA for postmarket devices changes [27]. Various types of PMA supplement review tracks exist (Table 2), each intended for different types of device modifications (changes in device design, labeling, production, and postmarket testing) and requiring varying amounts of clinical or preclinical data before approval.

Despite the evidentiary requirements of the PMA pathway, there has been concern that the clinical studies forming the basis of PMA applications may lack adequate strength and be prone to bias [3, 5, 6, 12, 13, 20, 34]. This is especially worrisome for implantable devices that cannot be easily removed or discontinued. For example the PMA-approved Sprint Fidelis implantable cardioverter-defibrillator lead (Medtronic, Dublin, Ireland) was found to have increased risk of fracture only after 3 years on the market and 268,000 implants [25].

These concerns also extend to postmarket device changes made after initial PMA approval [11, 12]. Although the expectation is that individual postmarket device changes will have a limited effect on device safety or effectiveness, cumulative iterations of device changes may cause "drift" away from the originally approved device design. A previous study of PMA supplements found that cardiac implantable electronic devices

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Table 1. FDA device classes

FDA device class	Examples	Regulatory controls
Class I (low risk)	Bone tamp, screw driver, rongeur, cast saw, compression device	General controls (most are exempt from 510(k) Premarket Notification)
Class II (moderate risk)	Intramedullary nails, ORIF plates, screws, arthroplasty components, spinal fixation implants, vertebral body replacements, bone void fillers	General controls, 510(k) Premarket Notification (few are exempt)
Class III (high risk)	Alternative bearing THA systems, hip resurfacing systems, mobile bearing TKA systems, total ankle replacements, total disc replacements	General controls, Premarket Approval (few are exempt)

ORIF = open reduction internal fixation.

Table 2. Types of PMA supplement review tracks

Supplement Review Track	Description
180-day track	Formally introduced in 1986
	Reviewed by FDA staff or, in some cases, expert panel
	Requires preclinical data and, in some cases, clinical data
	Intended for design and labeling changes affecting safety and efficacy,
	eg, approval of new acetabular shell to be used with ceramic liner in hip prosthesis
Special track	Formally introduced in 1986
	Reviewed by FDA staff
	Requires no specific new data
	Intended for labeling changes meant to enhance device safety,
	eg, revisions to patient and physician labeling or surgical technique manual
Panel track	Formally introduced in 1990
	Reviewed by subject matter expert panel
	Requires substantial new clinical data in most cases
	Intended for labeling changes expanding indications for use or removing contraindications,
	eg, expanded indications for intervertebral body fusion device for one- or two- level fusions
Real-time process	Formally introduced in 1997
	Reviewed by FDA staff
	Requires preclinical data
	Intended for minor changes in design, software, or labeling,
	eg, addition of a tamp extractor instrument to a total hip prosthesis system
30-day notice	Formally introduced in 1997
	Reviewed by FDA staff
	Requires no specific new data
	Intended for changes in manufacturing processes that may affect device safety and efficacy,
	eg, change in component supplier or sterilization testing procedure
135-day review	Formally introduced in 1997
	Reviewed by FDA staff
	Requires new information per FDA request
	Intended for 30-day notice applications requiring further review before clearance,
	eg, change in polishing process and equipment for total hip prosthesis system

underwent more than 30 postmarket changes to device design or labeling that often were not supported by new clinical data [21]. This "drift" phenomenon is similar to what has been described for metal-on-metal hip implants, which have long received clearance through the 510(k) pathway [1, 9]. The ASR™ XL Acetabular Cup System (DePuy Inc, Raynham, MA, USA), for example, first cleared in 2008, was recalled from the market in 2010 because of high revision rates [1, 7]. This implant received original 510(k) clearance based on six predicate devices, each with unique design features that were combined in the ASR™ XL. These six devices did not undergo PMA

approval, but instead received 510(k) clearance based on a long lineage of more than 60 predicate devices during 50 years, including three now-discontinued devices.

The field of orthopaedic surgery relies heavily on implants, which can have a high-cost of failure to the patient [18]. In the past, high-risk orthopaedic devices cleared through the 510(k) pathway have been shown to lack adequate evidence supporting safety and effectiveness [16], and therefore undergo recalls [1]. Although orthopaedic devices cleared via the 510(k) pathway have been studied [1, 7, 22], numerous commonly used, high-risk orthopaedic devices currently require PMA approval and may undergo postmarket changes via PMA supplements, including alternative bearing THA systems, hip resurfacing systems, and mobile bearing total knee systems. In addition, there have been reports of PMA-approved devices being recalled from the market, such as certain sizes of the Birmingham Hip™ Resurfacing (BHR®) System (Smith & Nephew, London, UK) and the New Jersey LCS® Total Knee System (DePuy Inc), both recalled in 2015 owing to high revision rates [2, 23]. As PMA-approved orthopaedic devices have not been analyzed in the literature, to our knowledge, the current study characterizes all orthopaedic devices approved through the FDA PMA pathway (since passage of the 1976 Medical Device Amendments Act, which formalized evaluation and market clearance of medical devices by the FDA) and all postmarket device changes subsequently cleared for these devices.

We therefore asked, what are (1) the types of original orthopaedic devices receiving FDA approval through the PMA process, (2) the number and rate of postmarket device changes cleared per device, (3) the types of PMA supplement review tracks used, (4) the types of device changes approved via the various review tracks, and (5) the number of device recalls and market withdrawals that have occurred for these devices?

Materials and Methods

A retrospective, cross-sectional analysis was conducted of the publically accessible FDA PMA database (assessed December 2014) containing records of all original and supplemental PMA approvals [33]. Supplement approvals may include newly marketed products that represent modifications to existing PMA-approved devices. All PMA supplement approvals are linked in the database to the original PMA application for the initial version of the device to create a lineage of device iterations.

All FDA PMA devices that were approved between January 1982 (year of first PMA-approved orthopaedic device) through December 2014 and assigned to the FDA Orthopaedic and Rehabilitation Devices Panel were identified [32]. All these devices were designated as high-risk, or FDA Class III, at the time of application. The type of PMA application was determined based on coding in the FDA database. All applications were characterized by date of approval.

In addition, device recall history was characterized by searching the FDA Medical Device Recalls Database, containing all device recalls issued since November 1, 2002, for each PMA application number to determine any device recall dates.

For analysis of the types of original orthopaedic devices receiving FDA PMA approval, the total number of devices in each device category was simply computed and reported. Device type was determined by using FDA-designated product classification codes and categorized by us in the following groups: peripheral joint implant/prosthesis, spinal joint implant/prosthesis, and other orthopaedic device. The numbers of original devices approved via the PMA pathway were determined for each year. Linear regression was used to determine the change in annual PMA approvals with time.

For analysis of postmarket device changes, the number of postmarket changes approved via PMA supplements for active device was determined. The median (and interquartile range) postmarket device changes per device and per device-year were reported, as certain outlier devices showed substantially greater numbers of postmarket changes, skewing a calculation of the mean. The devices with the greatest total postmarket changes and greater rate of postmarket changes per year were reported. Linear regression was used to determine the change in annual rate of postmarket changes with time.

For analysis of the types of PMA supplement review tracks, the number of PMA supplements approved each year was broken down by review tracks. The percentage of each review track type from all PMA supplements was determined for each review track type since its inception. The FDA currently uses six PMA supplement review tracks (Table 2). Changes that alter device design or components are intended for review via the 180-day track (major design changes) or the real-time track (minor design change). Changes in production processes (eg, sterilization) are intended for review via the 30-day notice track. The FDA may convert process changes to the 135-day review track when additional supporting information is required. Changes in device labeling are intended for review via the panel track (changes expanding indications or removing contraindications for a device) or the special track (labeling that enhances device safety). Certain supplements cleared before 1990 are unclassified in a specific review track in the PMA database.

For analysis of the types of postmarket device changes, the types of postmarket device changes were characterized for all 180-day track, real time, 30-day notice, 135-day review, special track, and panel track supplements. Types of device changes were reported in the PMA database by

the FDA using the following categories (Appendix 1. Supplemental material is available with the online version of CORR®): Instructions labeling change, Indications labeling change, Other labeling change, Minor design change, Component design change, Other design change, Manufacturing production change, Other production change, Location change, Postapproval study protocol change, and Other device change. As an added analysis the most common type of supplement review track used to approve design changes was determined.

Finally, for analysis of the number of device recalls and market withdrawals that have occurred for these devices, all recalls and withdrawals were simply assessed and reported. Reasons for market withdrawal are not given in the PMA database. Device recall history was characterized by searching the FDA Medical Device Recalls Database [31], containing all device recalls issued from November 1, 2002 to September 1, 2015, for each PMA application number to determine any device recall dates. Recall date, recall classification, and reason for recall were assessed. The FDA classifies medical device recalls in three classes [29]. A Class I recall is a "situation in which there is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death." A Class II recall is a "situation in which use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote." A Class III recall is a "situation in which use of, or exposure to, a violative product is not likely to cause adverse health consequences." Devices recalled specifically owing to high revision rates were identified. Market withdrawals are reported in the FDA PMA database. The mean time from original PMA approval to market withdrawal was computed for devices that were withdrawn from the market.

All statistical analyses were performed using Stata® version 13.0 (StataCorp, LP, College Station, TX, USA). Statistical tests were two-tailed and a probability less than 0.05 was considered statistically significant.

Results

Orthopaedic Devices Receiving PMA Approval

A total of only 70 orthopaedic devices have been cleared via the FDA PMA pathway since passage of the 1976 Medical Device Amendments Act [24]. These devices included 34 peripheral joint implants/prostheses (Table 3), 18 spinal implants/prostheses (Table 4), and 18 other devices or materials (Table 5). In linear regression analysis (Fig. 1), the rate of original PMA device approvals increased by 0.07 per year (95% CI, 0.01–0.13; $p = 0.023$; $R^2 = 0.1549$).

Postmarket Changes for PMA-approved Devices

A total of 765 postmarket changes were approved for these 70 devices through December 2014. The median number of postmarket device changes approved per device via PMA supplements was 6.5 (interquartile range [IQR], 3–13), or 0.9 PMA supplements approved per active device–year (IQR, 0.4–1.8). The rate of new postmarket device changes approved per active device, increased from less than 0.5 device changes per year in 1983 to just fewer than three device changes per year in 2014 (Fig. 2). In linear regression analysis the rate of new postmarket device changes approved per active device, increased by 0.05 device changes per year (95% CI, 0.04–0.07; $p < 0.001$; $R^2 = 0$ .6235).

For peripheral joint prostheses, the median number of postmarket changes per device was 7.5 (IQR, 3–14), or 0.9 changes (IQR, 0.4–1.9) per active device-year. For spinal implants/prostheses, the median number of postmarket changes per device was seven (IQR, 3–13), or 1.4 changes (IQR, 0.9–1.8) per active device-year. For other devices, the median number of postmarket changes per device was five (IQR, 0–11), or 0.6 changes (IQR, 0.0–1.5) per active device-year.

The New Jersey LCS® Total Knee System had the highest total number of postmarket changes, with 135 device changes approved during its 30.5-year lifespan, or 4.4 device changes per device–year (Fig. 3). The highest rate of postmarket device changes per device–year was for the Ceramax® Ceramic Hip System (DePuy Inc), with 4.5 supplements approved per device–year during a 4.4-year lifespan.

PMA Supplement Review Tracks

Use of different types of PMA supplement review tracks has changed with time (Fig. 3). The 180-day track was the most common type of supplement review track used since the PMA program began, accounting for more than 34% of all supplements for orthopaedic devices. Since their introduction in 1997, the 30-day notice and 135-day reviews, intended for process changes and not requiring any new clinical data, have accounted for 37% of all PMA supplements approved since that time. Of the original 30-day notice applications that eventually were approved, 47%, or 118 applications, were converted to 135-day review track after the FDA deemed the information supporting the change to be inadequate. Only seven panel track supplements have been approved for orthopaedic devices. The

Table 3. FDA PMA-approved peripheral joint prostheses

Device trade name	PMA number	Device manufacturer	Year of original FDA clearance	Number of PMA supplements cleared	Year of voluntary withdrawal from market	Product lifespan (years)
Ankle prosthesis						
Scandinavian Total Ankle Replacement System (STAR™ Ankle)	P050050	Small Bone Innovations Inc.	2009	7	NA	NA
Finger prosthesis						
Braun-Cutter Trapezo-Metacarpal Prosthesis	P960053	Small Bone Innovations Inc.	1997	5	NA	NA
Ascension® Metacarpal Prosthesis	P000057	Integral Lifesciences Corp.	2001	8	NA	NA
Hip prosthesis						
Osteo Ceramic Hip	P810048	Smith & Nephew, Inc.	1982	10	2007	25
DePuy® Hip System	P820024	DePuy Orthopaedics, Inc.	1984	15	NA	NA
Bias™ Fiber Metal Total Hip System	P850061	Zimmer, Inc.	1989	2	NA	NA
AML Porocoat® Acetabular Cup Prosthesis	P880025	DePuy Orthopaedics, Inc.	1990	3	NA	NA
Whiteside EPS™ Femoral Hip Prosthesis	P880076	Dow Corning Corp.	1991	1	NA	NA
S-ROM Poly-Dial® Constrained Liner	P960054	DePuy Orthopaedics, Inc.	1997	4	NA	NA
Osteonic Constrained Acetabular Insert	P960047	Howmedica Osteonics Corp.	1997	4	NA	NA
Keramos™ Ceramic/Ceramic Total Hip System	N980003	DJO Global, Inc.	2003	2	NA	NA
Ceramic Transcend® Hip Articulation	P010001	Microport Orthopedics Inc.	2003	6	NA	NA
ABC/Trident® Ceramic-Ceramic Hip Articulation	P000013	Howmedica Osteonics Corp.	2003	11	NA	NA
Ceramic Transcend® Hip Articulation System	P030027	Ceramtec GmbH	2003	11	NA	NA
Reflection® Ceramic Acetabuluar System	P030022	Smith & Nephew, Inc.	2004	31	NA	NA
C2a-Taper™ Acetabular System	P050009	Biomet, Inc.	2005	7	NA	NA
Duraloc® Option Ceramic Hip System	P040023	DePuy Othopaedics, Inc.	2005	23	2014	9
Trilogy® AB Acetabular System	P040048	Zimmer, Inc.	2006	15	2012	6
SkelKast Surpass™ Acetabular System	P040051	StelKast, Inc.	2006	3	NA	NA
Birmingham Hip™ Resurfacing (BHR®) System	P040033	Smith & Nephew, Inc.	2006	26	2015	NA
Novation™ Ceramic Articulation Hip System	P050039	Exactech, Inc.	2007	16	NA	NA
Cormet Hip Resurfacing System	P050016	Corin Group P.L.C.	2007	11	NA	NA
Conserve® Plus Total Resurfacing Hip System	P030042	Microport Orthopedics Inc.	2009	4	2014	5
Ceramax® Ceramic Hip System	P070026	DePuy Orthopaedics, Inc.	2010	21	NA	NA
Pinnacle® CoMplete® Acetabular Hip System	P090002	DePuy Orthopaedics, Inc.	2011	9	2013	2
Knee prosthesis						
LCS® Total Knee System	P830055	DePuy Orthopaedics, Inc.	1985	136	NA	NA
PCA Total Knee System	P840049	Howmedica Corp.	1991	1	NA	NA
New Jersey LCS® Total Knee System	P910016	DePuy Orthopaedics, Inc.	1992	14	2012	20
Natural-Knee® and Natural Knee® II with CSTI	P940002	Sulzer Medica Ltd.	1997	5	NA	NA

Table 3. continued

Device trade name	PMA number	Device manufacturer	Year of original FDA clearance	Number of PMA supplements cleared	Year of voluntary withdrawal from market	Product lifespan (years)
Oxford™ Meniscal Unicompartmental Knee System	P010014	Biomet, Inc.	2004	42	NA	NA
Nexgen® LPS-Flex Mobile and LPS-Mobile Bearing Knee System	P060037	Zimmer, Inc.	2007	29	NA	NA
Ligament graft						
Gore-Tex Expanded PTFE Prosthetic Ligament	P850074	W.L. Gore & Associates, Inc.	1987	5	2013	26
Stryker Knee Augmentation Graft	P850054	Meadox Medicals Inc.	1988	1	–	–
Kennedy LAD Ligament Augmentation Device	P850069	3M Company	1988	11	2009	21

NA = Not applicable.

special track has accounted for 11% of all supplements approved since its formal introduction in 1986. Finally, since its introduction in 1997, the real-time process review track, intended for more minor design changes, has accounted for 21% of all approved PMA supplements.

Types of Postmarket Device Changes

A total of 294 (38.4%) PMA supplements were approved for process changes related to devices (Fig. 4). Design changes accounted for 172 (22.5%) PMA supplements. The majority of design changes were approved through either the real-time process (57.0%) or the 180-day track (41.3%). Labeling changes accounted for 117 (15.3%) PMA supplements. The remaining 182 (15.5%) supplements were approved for location changes, postapproval study protocol changes, or other reasons not otherwise specified.

Device Recalls and Market Withdrawals

A total of 12 PMA-approved devices had FDA recalls documented in the FDA Medical Device Recall database, with three having multiple FDA recalls (Table 6). Of the 17 total product recalls, 16 were Class II recalls, indicating that "use of or exposure to a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote [29]." The remaining recall was a Class III, indicating that "use of or exposure to a violative product is not likely to cause adverse health consequences [29]." Two devices, the BHR® System and the New Jersey LCS® Total Knee System were withdrawn owing to high revision rates. The BHR® system had 26 postmarket device changes approved via PMA Supplements since initial approval in 2006 (2.9 per year). The New Jersey LCS® system had 136 postmarket device changes approved via PMA Supplements since initial approval in 1985 (4.5 per year).

A total of nine devices were voluntarily withdrawn from the market at some point by manufacturers (Tables 3–5), with a mean time to withdrawal of 13.5 years (range, 2–26 years; SD, 9.3 years). Reasons for these market withdrawals were not given. Voluntarily withdrawn devices (and total time on market) were the: Conserve® Plus Total Resuracing Hip System (4.7 years), Charite™ Artificial Disc (7.2 years), Duraloc® Option Ceramic Hip System (8.9 years), Trilogy® AB Acetabular System (6.2 years), Pinnacle® Complete Acetabular Hip System (2.2 years), Osteo Ceramic Hip (24.9 years), Stryker Knee Augmentation Graft (24.1 years), Kennedy Ligament Augmentation Device (22.3 years), and LCS® Total Knee System (19.5 years).

Table 4. FDA PMA-approved spinal implants and prostheses

Device trade name	PMA number	Device manufacturer	Year of original FDA clearance	Number of PMA supplements cleared	Year of withdrawal from market	Product lifespan (years)
Intervertebral body fusion devices						
Ray Threaded Fusion Cage™ with Instrumentation	P950019	Stryker Corp.	1996	17	NA	NA
Bak® Interbody Fusion System	P950002	Zimmer, Inc.	1996	14	NA	NA
Inter Fix™ Threaded Fusion Device	P970015	Medtronic Sofamor Danek USA, Inc.	1999	23	NA	NA
Brantigen I/F Cage® used with VSP® Spine Plates and Pedicle Screws	P960025	DePuy Spine, Inc.	1999	12	NA	NA
Bak/Cervicle® Interbody Fusion System	P980048	Sulzer Spine-Tech	2001	4	NA	NA
Affinity™ Cage System	P000028	Medtronic Sofamor Danek USA, Inc.	2002	8	NA	NA
Intervertebral disc prostheses						
Charité™ Artificial Disc	P040006	DePuy Spine, Inc.	2004	6	2012	8
Prodisc®-L Total Disc Replacement Device	P050010	Synthes Holding AG	2006	15	NA	NA
Prodisc® TM-C Total Disc Replacement	P070001	Synthes Holding AG	2007	12	NA	NA
Prestige® Cervical Disc System	P060018	Medtronic Sofamor Danek USA, Inc.	2007	4	NA	NA
Bryan® Cervical Disc Prosthesis	P060023	Medtronic Sofamor Danek USA, Inc.	2009	5	NA	NA
Nuvasive® PCM Cervical Disc System	P100012	Nuvasive, Inc.	2012	6	NA	NA
Secure®-C Artificial Cervical Disc System	P100003	Globus Medical Inc.	2012	4	NA	NA
Mobi-C® Cervical Disc Prosthesis (Two-Level Indication)	P110009	LDR Spine USA, Inc.	2013	8	NA	NA
Mobi-C® Cervical Disc Prosthesis (One-Level Indication)	P110002	LDR Spine USA, Inc.	2013	8	NA	NA
Prestige® LP Cervical Disc	P090029	Medtronic Sofamor Danek USA, Inc.	2014	1	NA	NA
Spinous process spacers						
X-Stop® Interspinous Process Decompression System	P040001	Medtronic Sofamor Danek USA, Inc.	2005	19	NA	NA
Coflex® Interlaminar Stabilization Device	P110008	Paradigm Spine, LLC	2012	3	NA	NA

NA = not applicable.

Discussion

The FDA PMA process is currently the most rigorous pathway for high-risk medical devices to reach the market. Because of additional innovation or safety reasons, these devices often may require modifications after initial approval and marketing. The PMA supplement pathway allows these postmarket device changes to be approved in a more rapid fashion than formal PMA application. However, only limited new supporting evidence is required for these supplements compared with original PMA device clearances, and many postmarket device changes are approved without any new clinical data. As a result, these PMA supplements allow for potential device "drift" away from the originally approved device design. As device "drift" without new supporting clinical data in the 510(k) premarket notification process has been implicated in the high-profile recall of the ASR™ XL Acetabular Cup System [1], there is potential for patient safety risks with inadequate oversight of postmarket device changes. With implanted orthopaedic devices, the cost of device failure can be especially high for patients, and there is a need for surgeons to understand how devices are changing after initial FDA PMA approval. In light of this need, we reviewed all PMA-approved orthopaedic devices in the publically available FDA PMA database from 1982 to 2014. Only 70 original orthopaedic devices have been approved via the PMA pathway, a finding which may be

Table 5. Other FDA PMA-approved orthopaedic devices

Device trade name	PMA number	Device manufacturer	Year of original FDA clearance	Number of PMA supplements cleared
Hyaluronic acid				
Synvisc-One®	P940015	Genzyme Corp.	1997	23
Hyalgan®	P950027	Fidia Farmaceutici SPA	1997	11
Supartz™ Dispo	P980044	Seikagaku Corp.	2001	2
Euflexxa® (1% Sodium Hyaluronate)	P010029	Ferring Pharmaceuticals, Inc.	2004	6
Orthovisc® High Molecular Weight Hyaluronan	P030019	Anika Therapeutics, Inc.	2004	12
Gel-One®	P080020	Seikagaku Corp.	2011	13
Sinovial® (0.8% Sodium Hyaluronate)	P110005	Ibsa Institut Biochimique SA	2014	1
Monovisc®	P090031	Anika Therapeutics, Inc.	2014	3
Bone cement				
Palacos® R Bone Cement	P810020	Smith & Nephew Richard, Inc.	1984	6
DePuy 1 Bone Cement	P960001	DePuy Orthopaedics Inc.	1997	9
Bone graft and filler				
Alveoform™ Biograft	P860012	Collagen Corp.	1988	5
Pro Osteon® Implant 500 Hydroxyapatite Bone Void Filler	P860005	Interpore Intl.	1992	1
Collagraft Bone Graft Substitute	P900039	Neucoll, Inc.	1993	1
Infuse® Bone Graft/ LT-Cage® Lumar Tapered Fusion Device	P000058	Medtronic Sofamor Danek USA, Inc.	2002	49
Infuse® Bone Graft	P000054	Medtronic Sofamor Danek USA, Inc.	2004	17
Shock wave generator				
Orbasone™ Pain Relief System	P040039	Orthometrix, Inc.	2005	1
Bone growth stimulator				
Orthopak® Bone Growth Stimulator	P850022	Biolectron, Inc.	1989	6
OL1000/OL10000 SC and Spinalogic Bone Growth Stimulators	P910066	DJ Orthopedics, LLC	2012	1

unexpected for the device-heavy field of orthopaedic surgery. These devices underwent a median 0.9 PMA postmarket device changes per device-year, but the rate of postmarket changes increased steadily during the past 20 years. The use of the various supplement review tracks has shifted with the introduction of quicker review tracks, however. In addition, two PMA-approved joint prostheses were recently recalled owing to high-revision rates, both having numerous postmarket changes approved via PMA supplements.

The current study has important limitations to consider. First, earlier records of PMA supplements (earlier than 1986) do not have information regarding the type of supplement review tracks or detail on the type of device change made. However, this represents only a minority of supplement review tracks for orthopaedic devices (most occurred after 1986; Fig. 3). Next, for more recent records, there is no detail regarding whether new clinical or preclinical data were provided to the FDA. This does not meaningfully affect our analysis because the specific data requirements for most PMA supplements are known, based on the type of supplement review tracks used. However, for 180-day tracks, this requirement is variable. Since 2010, the FDA has not published review memos for select 180-day supplements specifying the amount and type of new clinical or preclinical data submitted. However, no review memos were published or are available for orthopaedic devices.

Orthopaedic Devices Receiving PMA Approval

In the device- and implant-driven field of orthopaedic surgery, it is surprising that only 70 original devices have received PMA approval since 1976. For comparison, by December 2015, more than 169 different Class III metal-on-metal hip prostheses had been cleared through the 510(k) pathway, which requires only proof of similarity or "substantial equivalence" to a previously cleared device, and not original clinical testing [30]. In addition, 18 of the 28 FDA device codes for hip prostheses are classified as Class II, which do not require PMA approval (Table 7).

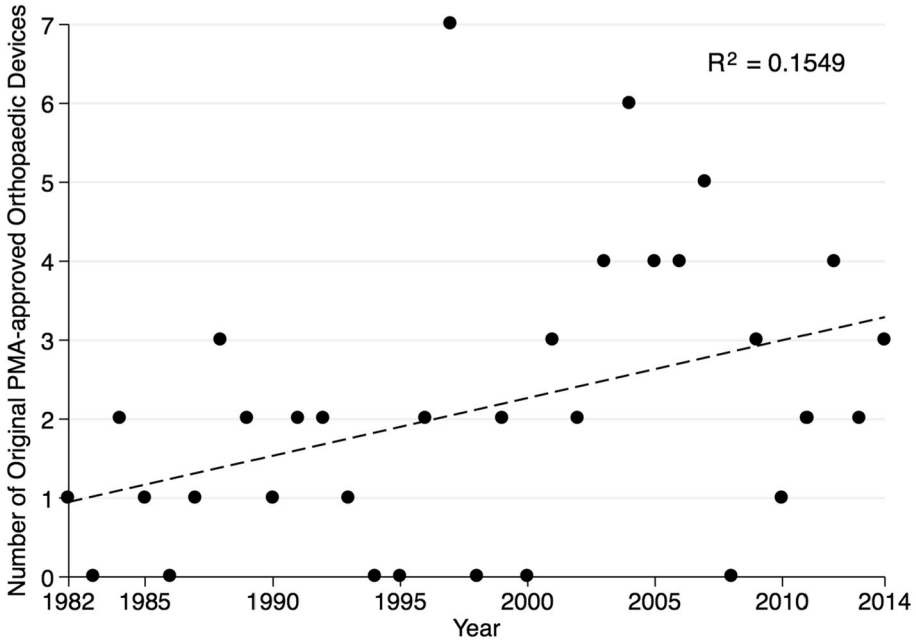

Fig. 1 The number of original Class III orthopaedic devices approved via premarket approval (PMA) has increased with time. Best-fit linear regression function is shown with R^2.

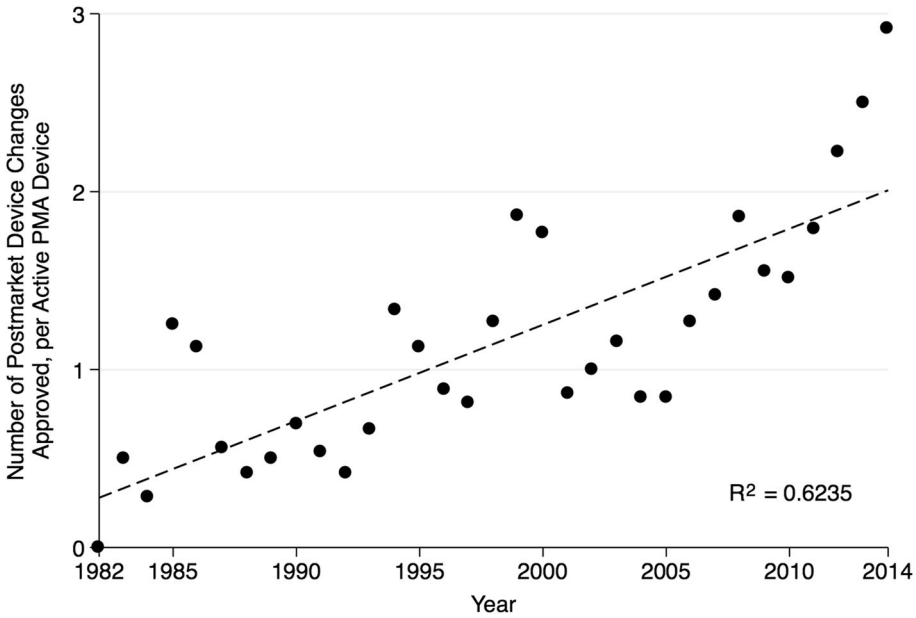

Fig. 2 The number PMA supplements approved per active orthopaedic PMA-approved device has increased with time. Best-fit linear regression function is shown with R^2. PMA = premarket approval.

The regulatory exemption for certain Class III devices and widespread classification of many orthopaedic prostheses as Class II (moderate risk) devices contribute to the low utilization of PMA approval for orthopaedic devices compared with 510(k) clearances. Even in other fields, the 510(k) premarket notification process historically has been the most widely used pathway to market for high-risk devices. Rome et al. [21] reported on 77 original PMA approvals for cardiac implantable electronic devices between 1979 and 2012. Garber [9] reported that from 2003 to 2007, a total of 228 Class III devices were cleared for marketing via the 510(k) process versus 170 device receiving PMA-approval. However, owing to criticism of the 510(k) pathway in the wake of high-profile metal-on-

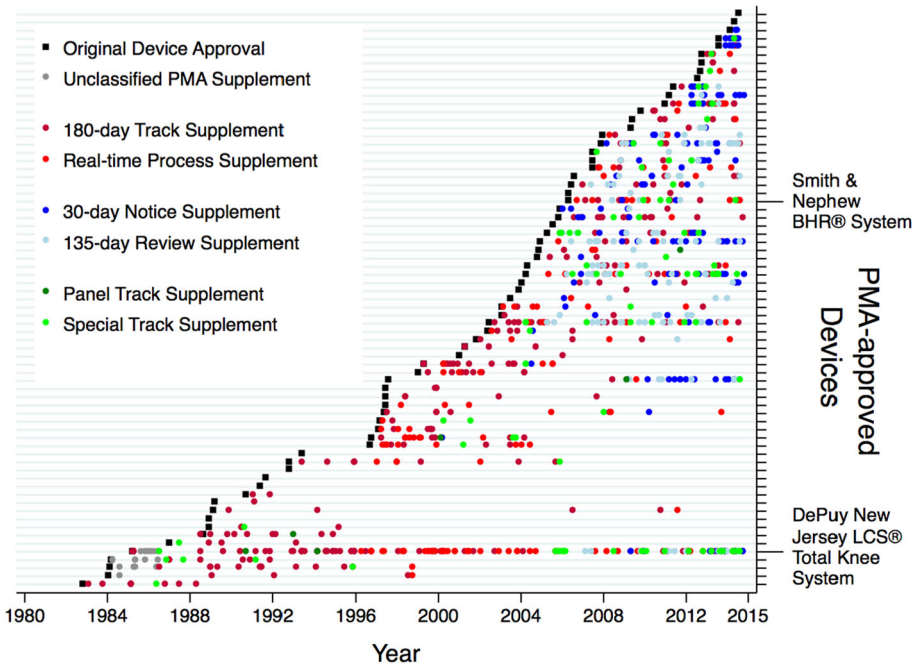

Fig. 3 There is substantial variability in the use of the different types of PMA supplement review tracks with time and in the use of PMA supplements between different devices. PMA = premarket approval.

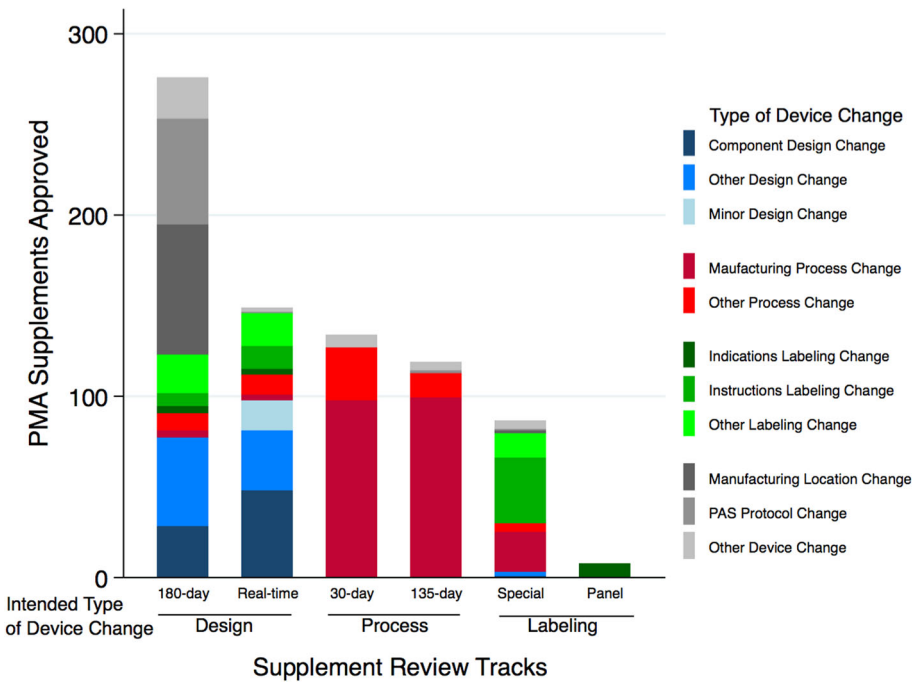

Fig. 4 The types of device changes approved vary by PMA supplement review track. PMA = premarket approval; PAS = postapproval study.

metal hip implant failures, transitioning away from the 510(k) pathway in the near future was encouraged [4]. In 2009 the FDA launched the 515 Program Initiative to transition all high-risk devices to the PMA pathway [26]. Through this program, the FDA plans to review 515 Class III devices that originally underwent only 510(k) premarket notification, rather than PMA-approval. Each device either will be reclassified as a Class I or Class II device, or a formal PMA will be required. The expected increase in PMA pathway use ultimately will result in more supporting

Table 6. FDA Recalls of PMA-approved orthopaedic devices

Date of recall	Device trade name	PMA number	Device manufacturer	FDA recall class	Reason for recall	Recall termination date
June 7, 2007	Birmingham Hip™ Resurfacing (BHR®) System	P040033	Smith & Nephew Inc.	2	Mislabeling of sizes	Open
October 25, 2007	Birmingham Hip™ Resurfacing (BHR®) System	P040033	Smith & Nephew Inc.	2	Mislabeling of sizes	February 2, 2010
December 19, 2007	Prestige® Cervical Disc System	P060018	Medtronic Sofamor Danek USA, Inc.	2	Implant misseating	November 3, 2008
September 29, 2008	X-Stop® Interspinous Process Decompression System	P040001	Kyphon Inc.	2	Clarification of physician instructions	July 14, 2009
October 20, 2008	Ray Threaded Fusion Cage™ with Instrumentation	P950019	Stryker Corp.	2	Incorrect labeling	November 4, 2008
February 3, 2009	Oxford™ Meniscal Unicompartmental Knee System	P010014	Biomet, Inc.	2	Mislabeling of left/right	July 7, 2009
June 25, 2009	Nexgen® LPS-Flex Mobile and LPS-Mobile Bearing Knee System	P060037	Zimmer Inc.	2	Inadequate implant polishing	November 12, 2009
July 27, 2009	Trilogy® AB Acetabular System	P040048	Zimmer Inc.	2	Inadequate package seal	December 22, 2009
August 4, 2009	ABC/Trident® Ceramic-Ceramic Hip Articulation	P000013	Stryker Corp.	2	Clarified physician instructions	Open
May 21, 2010	Euflexxa ®(1% Sodium Hyaluronate)	P010029	Ferring Pharmaceuticals Inc.	3	Viscosity out of specification	July 27, 2010
April 22, 2011	Reflection® Ceramic Acetabuluar System	P030022	Smith & Nephew Inc.	2	Damaged during processing	February 8, 2012
February 4, 2013	Trilogy® AB Acetabular System	P040048	Zimmer, Inc.	2	Low porosity specification	June 20, 2014
June 25, 2013	Infuse® Bone Graft/ LT-Cage® Lumar Tapered Fusion Device	P000058	Medtronic Sofamor Danek USA, Inc.	2	Possible contamination	May 13, 2014
October 25, 2013	Nexgen® LPS-Flex Mobile and LPS-Mobile Bearing Knee System	P060037	Zimmer, Inc.	2	Packaging breakdown	September 25, 2014
February 20, 2014	Trilogy® AB Acetabular System	P040048	Zimmer, Inc.	2	Poor packaging at one manufacturing plant	Open
May 26, 2015	LCS® Total Knee System	P830055	DePuy Orthopaedics, Inc.	2	High revision rates	Open
September 10, 2015	Birmingham Hip™ Resurfacing (BHR®) System	P040033	Smith & Nephew Inc.	2	High revision rates	Open

Table 7. FDA classification of hip prostheses

FDA device class	FDA-designated product code*	FDA device classification description	FDA regulatory process
Class II hip prostheses	KWZ	Prosthesis, Hip, Constrained, Cemented Or Uncemented, Metal/Polymer	510(k)
	PBI	Prosthesis, Hip, Constrained, Cemented Or Uncemented, Metal/Polymer, + Additive	510(k)
	JDG	Prosthesis, Hip, Femoral Component, Cemented, Metal	510(k)
	KXA	Prosthesis, Hip, Femoral, Resurfacing	510(k)
	KWL	Prosthesis, Hip, Hemi-, Femoral, Metal	510(k)
	LZY	Prosthesis, Hip, Hemi-, Femoral, Metal Ball	510(k)
	KWY	Prosthesis, Hip, Hemi-, Femoral, Metal/Polymer, Cemented Or Uncemented	510(k)
	KMC	Prosthesis, Hip, Semi-Constrained, Composite/Metal	510(k)
	OQI	Prosthesis, Hip, Semi-Constrained, Cemented, Metal/Ceramic/Polymer + Additive, Porous Uncemented	510(k)
	OQH	Prosthesis, Hip, Semi-Constrained, Cemented, Metal/Polymer + Additive, Cemented	510(k)
	OQG	Prosthesis, Hip, Semi-Constrained, Cemented, Metal/Polymer, + Additive, Porous, Uncemented	510(k)
	MAY	Prosthesis, Hip, Semi-Constrained, Metal/Ceramic/Polymer, Cemented Or Non-Porous Cemented, Osteophilic Finish	510(k)
	LZO	Prosthesis, Hip, Semi-Constrained, Metal/Ceramic/Polymer, Cemented Or Non-Porous, Uncemented	510(k)
	JDI	Prosthesis, Hip, Semi-Constrained, Metal/Polymer, Cemented	510(k)
	LPH	Prosthesis, Hip, Semi-Constrained, Metal/Polymer, Porous Uncemented	510(k)
	LWJ	Prosthesis, Hip, Semi-Constrained, Metal/Polymer, Uncemented	510(k)
	MEH	Prosthesis, Hip, Semi-Constrained, Uncemented, Metal/Polymer, Non-Porous, Calicum-Phosphate	510(k)
	MBL	Prosthesis, Hip, Semi-Constrained, Uncemented, Metal/Polymer, Porous	510(k)
Class III hip prostheses	KXD	Prosthesis, Hip, Constrained, Metal	PMA
	KWB	Prosthesis, Hip, Hemi-, Acetabular, Cemented, Metal	PMA
	KXB	Prosthesis, Hip, Pelvifemoral Resurfacing, Metal/Polymer	PMA
	OCG	Prosthesis, Hip, Pelvifemoral Resurfacing, Metal/Polymer, Uncemented	PMA
	JDL	Prosthesis, Hip, Semi-Constrained (Metal Cemented Acetabular Component)	Exemption - 510(k)
	KWA	Prosthesis, Hip, Semi-Constrained (Metal Uncemented Acetabular Component)	Exemption - 510(k)
	OVO	Prosthesis, Hip, Semi-Constrained, Ceramic-On-Metal Articulation	PMA
	LPF	Prosthesis, Hip, Semi-Constrained, Metal/Ceramic/Ceramic, Cemented	PMA
	MRA	Prosthesis, Hip, Semi-Constrained, Metal/Ceramic/Ceramic/Metal, Cemented Or Uncemented	PMA
	NXT	Prosthesis, Hip, Semi-Constrained, Metal/Metal, Resurfacing	PMA

* FDA-designated product codes are three-character unique identifiers used by the FDA to classify devices in unique product categories.

evidence for original high-risk devices and improved monitoring of postmarket device changes by the FDA and the public, as FDA tracking of changes implemented through the 510(k) pathway is considerably less organized [10].

Postmarket Changes for PMA-approved Devices

A median 6.5 postmarket device changes were approved per original orthopaedic PMA device, or 1.0 change per device-year. In the only other analysis of PMA supplement-approved postmarket device changes, Rome et al. [21] reported a median of 50 device changes per cardiac implantable electronic device, or 2.6 changes per device-year—more than observed for orthopaedic devices. These differences may reflect the high rate of software modifications that may occur during the lifespan of a cardiac implantable electronic device. Although our results suggest that orthopaedic devices undergo relatively fewer postmarket changes, experience with devices cleared via the 510(k) pathway suggests otherwise. The previously noted ASR™ XL Acetabular Cup System first received 510(k) clearance in

2008. This clearance for this metal-on-metal hip prosthesis was issued without supporting clinical data, but rather was based on substantial equivalence to six predicate devices that each had unique features that were combined in the ASR™ XL (the metal-on-metal articulation, porous bone ingrowth surface, and large femoral head sizes). These six devices also were never clinically tested before their marketing, and similarly received 510(k) clearance owing to substantial equivalence to prior devices. It ultimately was found that the ASR™ XL was derived from a lineage of 95 510(k) devices cleared during 50 years, including several that since have been withdrawn from the market [1]. This substantial lack of supporting clinical data was implicated when the ASR™ XL was later recalled owing to high revision rates. Although this degree of device "drift" is substantially greater than seen with most PMA devices, the most-heavily modified orthopaedic device under the PMA system, the New Jersey LCS® Total Knee System, did have 135 postmarket supplements approved during 30 years. This prosthesis was similarly recalled by the FDA in 2015 owing to high revision rates when used with a native, nonresurfaced patella. Although the specific relationship between postmarket device modifications and revision rates warrants further investigation, there is clear potential for device "drift," similar to the 510(k) pathway, with modifications being rapidly marketed to and adopted by providers without new supporting clinical evidence.

PMA Supplement Review Tracks

The types of supplement review tracks used appear to have changed with time with the introduction of quicker review tracks such as the 30-day notice. The most commonly used supplement review track since the start of the program has been the 180-day track (36%), intended for significant device modifications [27], while the 30-day notice and 135-day review, intended for minor manufacturing process changes, have become more common. For cardiac implantable electronic devices, the most commonly used supplement review track since the start of the PMA program has been the 30-day notice (47%) [21]. With the introduction of new supplement review tracks, corresponding increases in the total rates of supplements cleared also has been observed. Notably, the increases in postmarket changes approved per active device during the early 2000s (for orthopaedic devices and cardiac implantable electronic devices) seem to correspond with increased use of the newly available 30-day notice for production process changes, which requires limited supporting evidence before approval. Interestingly, the New Jersey LCS® Total Knee System, which was recalled from the market in 2015 owing to high revision rates, had 18 PMA supplements approved via the 30-notice and 135-day review tracks alone. These supplements were largely for manufacturing process changes.

Types of Postmarket Device Changes

The types of device changes approved via the various PMA supplement review tracks largely correspond with the intended use of each review track. However, some discrepancies were present. The real-time process track is intended for minor design modifications and requires less new supporting preclinical data than the 180-day review. However, only 17% of design changes approved via real-time process were classified as minor. Furthermore, a large percentage of changes in device indications (46.2%), were approved via real-time and 180-day tracks, despite that the changes in indication are intended to undergo formal panel track approval, which requires submission of new clinical data. For cardiac implantable electronic devices, the majority of real-time and 180-day track supplements were used for changes in device design or components (76%) [21], whereas for orthopaedic devices, design and component changes accounted for only 41% of all 180-day track and real-time supplements. While the FDA has ultimate control over which supplement review tracks are used for device changes, there is potential for overuse of certain review tracks to expedite time to approval. In the future, the controls over what types of device changes are approved through the various supplement review tracks should be reviewed.

Device Recalls and Market Withdrawal

The high profile failure of the ASR™ XL Acetabular Cup System brought to light the inadequacies of the FDA's 510(k) premarket notification system [1]. Because the PMA process is more rigorous and thorough, fewer device failures should be expected. Now with the recent FDA recalls of the New Jersey LCS® Total Knee System for certain uses and certain sizes of the BHR® System owing to high revision rates, additional scrutiny of the PMA approval process and PMA supplements may be expected. Overall, most FDA recalls of PMA devices were not attributable to design flaws but rather issues with processing, packaging, or labeling. Nevertheless, with modern orthopaedic implants being designed for durability for up to decades, we may just now be understanding the long-term outcomes of these implants which were not previously studied for such periods. Because poor performance of these prostheses has been identified speaks to the effectiveness of current postmarket surveillance measures. Prospective registries such as the Australian Orthopaedic

Association National Joint Replacement Registry, which identified higher revision rates with the New Jersey LCS® System [2], and Smith & Nephew, which identified higher revision rates with smaller sizes of the BHR® system using data from the National Joint Registry of England and Wales [23], were able to rapidly notify manufacturers of poor outcomes and initiate a product recall.

Orthopaedic surgeons should be aware that even among high-risk medical devices cleared via the FDA's PMA pathway, considerable postmarket device modification occurs often without new supporting clinical data. This is particularly true given that new models of devices are rapidly incorporated in clinical practice [11]. Several studies have shown poor performance of various newly released orthopaedic devices without supporting premarket clinical data [7, 14, 16]. In addition, remarketing of new devices based on changes implemented via PMA supplements may permit devices that may be used for substantially different purposes than supported by original clinical evidence [34]. As a result, continued postmarket surveillance of high-risk orthopaedic devices is critical to ensure patient safety [5]. Although the quality of FDA-mandated postapproval studies has been questioned [19], efforts to build national and international orthopaedic device registries [15] and electronic health record-based monitoring systems [8, 17] are underway. Programs such as these may enable continued manufacturer innovation through least burdensome premarket regulation, while still maintaining sufficient postmarket oversight to limit patient safety risks.

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