Pediatric Device Innovation

An Analysis of Food and Drug Administration Authorizations Over Time

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Background: Despite a tremendous increase in the number of orthopaedic devices authorized by the U.S. Food and Drug Administration (FDA), novel devices designed specifically for the pediatric population remain sparse. Surgeons frequently repurpose adult implants for "off-label" use in pediatric patients, with both legal and technical ramifications. This study seeks to objectively quantify and characterize the nature of pediatric device innovation over time.

Methods: The FDA employs 4 pathways for assessing safety and effectiveness of novel devices prior to authorization. Perceived device risk and novelty determine the pathway. Orthopaedic devices were identified from the FDA's online database. All devices approved since inception via the Humanitarian Device Exemption, Pre-Market Approval, and De Novo regulatory pathways were included and grouped as "highly innovative." Because of their number and the rapidity of their development, the evaluation of 510(k) devices was limited to those cleared from January 1, 2018, to December 31, 2022. Such 510(k) devices make up ~97% of devices and by definition are less risky and less novel. Approval statements were assessed for pediatric indications within the approved labeling. As a secondary analysis, the impact of company size on developing a product with a pediatric indication was analyzed.

Results: Of the 1,925 devices cleared via the 510(k) pathway, 9 (0.5%) were designed exclusively for pediatrics and 160 (8.3%) included pediatric indications. Five of the 9 pediatrics-only devices were for spine and 4 were for trauma indications. Of the 97 highly innovative devices, only 2 (2%) were exclusively pediatric and another 2 (2%) included pediatric indications. The 2 pediatrics-only devices were for the spine. Large and medium-sized companies were 1.9 times and 1.6 times more likely to bring to market a device with pediatric indications than a small company, respectively.

Conclusions: Innovation for pediatric orthopaedic devices lags substantially behind that for adult orthopaedic devices. These findings are consistent with clinical experience and the common practice of modifying adult implants for "off-label" use in pediatric patients. Despite long-standing efforts to stimulate innovation for this vulnerable population, our results suggest little progress.

Medical device innovation is vital to improve the daily lives of patients. Even though individuals ≤18 years old comprise nearly a quarter of the U.S. population, <10% of all health-care spending is devoted to pediatrics and <12% of the National Institutes of Health budget is devoted to pediatric research[1]. Furthermore, lower incidences of pediatric disease, higher relative costs of device development with lower prospects of profit, and challenges enrolling children in clinical trials have all led to an "innovation gap" regarding dedicated pediatric devices[2-4]. As a result, many orthopaedic surgeons opt to implant devices "off-label," or to modify adult-designed implants. However, pediatric patients have stark differences in physiology, growth and development, and metabolism, thereby necessitating devices with unique sizes and capabilities. Despite widespread acceptance of this innovation gap, there is little literature available that rigorously investigates the difference in novel adult versus pediatric devices approved by the U.S. Food and Drug Administration (FDA) over time[1,5-8].

There are 4 main pathways by which the FDA can authorize a novel device for marketing[9]. The appropriate pathway is determined by the perceived risk of the device and whether a similar device already exists on the market. The highest-risk devices, Class III (e.g., total disc replacement, ceramic total hip replacement), must undergo clinical trials and pass through the Pre-Market Approval (PMA) pathway. Class-III devices that are expected to be utilized in <8,000 patients per year in the U.S. are eligible for the Humanitarian Device Exemption (HDE) pathway. Moderate-risk devices, Class II (e.g., intramedullary nails, screws, most total joint

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replacements), go through the 510(k) pathway and must demonstrate "substantial equivalence" to an existing device, typically by providing biomechanical and other non-clinical data. Over 95% of devices reach the market via the 510(k) pathway. Finally, Class-II devices that are unique enough that no predicate device exists to establish "substantial equivalence" may be authorized through the De Novo pathway (Table I)[10].

The FDA estimates that pediatric device development experiences a lag of 5 to 10 years behind that of adult device development[4]. In recognition of this, in 2007, Congress passed the Pediatric Medical Device Safety and Improvement Act, which devoted funding to encourage pediatric device innovation[11]. However, the trend in pediatric orthopaedic devices is contrary to the orthopaedic surgery field as a whole, which has seen a steady increase in FDA device authorizations[12]. In a study analyzing only high-risk devices, Pathak et al. reported that 124 devices were approved from 2016 to 2021, of which only 2 were specifically for pediatric use[13]. Of further concern was the authors' finding that "most pediatric devices were studied in adult populations or in small numbers of pediatric patients."

To our knowledge, no literature exists that systematically examines orthopaedic device authorizations through each of the FDA regulatory pathways. In particular, we could not identify existing literature that included 510(k) devices, presumably because they are considered less innovative, but this leaves unanalyzed the largest segment of clinically relevant devices. The primary purpose of the present study was to calculate the proportion of novel devices with a primary and/or ancillary indication for pediatric use authorized by the FDA via each pathway. Secondary end points include identifying subspecialties for which manufacturers are more likely to develop devices with a pediatric indication and whether manufacturer size is associated with the development of a pediatrics-indicated device. We hypothesized that the percentage of devices primarily indicated for use in pediatrics would be substantially lower than this vulnerable population's proportionate representation.

Materials and Methods

From the FDA website, data on all devices authorized via PMA, HDE, De Novo, and 510(k) pathways were downloaded. By filtering with the FDA "Advisory Committee" set to "Orthopaedics," we obtained a list of all relevant devices. For PMA, HDE, and De Novo, devices were included that had been approved between the pathway inception (1976, 1990, and 1997, respectively) and December 31, 2022. Although the devices designed for each of these 3 pathways are distinctly different, because of their overall rarity we grouped them into a single "highly innovative" category to simplify conceptualization. For both PMA and HDE devices, manufacturers can submit post-marketing changes to the device as "supplements" to the FDA; however, in this investigation we included only original approval orders, similar to the methods utilized in a previous study[14]. The 510(k) devices were limited to those with clearance dates between January 1, 2018, to December 31, 2022, because of the volume and rapidity of development in this device group compared with the others. Devices cleared via the "Special 510(k)" pathway were excluded because they are intended only as minor modifications to existing 510(k) devices[15]. The manufacturer's name, date of device approval, and unique device identification numbers were recorded.

On the FDA website, summaries of the FDA authorization statements and approval orders, which include the device description, indication, and labeling, can be obtained by conducting a search with each device's unique identification number. Devices without this document were excluded. No device approved before 1994 had this summary available. Utilizing this document, devices were coded as indicated for "pediatrics only," "both pediatrics and adult," "adult only," and "not specified (NS)." Not-specified devices were later combined with adults-only for analysis because the lack of specific labeling for pediatric use would imply that the device is not primarily indicated for use in that population. Although the law mandates that information regarding pediatric use be published for novel drug and biologic products, no such requirement exists for devices. Because of this, labeling tends to

TABLE I FDA Device Approval Pathways

FDA Approval Pathway	Devices Approved	Purpose	Year of Conception
Pre-Market notification 510(k)	Class II (moderate risk); e.g., intramedullary nail	Device must exhibit substantial equivalence in efficacy and safety to a currently marketed device, typically by providing biomechanical and other non-clinical data.	1976
PMA	Class III (high risk); e.g., total disc replacement	Device must prove reasonable assurance of safety and effectiveness with clinical trials.	1976
HDE	Class III (high risk); e.g., osseointegration limb prosthesis	Humanitarian use devices that treat and/or diagnose conditions affecting <8,000 patients in the U.S. annually. Device must show probable benefits greater than probable risks.	1990
De Novo	Class II (moderate risk); e.g., spinal interbody fusion system	De Novo requests are granted to novel, moderate-risk devices without a predicate device against which substantial equivalence can be demonstrated.	1997

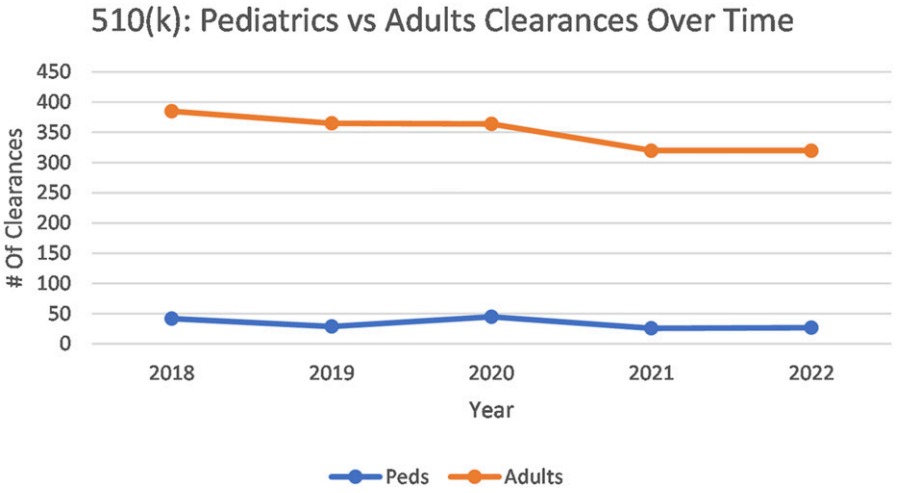

Fig. 1

Comparison of annual pediatric and adult novel 510(k) device clearances from 2018 to 2022. Pediatrics devices include those with any pediatric indication for use.

be less specific and does not necessarily follow FDA general guidelines that classify subgroups of pediatric populations as follows: infant (0 to 23 months old), toddler (2 to 11 years old), and/or adolescent (12 to 21 years old). For this investigation, pediatric was considered under the age of 18. Age limits were recorded when available; otherwise, the descriptive terms provided by the manufacturer (e.g., "adolescent") were utilized. The primary subspecialty (e.g., spine, trauma, etc.) was also recorded, as well as the manufacturer name and the date of approval. Data were recorded from the documents by 2 authors (K.S. and K.B.), with discrepancies resolved by consensus among 2 pediatric orthopaedic surgeons (C.G. and C.T.) and 1 trauma fellowship-trained orthopaedic surgeon (J.D.). During this review process, 4 devices were noted to be treating pectus excavatum and were excluded.

Microsoft Excel was utilized for simple descriptive statistics. As a secondary analysis, univariate logistic regression was utilized to assess the impact of company size on development of a device that included a pediatric indication. Manufacturer size for 510(k) devices was determined by the number of devices cleared during the study period: "micro" = 1 to 2 devices, "small" = 3 to 10 devices, "medium" = 11 to 20 devices, "large" = 21 or more devices. Lacking validated guidance, these ranges were chosen by consensus between J.D., C.G., and C.T.

Results

510(k)

There were 1,925 devices cleared via the 510(k) pathway during the 5-year study period, of which 9 (0.5%) were exclusively pediatric and 160 (8.3%) were indicated for both adult and pediatric use. Only 32 devices (18.9%) with a pediatric indication included the under-adolescent population. The proportion of cleared devices with a pediatric indication remained stable over the study period (Fig. 1).

Of the 9 pediatrics-only devices, 5 were spine "growing rod" implants and 4 were for trauma indications (3 epiphysiodesis plates and 1 flexible nail). Similarly, of the 160 devices indicated for both adult and pediatric use, spine and trauma subspecialties accounted for 65 (41%) and 73 (46%), respectively, with no other subspecialty contributing more than 10%.

Highly Innovative Devices

There were a total of 76 PMA, 11 HDE, and 9 De Novo-pathway devices included in the analysis. None of the PMA devices included were indicated for pediatric use. None of the De Novo-pathway devices were indicated for pediatrics-only use, but 1 (11%) was indicated for adult and adolescent use, with a sports subspecialty. There were 2 HDE-pathway devices (18%) indicated for pediatrics-only use, both with a spine subspecialty, and 1 (9%) approved for adult and pediatric use, with a tumor subspecialty. Table II shows subspecialty contributions to each pathway.

Analysis by Manufacturer Size

There were 464 unique manufacturers that brought a 510(k) device to market during the study period. Of these, 293

TABLE II Novel Highly Innovative Device Authorizations by Pathway and Subspecialty

Field	PMA	HDE	De Novo
Arthroplasty	33	0	1
Foot & ankle	8	1	0
Hand	2	3	0
Shoulder & elbow	1	0	2
Spine	27	4	2
Sports	1	0	1
Trauma	4	2	2
Tumor	0	1	1
No field	0	0	1
Total	76	11	10

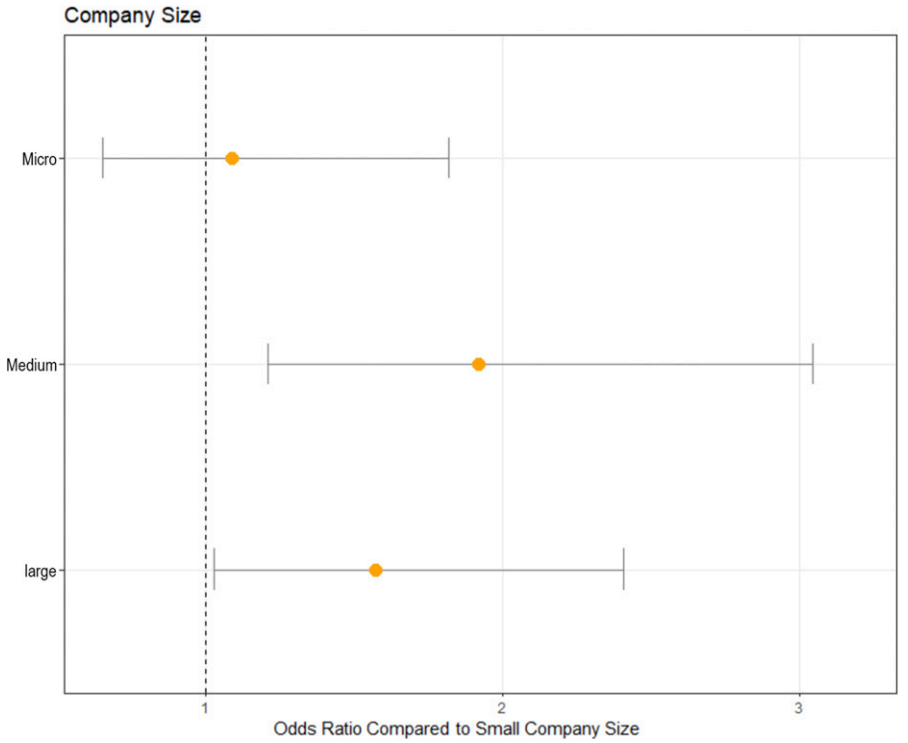

Fig. 2

Association of manufacturer size and pediatric device development. Relative to small companies, both large and medium-sized companies were more likely to develop a novel device with a pediatric indication. The error bars indicate the 95% confidence interval.

manufacturers (63.1%) were considered "micro" size; 130 (28%), "small;" 27 (5.8%), "medium;" and 14 (3.0%), "large." Compared with small companies, medium-sized companies were 1.9 times more likely (95% confidence interval [CI], 1.2 to 3.1) and large companies were 1.6 times more likely (95% CI, 1.0 to 2.4) to produce a device with a pediatric indication (Fig. 2). Of the 9 exclusively pediatric devices cleared during the study period, 6 (67%) were from large companies.

Discussion

The primary findings of this investigation demonstrate that novel devices indicated specifically for use in the pediatric orthopaedic population are exceedingly rare compared with those designed for use in adults. Over the 5-year study period, a total of 1,925 novel Class-II devices entered the market via the 510(k) pathway, and only 9 (0.5%) were primarily intended for children under the age of 18. Since the inception of the other FDA regulatory pathways intended to evaluate higher-risk and more innovative technologies, only 2 devices have been approved for use in the pediatric population, both through the HDE pathway. This innovation gap is concerning and deserves further exploration.

To our knowledge, the present study is the first to quantify and characterize medical device innovation in pediatric orthopaedics through each of the FDA's major authorization pathways. Several authors have uncovered similar findings in other fields. Pathak et al. reported that of the 124 PMA and HDE devices approved between 2016 and 2021, only 2 were for use in pediatrics only and 23 for use in adult and pediatric patients[13]. Lee et al. more comprehensively analyzed all PMA-approved devices from the pathway's inception up to 2020. Those authors found that 81 devices had pediatric indications, with most being for use in the ophthalmology and cardiovascular subspecialties. For medical devices, the FDA classifies pediatric as <21 years old. Lee et al. further refined their search to include only devices indicated for patients ≤17 years old, and the number of approved devices decreased nearly in half, to 42[6]. We were unable to identify comparable literature investigating pediatric devices cleared via the 510(k) pathway; however, orthopaedics constitutes the single largest contributing specialty for this device type, accounting for approximately 20% of 510(k) devices. As such, the identified pediatric innovation gap is likely present across most specialties, although that is beyond the scope of the current study[16].

The implications of our results are discouraging in light of the continued attempts to promote growth in pediatric device innovation. In 2007, Congress passed the Pediatric Medical Device Safety Improvement Act, which allowed manufacturers of pediatric HDE devices to legally earn a profit from sales, unlike HDE devices designed for adults[16]. It also provided grant funding for the Pediatric Device Consortia[1,4,5]. The FDA has also allocated substantial resources to recruiting pediatric experts, hosting workshops, and collaborating with professional medical societies[3]. In addition, many authors and medical societies have continually expressed concerns regarding this unmet need, and surgeons have been forced to repurpose adult-use devices for use in the pediatric

population[7,8]. This off-label use presents unique risks and challenges to both surgeons and patients. A recent FDA survey of pediatric physicians found that 66% of respondents reported a need for pediatric fracture fixation devices and for devices that grow with pediatric patients[16]. Our data support that this need is still present, and unfortunately, no growth in development was noted during the study period.

Several important secondary findings are worth mentioning. First, spine and trauma represented the largest portion of 501(k)-pathway devices with pediatric or adult plus pediatric indications (approximately 45% each). The only 2 approved highly innovative pediatric-only devices were in the spine subspecialty, which implies that many pathological conditions of the hand, foot, hip, pelvis, and other regions are not benefiting from innovation. The sports medicine subspecialty similarly lacked highly innovative devices; however, there was a single De Novo-pathway device indicated for anterior cruciate ligament repairs in adolescents ≥14 years old. Although the reasons for this concentration of spine and trauma devices is beyond the scope of this study, it is likely that manufacturers view these subspecialties as the main—if not only—avenues toward profitability in this patient population. In a letter to the FDA, the global medical device trade association, the Advanced Medical Technology Association, bluntly stated "pediatric diseases and conditions may not represent a commercially viable market opportunity for device companies."[2]

Second, large and medium-sized device companies were almost twice as likely to develop an orthopaedic device that included a pediatric indication compared with small companies. Costs have long been reported as a major constraint to innovation, with a PMA device costing approximately $54 million on average to bring to market and ranging up to $200 million, excluding expenditures for any post-approval studies required by the FDA[17]. At the 2012 American Academy of Orthopaedic Surgeons "Industry for Kids" forum, manufacturers reported that the PMA process was too expensive for the pediatric device market[8]. Our data suggest that this finding may be true in the 510(k)-pathway as well. Six of the 9 pediatrics-only devices were brought to market by large manufacturers, despite 91% of manufacturers being considered small or micro. The recent push from the FDA to accept real-world data, such as registry data, and evidence from foreign countries may ameliorate this issue and hopefully encourage attempts from smaller and start-up companies to usher in novel technologies for children. However, even with these efforts, proving the safety and effectiveness of high-risk medical devices in children will still likely require well-designed clinical trials. The inherent challenges of completing these have been well described, and concerted efforts should continue to facilitate obtaining this necessary evidence base[1,4,8].

Lastly, although not a specific end point in our investigation, we noted that many device labels provided no guidance regarding pediatric usage. Even when device labels reported pediatric indications, specific age cutoffs were seldom provided. By contrast, since 1994, drugs and biologics have been required to include a "Pediatrics Use" subsection on all labels. A recent FDA guidance document recommended that the phrasing in this subsection state that the product was for use in "pediatric patients, ages X to Y years old."[18] Similar standardization for medical devices should be considered.

Limitations

There were important limitations to this study. First, we only included original authorizations of devices. It is possible that a device could obtain a pediatric indication through a Special 510(k) pathway or a Panel Track supplement to a PMA or HDE device. However, indication extensions, especially to include a vulnerable population such as children, would be unlikely to meet Special 510(k) criteria[15]. Although it is possible for Panel Track supplements to extend PMA indications, those require substantial clinical data, and none of the previous literature has reported this pathway contributing substantially to pediatric device development[4,5,14].

Second, the study was not designed to answer why this innovation gap exists. Many authors have written about the complexities of bringing these devices to market, including financial costs, obtaining consent, study design, etc[1,4-8,11]. However, the precise contribution of these factors remains unknown and is worthy of further investigation.

Third, FDA categorizations may not reflect a surgeon's clinical perspective. For instance, magnetic growing rods for pediatric spinal deformity were initially cleared via the 510(k) pathway based on "substantial equivalence" to Harrington rods[19]. The recent recall of several of these devices, as well as an FDA safety communication reporting problems with mechanical failures and tissue incompatibility, raises a question regarding whether those 2 devices should be considered comparable[20]. Lacking another more contemporary comparator, magnetic growing rods could have been considered for authorization under 1 of the highly innovative pathways. For uniformity, however, our analysis abided by FDA determinations.

Lastly, there was no benchmark for an ideal proportion of innovation dedicated to pediatrics. Although individuals <18 years old make up about 25% of the population, devoting proportionate societal resources toward innovative technologies may not be an appropriate goal. It is possible that pediatric orthopaedic conditions requiring complex, innovative technologies are far rarer than orthopaedic conditions affecting adults. It is also possible, however, that the lack of incentive forces innovators and entrepreneurs to eschew many potential undiscovered opportunities. Regardless, we found a very low absolute number of devices authorized by the FDA for use in children. Furthermore, clinical experience supports the need for far greater innovation in the management of myriad childhood musculoskeletal conditions.

Conclusions

Despite these limitations, the present findings are robust and consistent with clinical experience. Innovation of pediatric devices lags substantially behind that of adult devices. Although the U.S. Congress has passed important legislation to stimulate progress, more is required. Increased awareness of

available opportunities, such as the Pediatric Device Consortium, for collaboration and support of innovative device research among biomedical engineers, industry leaders, and pediatric surgeons alike may help alleviate the current innovation gap. ■

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