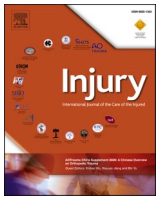
Injury 56 (2025) 112291

Contents lists available at ScienceDirect

Injury

journal homepage: www.elsevier.com/locate/injury



Review

FDA regulatory considerations for innovative orthopedic devices: A review

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ARTICLE INFO

Keywords:
Orthopedic devices
Orthopedic implants
Regulatory
Food and drug administration (FDA)
Medical devices

ABSTRACT

Novel and innovative orthopedic devices are needed to address clinical challenges in orthopedic practice. Obtaining regulatory authorization for such devices, however, can prove challenging. An inherent dilemma exists between innovation to address unmet needs and imitation to demonstrate substantial equivalence to a predicate device, which is required for the less burdensome 510(k) pathway. This article provides both an overview of highly innovative orthopedic devices over the last 10 years as well as considerations for FDA regulatory pathways and programs available to manufacturers of such devices. A review of 20 innovative orthopedic devices receiving Breakthrough Device Designation and/or a De Novo classification found that devices had diverse features and applications, but did possess shared technological trends including bioresorption, flexible components, and new substance/material use. A review of all new orthopedic devices authorized through the three major regulatory pathways in the last 10 years was also conducted. Spinal devices represented the largest share of recent orthopedic devices (38 % of 510(k) clearances and 25 % of De Novo classifications). Across all three pathways, decision time was on average around 30 % shorter for orthopedic devices with a Breakthrough Device Designation versus those without, though differences were not significant. New orthopedic devices authorized in the last 10 years were found to be highly reliant on the 510(k) pathway, with a 99 % utilization rate. However, the FDA Breakthrough Devices Program and De Novo pathway offer opportunities specific to innovative technologies, such as expedited review and potential market competition protection, as demonstrated through specific case studies in this review. As these FDA initiatives continue to evolve and manufacturers continue to take advantage of these opportunities, orthopedic device development, which has primarily prioritized incremental innovation, may too evolve to produce more breakthrough innovations.

Introduction

Novel and innovative orthopedic devices are needed to improve the quality of care for patients, reduce costs, and streamline surgical procedures. Innovation in the orthopedics space takes many forms, ranging from incremental innovation of legacy implant systems to breakthrough innovation introducing new materials, technologies, approaches, or entirely new devices. Historical examples of breakthroughs in orthopedics include Danis's compression plate in 1949 [1], Boucher and Roy--Camille's pedicle screws in 1959 [2], and Charnley's low-friction polyethylene arthroplasty components in the 1960′s [3]. More recent breakthrough areas in orthopedics include 3D printing of patient-specific implants [4,5], bioresorbable materials [6], and "smart" implants and instruments [7,8].

For these innovations to be legally marketed in the United States, they must obtain regulatory authorization through the U.S. Food and Drug Administration (FDA). Orthopedic devices are regulated by the Center for Devices and Radiological Health (CDRH) within the FDA. Many pathways exist for obtaining authorization – most notably the premarket notification, or 510(k) pathway, through which many orthopedic implants obtain clearance, as well as the premarket approval (PMA) pathway, through which high-risk class III devices are approved. However, as will be shown in this review, other pathways and initiatives are available through the FDA, each offering unique advantages and requirements.

Importantly, obtaining regulatory authorization for highly innovative devices presents unique challenges. As will be described, the most common and preferred regulatory pathway for device manufacturers, the 510(k) pathway, involves demonstrating 'substantial equivalence' to a legally marketed predicate device. In some ways this represents an inherent dilemma between *innovation* to address unmet needs and *imitation* to ease the path towards marketing authorization by remaining eligible for the 510(k) pathway. However, in recent years, more devices have utilized the FDA's De Novo pathway which grants authorization to

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https://doi.org/10.1016/j.injury.2025.112291
Accepted 20 March 2025
Available online 22 March 2025

novel moderate-risk devices for which there is no predicate, as well as the FDA's Breakthrough Devices Program which provides special advantages for innovative breakthrough technologies. Understanding and navigating these opportunities and the many constraints of the current regulatory landscape can be challenging for device developers seeking to obtain regulatory status for their innovations.

This article seeks to address this challenge by: (i) identifying highly innovative orthopedic devices on the market and their technological trends through a review of FDA Breakthrough Device and De Novo databases; (ii) providing overviews and usage statistics over the last 10 years for the 510(k), De Novo, and PMA pathways specific to orthopedic devices; and (iii) proposing regulatory considerations for developers of innovative orthopedic devices navigating current regulatory infrastructure.

Review methodology

The scope of this review is limited to the U.S. regulatory framework (FDA). Specific analyses are described below, with all devices being identified by searching the following FDA databases with all applicable review panels, advisory committees, and regulation medical specialties set to orthopedic: the Breakthrough Devices Program statistical summary [9]; the Premarket Notifications (510(k)) database [10]; the Premarket Approvals (PMA) database [11]; and the De Novo database [12]; All databases were searched as of July 2024.

First, this review explores the FDA breakthrough devices program. An overview of the program is provided and a systematic review of all cleared, granted, or approved orthopedic devices that have received breakthrough device designation (BDD) is conducted. Since BDD is not a marketing pathway but rather a designation that expedites review, this analysis provides a comprehensive overview of highly innovative orthopedic devices across multiple pathways.

Next, the three dominant regulatory pathways are explored (510(k), De Novo, and PMA), providing overviews of the pathways as well as analyses of orthopedic devices that have obtained marketing authorization. This analysis involves summary statistics for 510(k) and PMA pathways. Given the reasonable number of devices for the De Novo pathway and its relevance to highly innovative devices, a systematic review of all granted De Novo orthopedic devices is performed, similar to the BDD analysis. Analysis of devices in each pathway is limited to original submissions only to exclude supplemental submissions for minor device or process changes. Decision time (number of days between original submission and final decision) is calculated for De Novo and PMA pathways due to the reasonable number of records, but was determined through reference averaging for the 510(k) pathway. For each pathway, the reduction in decision time for devices with BDD versus without BDD is evaluated for statistical significance (if sample size allows) using a two-tailed student's t-test with $\alpha = 0.05$. Anatomical targets are assigned to 510(k) records based on product code descriptions.

Of all the databases reviewed, the BDD and De Novo databases received the most thorough analysis due to their specific relevance to highly innovative technologies. Technological trends are determined for BDD and De Novo devices by identifying key innovations, or characteristics, for each device. These are selected by reviewing supporting information including 510(k) summary letters, reclassification orders, approval orders, scholarly articles, and company marketing materials. More detailed device information can be found directly on manufacturer websites. Images are provided for each device that turned up in the BDD and De Novo searches. Images were hand drawn by the author to depict the general form and relevant characteristics of devices in a uniform manner. Drawings were based on available product images in publications and company marketing materials and are intended to be merely approximate representations of the cited devices.

Breakthrough devices program

Overview

The breakthrough devices program is an FDA program for medical devices that are both innovative in nature and provide improved treatment or diagnosis for high impact health problems. The breakthrough devices program is not a marketing authorization pathway (regulatory pathways are reviewed in the following section), but rather a program that grants designation for deserving devices. To be eligible for the program, manufacturers must show that their device meets the following two criteria: (i) it provides more effective treatment or diagnosis of life-threatening or irreversibly debilitating human diseases; and (ii) it meets one of the following: a) it represents a breakthrough technology; b) there are no approved or cleared alternatives; c) it offers significant advantages over existing alternatives; or d) the device's availability is in the best interest of patients [13].

If the designation is granted, manufacturers benefit from several advantages including priority review, sprint discussions, regular status updates, discussions around data development plans and clinical protocol agreement. There are also reimbursement advantages for devices that achieve regulatory status with Breakthrough Device designation [14]. Devices receiving BDD must still obtain marketing authorization prior to commercial use through one of the available regulatory pathways. However, FDA has acknowledged that the benefit-risk calculus for breakthrough devices may differ from non-BDD devices, and the agency may accept greater uncertainty for such devices during premarket review with an emphasis on post-market controls and evaluations [15].

Identified devices

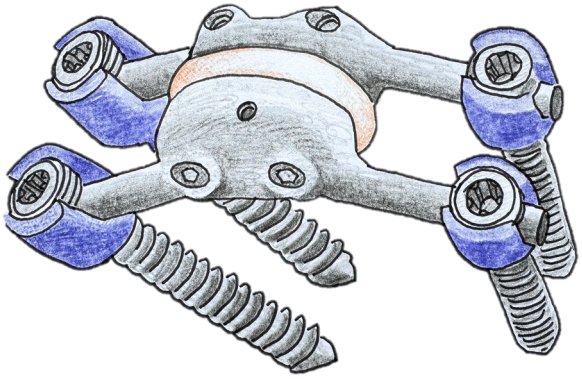
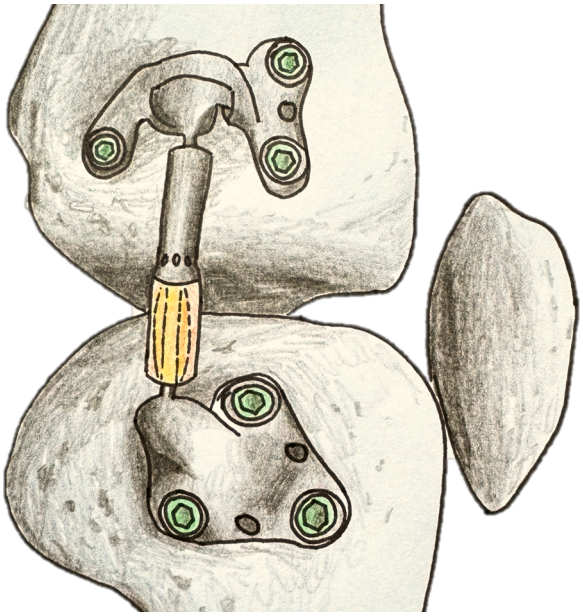
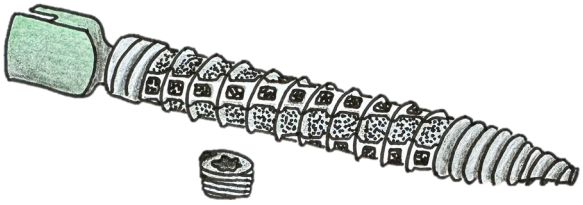
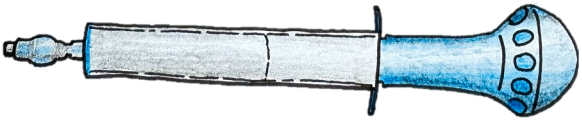
A search of the FDA's Breakthrough Devices Program statistical summary [9] revealed eight orthopedic technologies which have received the breakthrough device designation and marketing authorization, shown in Table 1

Trends in orthopedic breakthrough devices

The devices identified and shown in Table 1 illustrate the breadth and diversity of breakthrough orthopedic devices. Some devices represent novel modifications to existing types of devices, such as the iFuse Bedrock® system, incorporating additively manufactured fenestrations into an SI screw, or the aprevo® interbody device, using 3D-printing to custom manufacture implants unique to patients. While certainly novel, these devices were still able to obtain clearance through the 510(k) pathway. Other devices, however, proposed new types of products such as the MISHA knee system, the first ever implantable shock absorber for the knee, or the CERAMENT® G, the first ever antibiotic-eluting bone void filler. Half (4/8) of the orthopedic BDD devices were granted De Novo, demonstrating their novelty and the lack of relevant predicates. Average decision time of breakthrough orthopedic devices was 128 days for 510(k), 295 days for De Novo, and 332 days for PMA.

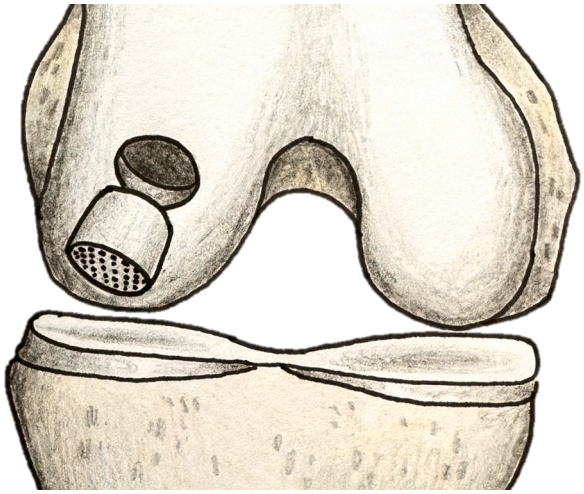
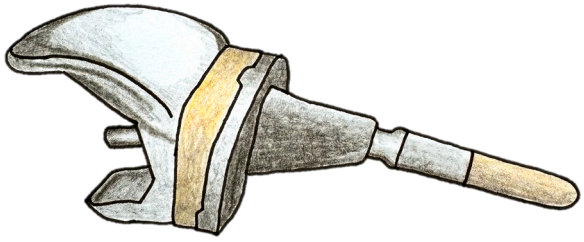
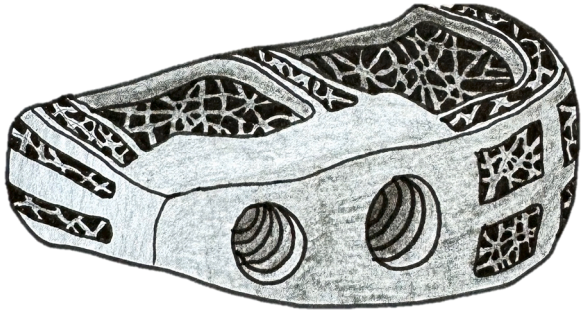
Several technological trends can be identified across these devices. All eight technologies were implantable and therapeutic as opposed to non-implantable or diagnostic. Shared technological themes included new substance/material development (2/8), 3-D printing of lattice structures (2/8), bioresorption (2/8), and motion-preservation with flexible components (2/8). Other unique characteristics included "smart" implants for patient monitoring (1/8) and patient-specific implants (1/8). These characteristics provide insight into technological developments in the field. However, their diversity also illustrates how innovative devices can obtain BDD through different technological approaches.

Table 1
Orthopedic Technologies Receiving Breakthrough Device Designation.

Representative Image	Device Name (Manufacturer)	Description	Date Cleared/ Approved	Pathway (Number) (Decision Time)	Product Code
	TOPS™ System (Premia Spine Ltd., Israel) [16]	A posterior spinal implant designed to both stabilize and preserve joint range of motion in the lumbar spine. The central capsule (titanium alloy and polycarbonate urethane) is intended to mimic the function of the facet joints. **Key innovations: flexible components**	06/2023	PMA (P220002) (484 days)	QWK
	MISHA Knee System (Moximed Inc., CA, USA) [17]	A shock absorber implant for unloading the medial knee compartment. Device includes two titanium base plates (distal femur and proximal tibia attachment) and a polycarbonate urethane shock absorber cylinder. **Key innovations: flexible components**	04/2023	De Novo (DEN220033) (308 days)	QVV
	RemeOs™ Screw LAG Solid (Bioretec Ltd., Finland) [18]	A resorbable magnesium-based lag screw (alloyed with zinc and calcium). **Key innovations: bioresorbtion**	03/2023	De Novo (DEN220030) (329 days)	QJD
	iFuse Bedrock® Granite Implant System (SI-BONE Inc., CA, USA) [19]	A titanium tulip head screw for sacro-iliac (SI) joint fixation and fusion. Device consists of a tulip head, a smooth internal shank, and a 3D-printed textured, porous external sleeve which mimics cancellous bone. **Key innovations: 3D printing of lattice structure**	05/2022	510(k) (K220195) (122 days)	OUR (NKB, OLO subsequent codes)
	CERAMENT® G (BoneSupport AB, Sweden) [21]	An injectable synthetic bone void filler for promoting ingrowth in bone defects. The filler consists of 40 % hydroxyapatite, 60 % calcium sulfate, and an antibiotic (gentamicin sulfate).	05/2022	De Novo (DEN210044) (231 days)	QRR

(*continued on next page*)

Table 1 (*continued*)

Representative Image	Device Name (Manufacturer)	Description	Date Cleared/ Approved	Pathway (Number) (Decision Time)	Product Code
		Key innovations: new substance/material use, microbial contamination prevention			
	Agili-C™ (CartiHeal Ltd., Israel) [22]	A porous, resorbable, bi-phasic scaffold for repairing cartilage and osteochondral defects. The scaffold consists of natural inorganic calcium carbonate (aragonite). **Key innovations: new substance/material use, bioresorbtion**	03/2022	PMA (P210034) (180 days)	QRU
	Canary Tibial Extension With Canary Health Implanted Reporting Processor (CHIRP®) System (Canary Medical, Inc., Canada) [23]	A tibial extension component of the Zimmer Persona IQ total knee arthroplasty (TKA) system which provides kinematic data post-operatively following TKA. Internal motion sensors are used to collect data pertaining to patient gait and activity level. **Key innovations: "smart" implants for patient monitoring**	08/2021	De Novo (DEN200064) (312 days)	QPP
	aprevo® Intervertebral Body Fusion Device (Carlsmed, Inc., CA, USA) [20]	A personalized titanium lumbar interbody fusion device that is 3D-printed to be specific to each patient. **Key innovations: patient-specific, 3D printing of lattice structure**	12/2020	510(k) (K202034) (133 days)	MAX

Note: For devices with breakthrough designations received for multiple product iterations, the originally designated device is referenced here. Only legally marketed orthopedic devices that received BDD are shown. FDA does not publish devices which have received BDD but have not received marketing authorization. Images were hand drawn by the author and are intended to be merely approximate representations of the cited devices.

FDA pathways for orthopedic devices

Prior to commercial use, all orthopedic devices must obtain marketing authorization through one of the FDA's regulatory pathways. This is required regardless of whether devices receive breakthrough designation. The three major pathways include the 510(k), De Novo, and PMA. Fig. 1 shows the number of new orthopedic devices that have received FDA marketing status through each pathway in the last 10 years.

Premarket notification – 510(k)

Overview

For Class II orthopedic devices, the premarket notification, or 510 (k), allows manufacturers to seek timely authorization of their device if they can demonstrate that it is 'substantially equivalent' to a predicate device in terms of its intended use and technological characteristics. To be deemed substantially equivalent, proposed devices must have the same intended use but can differ in technological characteristics so long as the manufacturer demonstrates that no new concerns arise regarding

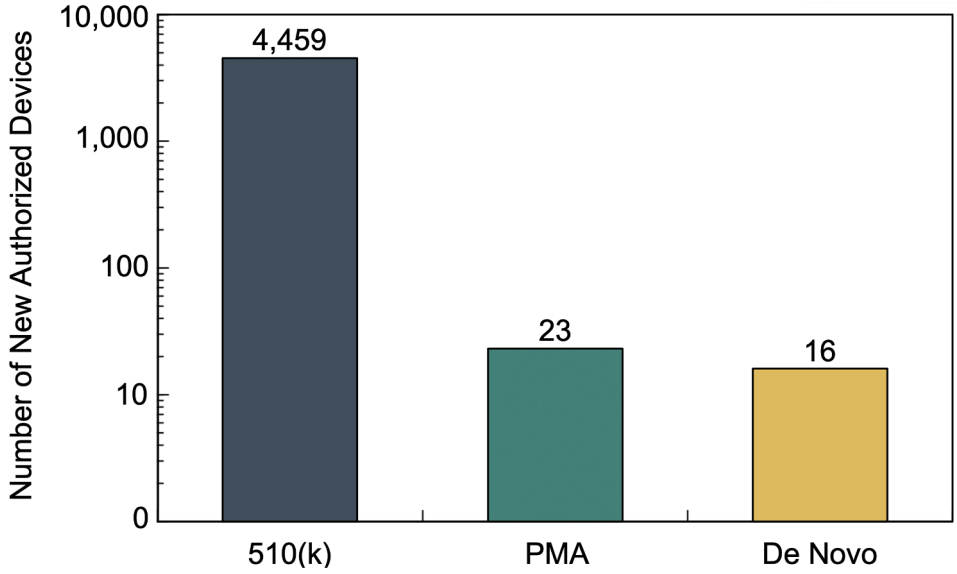


Fig. 1. Number of new orthopedic devices receiving FDA marketing authorization per pathway between July 2014 and July 2024. Only original submissions were included for each pathway. 510(k) clearances included Traditional ($N = 4443$) and Abbreviated ($N = 16$) types and did not include Special types. PMA records indicated 23 original submissions and 1116 non-originals (i.e. supplements for manufacturer changes, design changes, post approval study protocols, etc.).

device safety and effectiveness [24]. The FDA outlines standardized device-specific testing and can request additional testing for 510(k) submissions, though this rarely requires clinical data [25,26].

Summary statistics

4459 orthopedic devices have received 510(k) clearance in the last 10 years. This represents by far the most commonly used regulatory pathway for new orthopedic devices, as shown in Fig. 1, with a pathway usage rate of 99 %. Screw fixation into bone (HWC) was the most commonly listed product code (8.3 % of traditional 510(k) clearances), while five of the top ten product codes relate to spine. A breakdown of anatomical targets for all traditional 510(k)s reviewed is shown in Fig. 2. Spine was the most common anatomical target (38 %) followed by bone (multiple regions) (26 %), hip (13 %), and knee (8 %). While decision time was not calculated for all records, previous studies have found average decision time for 510(k) submissions to be approximately 180 days, though reported times vary considerably [27–29].

The challenge for highly innovative devices

The fundamental challenge for highly innovative devices seeking 510(k) clearance is that there exists an inherent dilemma between *innovation* to address unmet needs and *imitation* to demonstrate substantial equivalence. The 510(k) pathway certainly yields innovative orthopedic devices, yet the degree to which they are novel or incorporating new technologies must be limited to remain eligible. If a device is *too* innovative, it must go through the more burdensome De Novo or PMA pathway (described in the following subsections).

Some strategies have emerged to address this challenge. First, manufacturers of innovative devices can have conversations with FDA early in the product development process through pre-submission meetings.

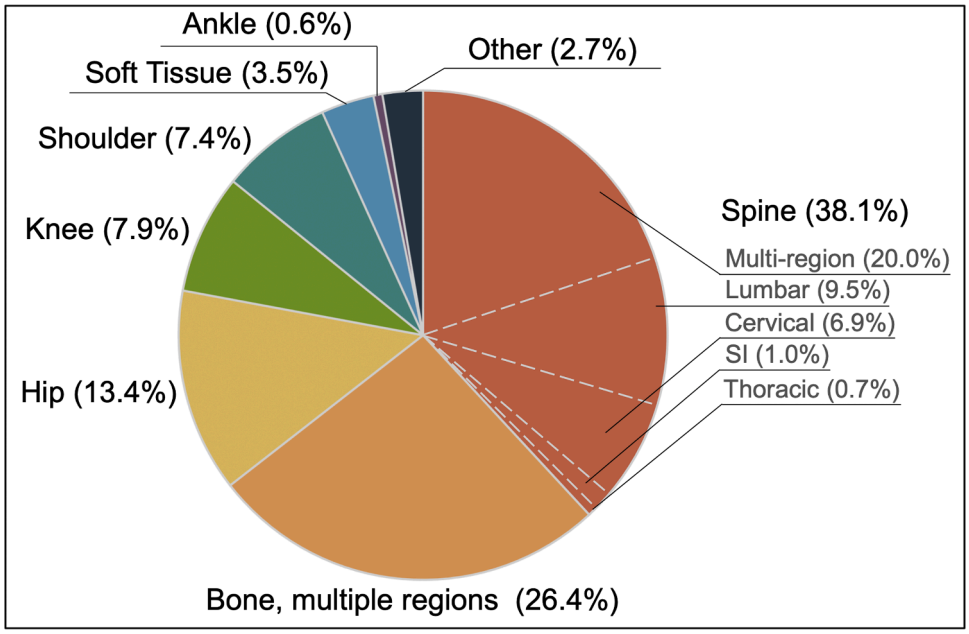


Fig. 2. Breakdown of anatomical targets for orthopedic devices receiving Traditional 510k clearance between July 2014 and July 2024.

This allows manufacturers to define testing requirements, and thus begin to constrain the type and degree of technological differences compared to available predicates [30]. Second, regulatory strategies can be and often are formed around multiple 510(k) clearances, developing and validating new technological innovations in sequence, as opposed to in conjunction [31]. SI Bone Inc.'s (Santa Clara, CA) breakthrough sacroiliac fusion technology is one such example. The recently cleared iFuse Bedrock® system (K220195) follows a trail of over 10 previous SI-Bone, Inc. iFuse 510(k) clearances used as predicates dating back to 2008 (K080398), which has included both manufacturing changes and expanded indications. Third, substantial equivalence rationales can be considered early in the product development process. Design decisions around device characteristics (dimensions, materials, principles of operation, etc.) can be made early to achieve similar specifications and performance metrics to available predicates. While many "design for" axioms inform product development strategy (i.e. design for manufacturability, design for assembly, etc.), perhaps a "design for regulatory clearance" (DfRC) approach best describes the strategic perspective device manufacturers have developed to innovate new devices that remain eligible for the 510(k) pathway. Still, certain innovations proposing new types of low-moderate risk devices with no available predicates, will require a De Novo classification request.

De novo

Overview

The De Novo classification request is a risk-based regulatory pathway for low to moderate risk devices which are deemed novel by the absence of predicate devices already on the market. Typically, manufacturers submit a De Novo request directly, though in some cases submission follows a not substantially equivalent (NSE) determination to a 510(k) submission [32]. Manufacturers work with the FDA to establish appropriate general controls and special controls (for Class II devices) that allow FDA to conclude there is reasonable assurance the device is safe and effective for its intended use. This often requires clinical data, contributing to the De Novo process being lengthier [28,32] and more costly [33] than its counterpart, the 510(k) pathway.

Identified devices

A search of the FDA's De Novo database [12] revealed 16 orthopedic technologies which have been granted a De Novo request, as shown in Table 2.

Trends in orthopedic de novo devices

The devices shown in Table 2 highlight innovative and novel orthopedic technologies over the last seven years. These orthopedic De Novo devices were therapeutic and generally implantable, with only the Osteoboost® belt, Ruthless Spine RJB™, OsteoProbe®, and LoadPro™ sensor being non-implantable. Average decision time for orthopedic De Novo devices was 359 (±196) days. Decision time was faster for orthopedic De Novo devices with breakthrough designation (295 ± 44 days, $N = 4$) compared to those without (380 ± 223 days, $N = 12$), though the difference was not significant ($p = 0.47$).

Shared technological themes included bioresorption (4/16), flexible components (4/16), new substance/material use (3/16), intraoperative device expansion (3/16), "smart" instruments (3/16), and microbial contamination prevention (3/16). Other unique characteristics included 3D printing of lattice structures (1/16), wearable devices (1/16), "smart" implants for patient monitoring (1/16), and photodynamic solidification (1/16).

Market competition considerations with de novo

In some ways, a device that is granted a De Novo classification opens the doors to competitors using the device as a predicate for a subsequent 510(k) submission. However, the nature of the De Novo pathway – in which the sponsor of the granted device sets the requirements for any future devices of the same product code – creates opportunities for De Novo applicants to increase barriers to entry for competitors. De Novo applicants with medium-risk devices propose to FDA special controls that, when met, provide reasonable assurance of the safety and effectiveness of the newly classified device type. Manufacturers can use this to their advantage by linking the special controls with their patented fundamental technological characteristics, creating barriers for competitors looking to use their device as a predicate in a 510(k) submission.

The first De Novo classified orthopedic device, the IlluminOss® system, serves as a useful example for how De Novo orthopedic applicants may obtain protection from competitors. IlluminOss Medical has been granted patents on their novel technology [46] which claim "a device for repairing a bone comprising a balloon portion configured for placement into a cavity of a bone", among other characteristics, such as curing methods for injected materials. The special controls for the new product code QAD (in vivo cured intramedullary fixation rod) require testing device aspects including "the integrity of the balloon", "the reliability and accuracy of the curing method", and "the temperature rise during curing". To obtain a 510(k) clearance as a competitor QAD device manufacturer, one must show to the FDA that their device is in fact a balloon-based cured IM rod that meets these special controls, while also not infringing on IlluminOss's patent claims. With the special controls requiring testing of the very technological features that are patented, major challenges are created for competitors. Conversely, major opportunities are created for follow-on development by IlluminOss through the 510(k) pathway. To date, all 510(k) submissions of this device type (QAD) belong to IlluminOss.

This example is a result of a highly innovative technology which warrants new and specific special controls to evaluate safety and performance. However, other cases involving anticompetitive strategies through the De Novo process for product types of other medical device specialties have been identified and criticized [32,47]. The agency has issued guidance on De Novo special controls, however, they have not assumed the posture of reviewing applicants' proposed special controls to prevent patent blocking, as some have called for [47].

Premarket approval (PMA)

Overview

The premarket approval pathway is the pathway by which manufacturers obtain regulatory approval for their high-risk Class III devices, for which general and special controls alone are insufficient to satisfy safety and effectiveness questions. Unlike Class II devices, manufacturers cannot claim substantial equivalence to already marketed devices of the same product code to ease their path towards marketing authorization. The PMA pathway requires extensive non-clinical and clinical data to rigorously assess the safety and effectiveness of high-risk devices, resulting in significantly greater time and capital investments from manufacturers compared to the pathways for class II devices.

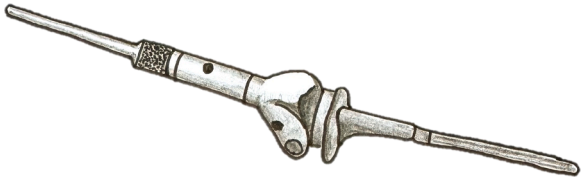
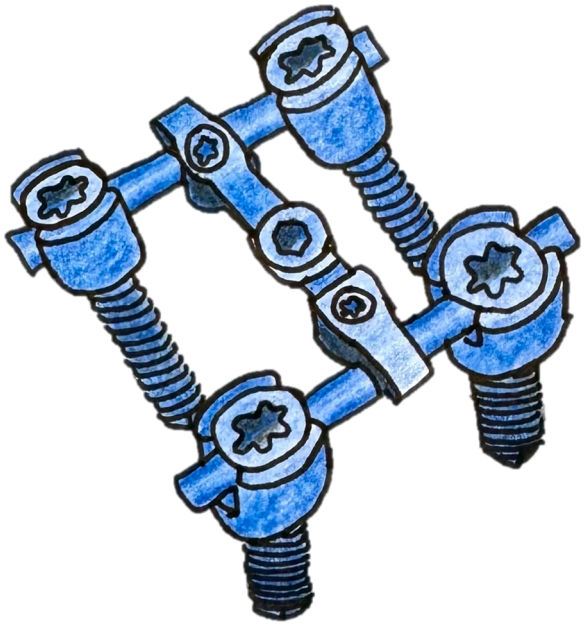
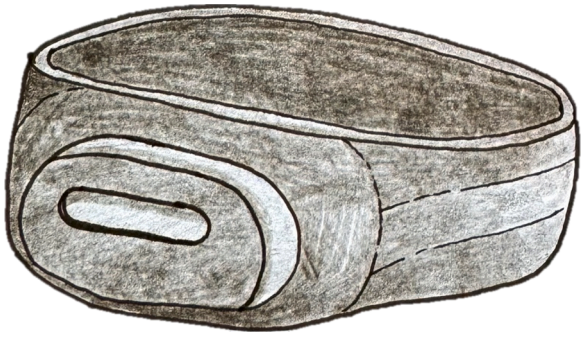
Summary statistics

A search of the FDA's PMA database [11] revealed 23 original submission PMA approvals for orthopedic devices in the last 10 years. 1116 additional supplement records were approved in the same time span. Fig. 3 shows a breakdown of the PMA orthopedic devices by product code. The four device types with multiple new device approvals in the last 10 years were intraarticular hyaluronic acid treatment (MOZ), intervertebral disc prostheses (MJO), bone growth stimulators (LOF), and bone void fillers (NOX). Decision time varied significantly, with an average of 547 ± 480 days, as short as 153 days (for a hyaluronic acid treatment), and as long as 2035 days (for a bone void filler combination device).

PMA pathway considerations

Importantly, the interplay between innovation and regulatory complexity is different for Class II and Class III devices. Generally, for

Table 2
Orthopedic Devices Granted FDA De Novo Status.

Representative Image	Device Name (Manufacturer)	Description	Date De Novo Granted	De Novo Number (Decision Time)	Product Code	Clinical Testing Submitted?
	ELEOSx™ Limb Salvage System (Onkos Surgical, NJ, USA) [34]	A limb salvage implant system for the hip and knee with a quaternary ammonium compound coating intended to reduce bacterial contamination prior to implantation. **Key innovations: microbial contamination prevention, 3D printing of lattice structure**	04/ 2024	DEN210058 (827 days)	QZZ	No. Not required in special controls.
	Orthobond Mariner Pedicle Screw System (Orthobond Corporation, NJ, USA) [35]	A spinal fusion pedicle screw system with quaternary ammonium compound coating. The coating is intended to reduce microbial surface contamination prior to implantation. **Key innovation: microbial contamination prevention**	04/ 2024	DEN220015 (767 days)	QZY	No. Not required in special controls.
	Osteoboost® Belt (Bone Health Technologies, Inc., CA, USA) [36]	A vibration belt designed to reduce the loss of bone strength and bone density in postmenopausal women. **Key innovations: wearable device**	01/ 2024	DEN230015 (329 days)	QZO	Yes. $N = 126$, 12-month randomized, sham controlled, prospective trial.

(*continued on next page*)

Table 2 (*continued*)

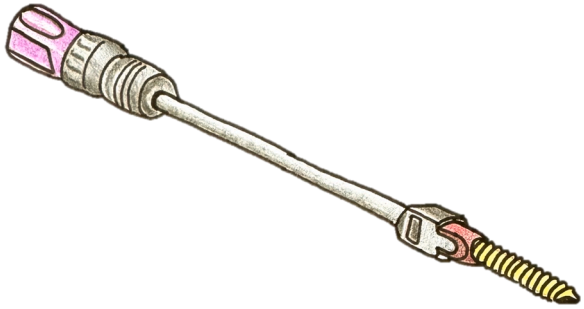
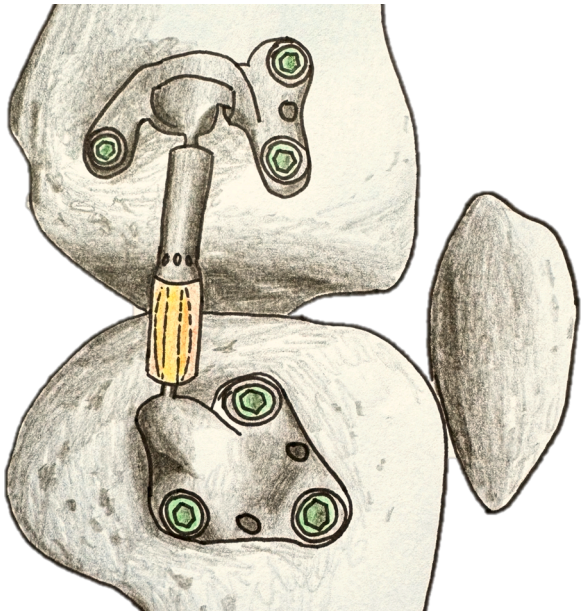
Representative Image	Device Name (Manufacturer)	Description	Date De Novo Granted	De Novo Number (Decision Time)	Product Code	Clinical Testing Submitted?
	Ruthless Spine RJB™ (Ruthless LLC, CA, USA) [37]	A single-use intraoperative device which measures the angles of surgical instruments in two planes, relative to a vertical vector in line with gravity. **Key innovations: "smart" instruments**	07/ 2023	DEN230012 (148 days)	QWL	No. Not required in special controls.
	MISHA Knee System (Moximed Inc., CA, USA) [17]	A shock absorber implant for unloading the medial knee compartment. Device includes two titanium base plates (distal femur and proximal tibia attachment) and a polycarbonate urethane shock absorber cylinder. **Key innovations: flexible components**	04/ 2023	DEN220033 (308 days)	QVV	Yes. $N = 81$ prospective, multi-center 5-year study with 24-month results published.
	RemeOs™ Screw LAG Solid (Bioretec Ltd., Finland) [18]	A resorbable magnesium-based lag screw (alloyed with zinc and calcium). **Key innovations: bioresorbtion**	03/ 2023	DEN220030 (329 days)	QJD	Yes. $N = 20$ prospective, non-randomized study.

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Table 2 (*continued*)

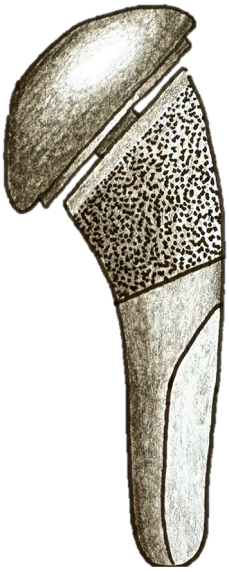
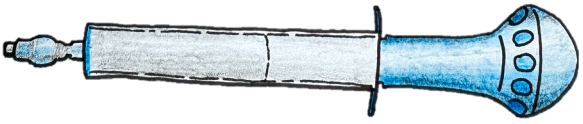
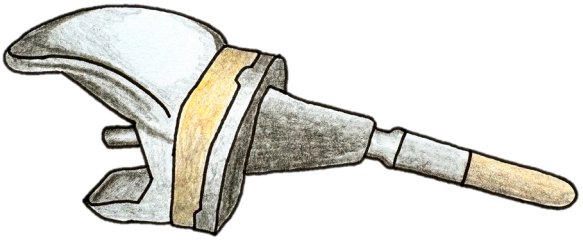
Representative Image	Device Name (Manufacturer)	Description	Date De Novo Granted	De Novo Number (Decision Time)	Product Code	Clinical Testing Submitted?
	Tornier Pyrocarbon Humeral Head (Tornier SAS, France) [38]	A humeral head device with a pyrolytic carbon head and metallic stem for use in hemi shoulder arthroplasty. **Key innovations: new substance/ material use**	12/ 2022	DEN220012 (311 days)	QKW	Yes (G140202). *N* = 157, 24-month prospective, multi-center, non-inferiority trial.
	CERAMENT® G (BoneSupport AB, Sweden) [21]	An injectable synthetic bone void filler for promoting ingrowth in bone defects. The filler consists of 40 % hydroxyapatite, 60 % calcium sulfate, and an antibiotic (gentamicin sulfate). **Key innovations: new substance/ material use, microbial contamination prevention**	05/ 2022	DEN210044 (231 days)	QRR	Yes. Required in special controls. Data not available.
	Canary Tibial Extension With Canary Health Implanted Reporting Processor (CHIRP®) System (Canary Medical, Inc., Canada) [23]	A tibial extension component of the Zimmer Persona IQ total knee arthroplasty (TKA) system which provides kinematic data post-operatively following TKA. Internal motion sensors are used to collect data pertaining to patient gait and activity level. **Key innovations: "smart" implants for patient monitoring**	08/ 2021	DEN200064 (312 days)	QPP	No. Not required in special controls.
	OsteoProbe® (Active Life Scientific, Inc., CA, USA) [39]	A cortical bone microindentation device to measure the bone material strength index (BMSi). **Key innovations: "smart" instruments**	08/ 2021	DEN210013 (142 days)	QGQ	Yes (G200139). *N* = 40, single-center open label study.

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Table 2 (*continued*)

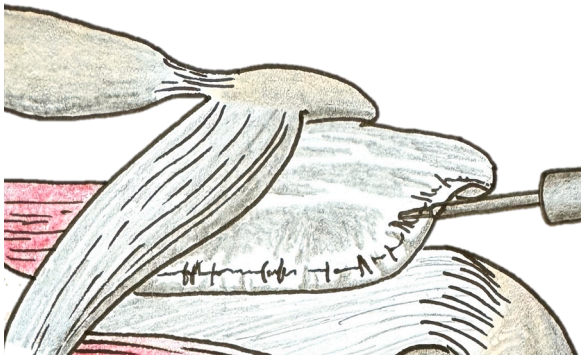
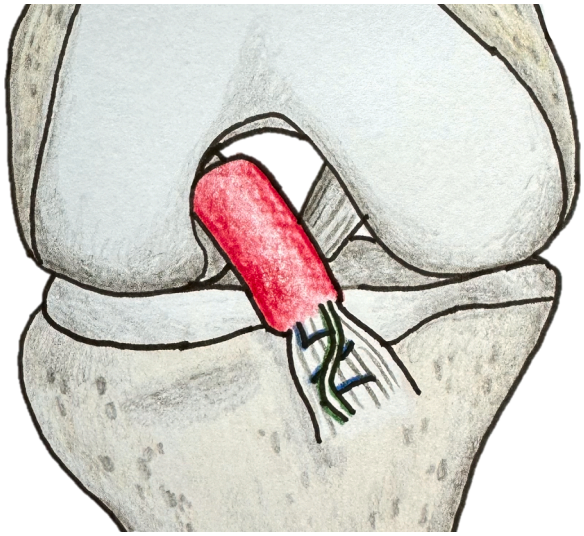
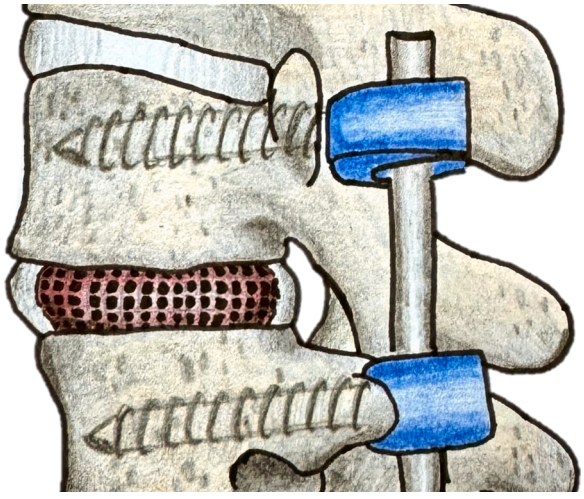
Representative Image	Device Name (Manufacturer)	Description	Date De Novo Granted	De Novo Number (Decision Time)	Product Code	Clinical Testing Submitted?
	InSpace™ Subacromial Tissue Spacer System (Ortho-Space Ltd., IL, USA) [40]	A resorbable shoulder spacer which acts as a temporary subacromial spacer in patients with significant rotator cuff tears. A deployer is used to deploy, inflate with saline, seal, and detach the implant. **Key innovations: bioresorbtion, flexible components, intraoperative device expansion**	07/ 2021	DEN200039 (395 days)	QPQ	Yes. *N* = 184, 24-month randomized, non-inferiority prospective trial.
	BEAR® (Bridge-Enhanced ACL Repair) Implant (Miach Orthopaedics, Inc., MA, USA) [41]	A sponge-like cylindrically shaped resorbable implant comprised of bovine-derived extracellular matrix and collagen. The implant is injected with the patient's own blood and fixed to both ends of a torn ACL. **Key innovations: bioresorbtion, new substance/ material use**	12/ 2020	DEN200035 (195)	QNI	Yes. (G150268). *N* = 100, 24-month single-center randomized trial.
	Spineology Interbody Fusion System (Spineology, Inc., MN, USA) [42]	A lumbar interbody fusion device consisting of a polyethylene terephthalate (PET) mesh bag which contains allograft and/or autograft. The device is supplemented with posterior fixation. **Key innovations: flexible components, intraoperative device expansion**	09/ 2020	DEN200010 (212 days)	OQB	Yes. (G140140). *N* = 96, 24-month multi-center prospective trial.

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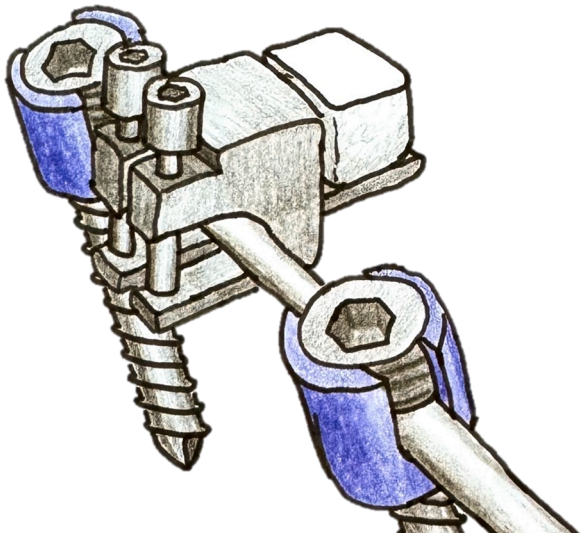
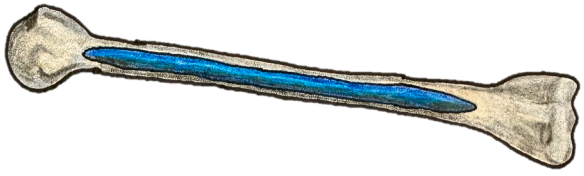
Table 2 (*continued*)

Representative Image	Device Name (Manufacturer)	Description	Date De Novo Granted	De Novo Number (Decision Time)	Product Code	Clinical Testing Submitted?
	Ogmend® Implant System (Woven Orthopedic Technologies, LLC, CT, USA) [43]	A woven polyethylene terephthalate (PET) sleeve which fits between a metallic screw's threads and a drilled hole in bone. The device uses interference fit to restore stability of a fracture fixation plate after screw loosening, breakage, backout, etc. **Key innovations: bioresorbtion, flexible components**	05/ 2020	DEN180065 (505 days)	QAC	No. Not required in special controls.
	LOADPRO™ Intraoperative Rod Strain Sensor (Intellirod Spine, Inc., OH, USA) [44]	A device which provides mechanical strain readings for rods used in pedicle screw and rod systems. **Key innovations: "smart" instruments**	03/ 2019	DEN180012 (379 days)	QFP	No. Not required in special controls.
	IlluminOss® Bone Stabilization System (IllminOss Medical, Inc., RI, USA) [45]	An in vivo cured intramedullary fixation rod which consists of a balloon inserted into the medullary canal of long bones for fracture fixation. The balloon is infused with a liquid monomer which cures and solidifies once exposed to visible spectrum light. **Key innovations: photodynamic solidification, intraoperative device expansion**	12/ 2017	DEN160062 (356 days)	QAD	Yes. Not required in special controls. $N = 81$, 12-month, multi-center non-inferiority prospective trial.

Note: Images were hand drawn by the author and are intended to be merely approximate representations of the cited devices.

class II devices, the degree to which a device is innovative significantly affects its regulatory pathway and its required testing since it must show substantial equivalence to a predicate device for a 510(k) clearance. For class III devices, however, innovation is not as confining, and the introduction of new features does not necessarily create additional regulatory hurdles. This is because the PMA process evaluates devices primarily through rigorous clinical testing as opposed to engineering rationales and comparative non-clinical testing against other devices.

Discussion

The orthopedic device landscape continues to rapidly evolve as new technologies, materials, and device types are introduced. Obtaining regulatory authorization for highly innovative orthopedic devices often presents challenges given current regulatory infrastructure. This article provides both an overview of highly innovative orthopedic devices over the last 10 years as well as considerations for FDA regulatory pathways available to manufacturers of such devices.

Characteristics of innovative orthopedic devices

The survey of orthopedic breakthrough designated and De Novo devices illustrated the breadth and diversity of innovation over the last 10 years. The most common technological trends of these devices (N = 20 total) included bioresorption (N = 5), flexible components (N = 5), new substance/material use (N = 4), 3D printing of lattice structures (N = 3), intraoperative device expansion (N = 3), "smart" instruments (N = 3), and microbial contamination prevention (N = 3). Many of these characteristics suggest continued efforts towards devices with 'dynamic' elements, either in their ability to resorb over time, elastically deflect under physiological load to restore joint motion, or change configuration during surgical insertion. Several of these innovation thrusts are correlated to minimally invasive techniques, in which implants resorb to restore natural anatomy after healing, for example, or procedures requiring smaller incisions through initially compact devices that expand/deploy once in the body. These trends allow us to understand certain areas of orthopedic innovation and may be indicators of continued trajectory. However, a major finding from surveying these devices is the absence of overly unified or dominant trends; instead, these devices portray a technological mosaic of diverse innovations across orthopedic applications.

Pathway usage statistics

The analysis of pathway usage demonstrated the overwhelming dependence of orthopedic devices on the 510(k) pathway. Of the 4505 new orthopedic devices receiving FDA authorization in the last 10 years, 4459 (99 %) were cleared through the 510(k) process (Fig. 1). The rate of orthopedic device dependence on the 510(k) pathway has been found to be greater than for other non-orthopedic specialty devices [48] and recent studies have suggested this trend is increasing [49]. Another important finding is that spinal devices comprise the largest percentage of new authorized devices during the study period. 38 % of all new orthopedic 510(k) clearances and 25 % of orthopedic De Novo classifications were for spinal applications. Some have correlated this increase in spinal device innovation to expanding surgical intervention [50] and reimbursement increases [51,52].

Decision time

Average decision time for orthopedic devices across each major pathway is shown in Fig. 4. Decision time for the De Novo and PMA pathways was 359 (±196) and 547 (±480) days, respectively (p = 0.15). While decision time was not analyzed for all 510(k) orthopedic devices, other studies have found 510(k) total decision time to be around 180 days [27–29]. Importantly, orthopedic devices receiving breakthrough device designation had approximately 30 % shorter review times than respective averages in all three major pathways: 128 days for 510(k) (~30 % reduction), 295 days for De Novo (18 % reduction), and 322 days for PMA (41 % reduction). These improvements were not statistically significant due to either large variance or insufficient sample sizes. However, the early data suggesting decision time improvements with the Breakthrough Devices Program is promising, and statistical significance may arise as more orthopedic devices receive the designation.

De novo considerations

Novel Class II devices requiring the De Novo pathway have often been viewed as having a greater risk given that clinical evidence is typically required and that it could ease the path for follow-on competitors. However, two key considerations are relevant for such devices. First, as illustrated with a case study in this work, De Novo applicants have opportunities to create barriers to entry for competitors while easing opportunities for follow-on 510(k) submissions by the applicant. This is dependent on the novelty of the device and the strength of its patent claims, as well as the degree to which the special controls are tied to such claims. Second, market adoption of innovative orthopedic devices is often dependent on clinical evidence. Thus, the cost and time associated with conducting clinical studies for a De Novo classification may be justified if the clinical data is going to be needed for physician

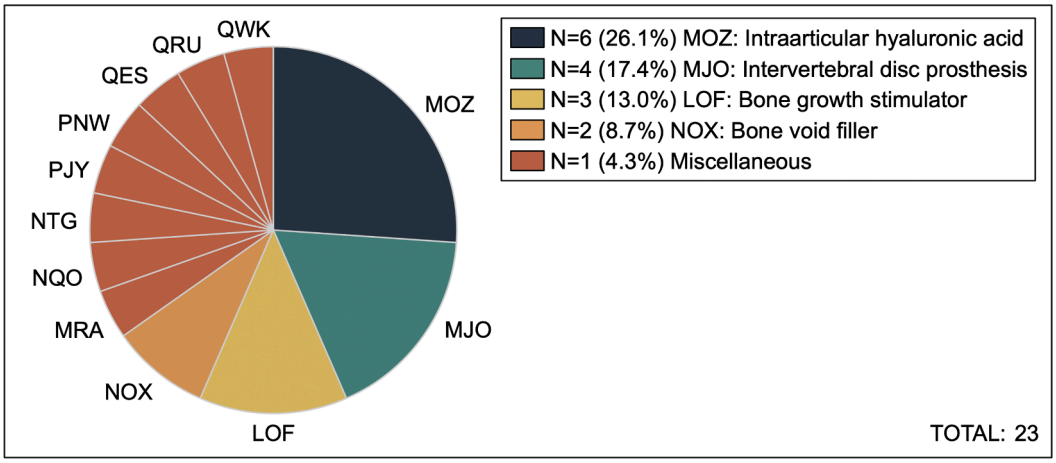


Fig. 3. Breakdown of product codes of orthopedic devices receiving PMA approval between July 2014 and July 2024. Results include original submissions only, excluding supplement PMA records.

adoption regardless of the regulatory pathway. By conducting clinical testing as part of the De Novo classification, sponsors can create a competitive barrier by requiring any competitors to complete equivalent clinical testing.

Regulatory infrastructure and orthopedic innovation

This review demonstrates that new orthopedic devices are highly reliant on the 510(k) pathway, with a 99 % pathway usage rate over the last 10 years. This finding warrants a fundamental question around whether current regulatory infrastructure discourages breakthrough innovation. In many ways, the affordability and rapid pace of the 510(k) pathway may have steered manufacturers towards smaller, incremental innovation to keep new product releases eligible. However, innovation through the 510(k) pathway is still evidently robust, as observed through the growth in new orthopedic device clearances [49], of which some are now receiving breakthrough device designation. Further, as this work has shown, FDA has made significant progress to encourage development of highly innovative orthopedic technologies through the Breakthrough Devices Program and the De Novo pathway. Recent beneficiaries of these initiatives include "smart" knee arthroplasty components, antibiotic-eluting bone void fillers, resorbable magnesium bone screws, and knee shock absorber implants – all highly novel medium-risk devices which received Breakthrough designation and obtained FDA De Novo authorization in under 300 days, on average.

It is difficult to speculate what the future interplay between regulatory policy and orthopedic device innovation may look like, especially with the emergence of new technologies like artificial intelligence. Nevertheless, it must be acknowledged that manufacturers' decisions to invest in the development of new devices is strongly influenced by regulatory policy [29]. The fact that 99 % of orthopedic devices in the last 10 years have utilized the 510(k) pathway suggests it is often financially more desirable to pursue new *iterations* of devices as opposed to entirely new *types* of devices. As diagnostic and therapeutic technologies continue to advance, FDA may need to further modify programs and policies to incentivize more investment in breakthrough innovation. For example, this could include: adjusting application fees and availability of review staff for De Novo devices; advancing the adoption of potentially accelerated methods of device evaluation (such as *in silico* clinical trials or computational modeling as performance evidence) for class II devices; or providing additional opportunities for startups and small business given that they are known to be major contributors of breakthrough innovation, particularly in the orthopedics industry. It must also be acknowledged, however, that novel devices bring new risks that should be appropriately evaluated, and accelerating the regulatory authorization of novel devices cannot come at the cost of patient safety. Arguably the most important step moving forward is to ensure that all stakeholders – including regulators and manufacturers, as well as physicians, payors, and patients – maintain discourse to understand and navigate the many pressures and influences on future orthopedic innovation.

Limitations

This review has some limitations worth noting. First, analysis was limited to the FDA's databases. Other international regulatory bodies were not analyzed, such as the Medical Device Regulations (European Union), HealthCanada, and the Therapeutic Goods Administration (Australia), which are known to regulate medical devices differently [53]. Second, FDA does not publicize breakthrough designated devices not yet authorized, thus the number of breakthrough orthopedic devices is likely much larger than the eight reviewed in this article. Third, individual analysis of all orthopedic 510(k) devices was not conducted due to the large number of clearances. This, combined with the limited nature of publicly available 510(k) substantial equivalence rationales prevented determining key innovations for such devices, and prevented uncovering more specific strategies employed by manufacturers to obtain clearances for innovative Class II devices. This also prevented obtaining precise decision time metrics for orthopedic devices during the study period; instead, approximate durations are obtained through references. Fourth, key innovations were assigned to each device systematically reviewed (BDD and De Novo orthopedic devices) to determine high level technological trends. These key innovations are determined qualitatively based on available device publications. Quantitative comparisons across devices (feature size, manufacturing process, etc.) are not compared due to limited public availability. Finally, this review offers comparisons of pathway usage for orthopedic devices, however, equivalent analyses for other non-orthopedic specialties are not conducted, which prevents head-to-head comparison over the last 10 years.

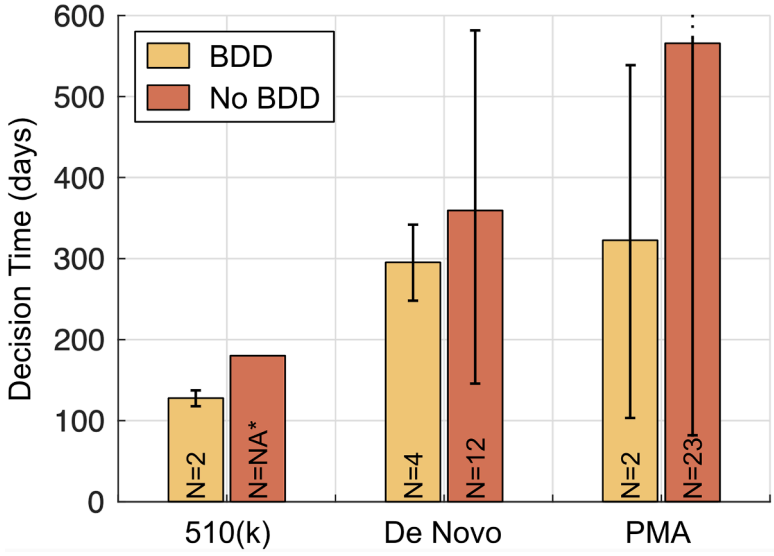


Fig. 4. Decision time for orthopedic devices with Breakthrough Device Designation (BDD) and without (No BDD). No comparisons were significant ($p < 0.05$) for any pathway due to large variance and/or insufficient sample sizes. *=data obtained by reference averaging.

Conclusion

Recent innovative orthopedic devices reviewed in this work had diverse features and orthopedic applications, but did possess shared technological trends including bioresorption, flexible components, and new substance/material use. Pathway usage statistics indicate orthopedic devices are highly dependent on the 510(k) pathway. However, the FDA Breakthrough Devices Program and De Novo pathway offer opportunities such as expedited review and potential market competition protection, respectively, for more innovative orthopedic technologies. As these programs continue to evolve and manufacturers continue to take advantage of these opportunities, orthopedic device development, which has primarily prioritized incremental innovation, may too evolve to produce more breakthrough innovations.

Ethical statement

This study adhered to the ethics and research standards of the journal. No ethical approval was sought for this research since this is a review article.

CRediT authorship contribution statement

Connor Huxman: Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

At the time of manuscript acceptance, the author is an employee of Spinal Simplicity, LLC. However, this work was entirely conceived, completed, written, and submitted during author's time at Penn State University prior to their current employment. The opinions expressed are those of the author and do not necessarily reflect the views of Spinal Simplicity, LLC. None of the technologies reviewed in this work belong to Spinal Simplicity, LLC or its affiliates.

Acknowledgements

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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