Peer reveiw

Liu, Michelle Z, and Kenley K Hoover. 2025. “Clinical Trials of Drugs in the Pediatric Population.” *Journal of High School Science* 9 (2): 103–22

I enjoyed reading the paper. The data was well presented, as was the rationale for the analysis; however the inclusion criteria for many drugs is questionable as is the premise. I have some concerns that will need to be addressed in the manuscript. Feel free to rebut with adequate justification.

1.a definition of an upper age for pediatric patients is needed.

2.You state “……..We then reviewed the prescribing information of drugs that ranked from 180-200 by sales in 2023 (10), to the extent that the information was searchable from Drugs@FDA…….” I do not understand the arbitrary choice of 180-200. Doubtless, there may be sources other than Drugs@FDA that could be searched and the corresponding clinical trials searched at clinicaltrials.gov ? Please explain and discuss in the manuscript.

3.There seems to be a disconnect between your title and content. Your title suggests that you are looking to see if pediatric clinical trials were performed SUBSEQUENT to the drug being approved (in the adult population), while your text and manuscript content include (or seem to include) clinical trials in the pediatric population BEFORE the drug was approved (for any population). For example, Figure 1 (pediatric trials included in label) would mean that such trials were conducted before drug approval. Similarly, “……About 70% of the biologics we analyzed have pediatric trial information on their approved labels as compared to less than 50% of the approved labels for small molecule drugs……” This implies (again) that pediatric trials were conducted BEFORE drug approval. Also check the drugs listed in Table 1 (see point 4 below). Please check to see that you are presenting content that is consistent with the title. Else, modify the title as necessary.

4.You have left out significant amount of information on drugs approved for pediatric rare diseases only (see point 5 and references). Please conduct a thorough literature search and add this information. Also, in Table 1, please indicate which of the drugs were approved specifically for the pediatric population (i.e. Spinraza, Trikafta?, Takhzryo, Cerezyme…. and other ERT (for both pediatric and adult - this would seem to disqualify these drugs from your manuscript per your title, see point 3).

5.You will need to mention and discuss that drugs that are approved for the adult population may not be suitable for pediatric rare diseases. For example, spinal muscular atrophy (SMA), Duchene Muscular Dystrophy (DMD), Cystic Fibrosis (CF) occur exclusively in children, as does Acute Lymphoblastic Leukemia (ALL). Additionally, inherited coagulopathies, lysosomal storage/metabolism disorders, ADA-SCID, deficiency of enzymes/proteins/hormones specific to children……. The drugs approved for these indications are (have to be) specific for children. These drugs are NCE (new chemical entities) specific for the pediatric population delivered by technology platforms specific for that population. Please discuss in detail and provide information about which of the rare diseases are specific to children and which are not.

6.The premise of your manuscript may be questionable if it turns out that there is very little overlap between rare diseases of children and rare diseases of adults. This would imply that the reason that pediatric clinical trials for approved drugs are not being performed (for rare diseases) is because approved drugs cannot treat rare diseases in children. Please search the literature and present this information, rationale and analysis in the manuscript.

7.My suggestion is to broaden the scope of your manuscript to include (as you seem to already have done) all drugs for which pediatric trials were performed before approval. The points of concern below are predicated on that premise; but may still be useful; should you decide to retain the current title.

8.you state “…..Alternatively, the government can also lower the standard of clinical trials in rare pediatric diseases…..” I suggest replacing the phrase ‘….lower the standard….’ with ‘adopt alternative clincal protocols suited for a limited cohort’ or something along that lines.

9.Double check this statement "…..For example, all drugs listed in Table 1 for treating rare diseases are biological drugs…."
10.Please also provide data for the prevalence of clinical trials for pediatric patients as correlated with:
2a. *the scientific platform: i.e. vector/gene delivery, targeting splicing factors, exon skipping, PROTACs (molecular glue), CAR-T cells, mRNA vaccines…….*
For example, the blood brain barrier physiology and construction is likely to be similar among pediatric and adult patients; hence if a therapy gets past pediatric BBB, it stands a good chance of getting past adult BBB as well. Similar is the case with splicing factors, targeting a particular splicing factor (for example RBM39) in pediatric patients as an anti-oncogenic mediation, is likely to prove as effective in adult patients due to function similarity. Finally, exon-skipping ….if the mutated or non-sense exons are similar in pediatric and adult patients, the therapy will be age-agnostic. The hypothesis is that if the platform is age-agnostic, there will be more pediatric clincal trials related to that drug(s), since they can be put to use in the adult population as well (even if for a different indication). or vice-versa (i.e. if the platform is successful in clinical trails in adult patients, it stands a good chance of being successful in pediatric patients as well)
Signaling pathways can be altered with age (see reference below), hence targeting those pathways or their products or their perturbations will not be age-agnostic.
2b. *the likelihood of death of permanent disability occuring within < 5 years of age (muscular dystrophy or Spinal Muscle Atrophy…etc.).* This is where pharma companies can win the public (empathy) debate and narrative and get insurance companies to pay for the approved drug, this is also where the FDA may accept clinical marker improvements which may not necessarily have translated into QOL (quality of life) improvements. For example, see how Elevidys, Serepta Therapeutics (priced at $3.2 million for a one time treatment) for DMD was approved despite failing the primary endpoint here: https://medcitynews.com/2024/06/sarepta-gene-therapy-duchenne-muscular-dystrophy-fda-approval-peter-marks-elevidys-srpt/
2c. *Providing a prophylactic disease-modifying therapy; rather than a curative one*. A gene therapy such as a one-time administration for SMA needs specialized chemistry-manufacturing-control protocols, whereas an oral medication such as Evrysdi can be manufactured in existing plants with minimal modifications, with sales lasting the lifetime of the patient and without a (perceived) exhorbitant price tag.
2d. *Off-label use.* The greater the prevalence of off-label use, the lesser the motivation to conduce a pediatric clinical trial.
My suggestion for how to dis-incentivize big pharma from buying out startups' that are researching pediatric diseases so that more of such clinical trials are performed faster and the resultant drugs (if approvable) are cheaper. You may include this (or variants) into the manuscript.
Novartis acquired AveXis (originated as biolife cell bank) for $9 billion in 2018-19. The cost of Zolgesma is $2.1 million per one-time treatment for SMA. Once the treatment is administered to 4000 patients, the excess patients contribute purely to profit (simplistically). Assuming 1 in 10000 births afflicted with the disease, there are 359 patients per year afflected. Assuming 10% penetration (insurance etc…), that is 40 patients per year or 100 years to recoup captial alone. This justifies the price of Zolgesma. However; the sordid saga begins with public funding and a non-profit organization (Nationwide Children's hospital in Colombus, Ohio, where; in 2009 or thereabouts, Dr. Kasper (whose lab was affiliated with the hospital) discovered a viral vector that could penetrate the BBB and deliver a gene for SMA. He licensed it to AveXIs, which in turn was bought out by Novartis. There are many stories such as these, which start out with public or non-profit funding but morph into private, for-profit enterprise (another egregious one is the Thermus acquaticus bacteria (the source of Taq polymerase and the PCR reaction) discovered in the sulfur springs from a public resource; Yellowstone park). This represents a gross and egregious appropriation of public taxpayer money and assets (and IP generated by public taxpayer money and assets) by private for-profit organizations. Please perform a thorough

search of the literature and present the results in the manuscript. A success story is how parents wrested control of the ADA-SCID gene therapy that was licensed to Orchard therapeutics and transferred the rights back to UCLA in 2021 (see: https://primaryimmune.org/resources/news-articles/gene-therapy-ada-scid-shows-promise)

I therefore propose that the valuation of any for-profit research related organization (in-particular; startups') be split between private and public inputs. This will likely deter the acquisition of start up pharma companies by multinationals because, they will either have to pay a larger buyout premium to the start up shareholders (with part of the offer going to a PTF; see later) or have those shareholders take a loss -due to a portion of the offer going to a public trust fund (PTF) - hence making them unwilling to sell. Subsequently, if and when these start up companies get to phase III clincal trials, these will be funded by the money in the PTF supplemented (as necessary) by taxpayers (the US Government). Consequently, Zolgesma would now be available at prices that would be within reach of the (family of the) patient.

splicing factors (small molecules, proteins, AO (spinraza), exon skipping,

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Pediatric Clinical Trials in FDA Approved Drugs

Michelle Z Liu[1], Kenley K. Hoover[2]

Revised the title per the reviewer's suggestion #3
Author
(no date)

Abstract

This paper reviews current trends in pediatric clinical trials conducted for marketed drugs in the United States. There are many known difficulties in conducting clinical trials in the pediatric population, including the lack of available patients, financial incentives, etc. In this paper, we found that the majority of marketed drugs are also approved in the United States for pediatric patients, which indicates that various government incentives and/or requirements are effective in encouraging pharmaceutical companies to conduct pediatric clinical trials. However, a gap still exists for some pediatric diseases. Based on our review, the rarity of diseases in the pediatric population is one of the main factors determining whether a medication is supported by pediatric clinical trials. For these diseases, further government incentives and requirements are unlikely to be effective in promoting pediatric clinical trials because of the inherent difficulties associated with the limited number of patients. While not ideal, we propose that adopting alternative clinical protocols suited for a limited cohort and/or imposing a duty to report off-label use to a centralized database may provide valuable information for physicians to use relevant medications for treating pediatric patients with such diseases.

Keywords

Pediatric Clinical Trials, Rare Disease, off-label use, Pediatric Exclusivity, Pediatric Research Equity Act

1. Introduction

A substantial number of the medicines administered to pediatric patients (up to 18 years old) constitute off-label uses of the medications (1a, 1b, 1c). That is, pediatric patients are given a drug to treat a disease or condition for which the drug has not been approved in children. While kids tend to be healthier than adults, when they get sick, they often have different needs and react differently to medications than adults (2). A common misconception that many people share is that kids are tiny adults and can take the same medications for the same or even just similar illnesses (3). Reducing the dosing amount of a corresponding medication approved for adults might, in some cases, be suitable for treating some pediatric patients and conditions. However, without supporting research and information gleaned from pediatric clinical trials, it is difficult to predict how a child will respond when underdosed with a medication for off-label use (4a). Off-label uses put vulnerable pediatric patients at an increased risk because they can result in unforeseen adverse drug reactions (4b). In 1994, the United States implemented the Pediatric Exclusivity Provision in an effort to encourage pediatric drug development and to address issues of inadequate pediatric clinical testing, drug labeling, treatment information, and regulation in general (5). Under the Pediatric Exclusivity Provision, a drug manufacturer that conducts pediatric clinical trials and meets certain requirements set by the government is entitled to add an additional 6 months of exclusivity to its patents that cover the drug (5). The United States government's efforts to encourage and regulate pediatric drug development were furthered in 2003, with the passing of the Pediatric Research Equity Act that gives the FDA the authority to require drug manufacturers to study their products in pediatric populations if the drugs are likely to be used in children, ensuring that medications are safe and effective for younger patients. Unfortunately, despite the incentives and requirements provided by the government, pediatric clinical trials, although

Addressed the reviewer's comment #1
Author
(no date)

1 Corresponding author: Michelle Liu, Thomas S. Wootton High School, 2100 Wootton Pkwy, Rockville, MD 20850
[2]Kenley K. Hoover, Nixon & Vanderhye PC, 901 N Glebe Rd #1100, Arlington, VA 22203

improving, are still lacking (6a, 6b). In fact, it was found that between 2007 and 2011, for the five conditions with the highest disease burden among children, only 12% of clinical trials registered were pediatric trials, whereas 60% of the disease burden was attributed to children (6b).

Many potential reasons may account for the lack of sufficient pediatric clinical trials (7a, 7b). For example, there may be ethical issues associated with clinical testing of the pediatric population (7c). The pediatric patient population may be small in number, which can increase the difficulty of conducting a randomized clinical trial (8). And for some uncommon conditions, there may not be enough financial incentive for pharmaceutical companies to develop and/or market a drug for pediatric use (9).

In this paper, we review the current trends in pediatric clinical trials conducted for marketed drugs in the United States in an attempt to understand some of the driving forces that influence a pharmaceutical company's decision regarding whether or not to conduct a pediatric clinical trial for a drug, either as a new drug or for an already approved drug. We first review the prescribing information for some of the top-selling drugs to identify whether any pediatric clinical studies have been conducted for the drugs. We then analyze the types of drugs that are more likely to have support from pediatric clinical studies, and if an adult version of the drugs is approved first, we analyze the time lag between the initial approvals of the drugs for adults and their later approval for treating pediatric patients. We also reviewed the more recently approved drugs for rare disease indications and those using new technologies to understand whether the pediatric population is sufficiently represented in these drug approvals. Lastly, we summarize the trends we identify and provide our point of view to rationalize the trends and our conclusions.

Revised the reviewer's comment #7, see also additional discussions throughout the revision.
Author
(no date)

2. Our Methodology

For this review, we obtained the prescribing information of the drugs we analyzed from the United States Food and Drug Administration's (FDA) database, Drugs@FDA, which is a public database that allows a user to search for and obtain information for an FDA-approved drug at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm. The Drugs@FDA database includes the FDA's approval history for approved drugs and includes the different versions, if any, of FDA-approved labels for such drugs. For example, for some drugs, the initially approved labels do not include pediatric clinical trial information; but afterward, updated labels are approved for such drugs, which include newly conducted pediatric clinical trial information. During our review, we analyzed the prescribing information of select best-selling drugs to determine whether they include any pediatric clinical trial information and to evaluate the lag time between the initial approval of the drug for its use in adults and the time when the first pediatric clinical trial information is included in an approved label for the drug.

We first reviewed the top 30 bestselling drugs worldwide in 2023 (10). We hypothesized that the economic incentives provided by pediatric exclusivity would be the strongest for top-selling drugs – a 6-month additional exclusivity can translate into billions of dollars of extra profit. However, to our surprise, there was no uniform inclusion of pediatric clinical trial information or data in the approved labels for these top-selling drugs. Overall, only about 66% of the top 30 selling drugs we reviewed include information on pediatric clinical trials. Our review also found that the lag time for the inclusion of pediatric clinical trial information in the label of the analyzed drugs varied greatly from 0, i.e., no lag time (Trikafta®), a few months (Farxiga®), to more than 11 years (Eylea®) from the initial approval of the drug by the FDA. Overall, this analysis did not identify any clear trend for the top 30 bestselling drugs.

We then reviewed the prescribing information of drugs that ranked from 180-200 by sales in 2023 (10). Our rationale was that if annule sale is a determining factor, then we may expect that the chance of a drug having pediatric clinical support in the bottom 20 of bestselling drugs would be lower than that for drugs appearing on the top 30 of bestselling drugs. Among the drugs ranked from 180-200 that we analyzed, about 60% included pediatric clinical trial information, which was slightly less but very close to the 66% observed for the top 30 bestselling drugs. See, Figure 1 below. The lag time for the labels of these dozen or so drugs to include pediatric clinical information in their labels ranged from 0 to more than 11 years from the initial drug approval for adult use by the FDA. Since our review found that there is little difference between the top 30 bestselling drugs and those ranked 180-200, in terms of the inclusion of pediatric clinical trial information in their labels, we conclude that the annual sale of a drug does not appear to be a determining factor for whether the pharmaceutical industry conducts pediatric clinical trials.

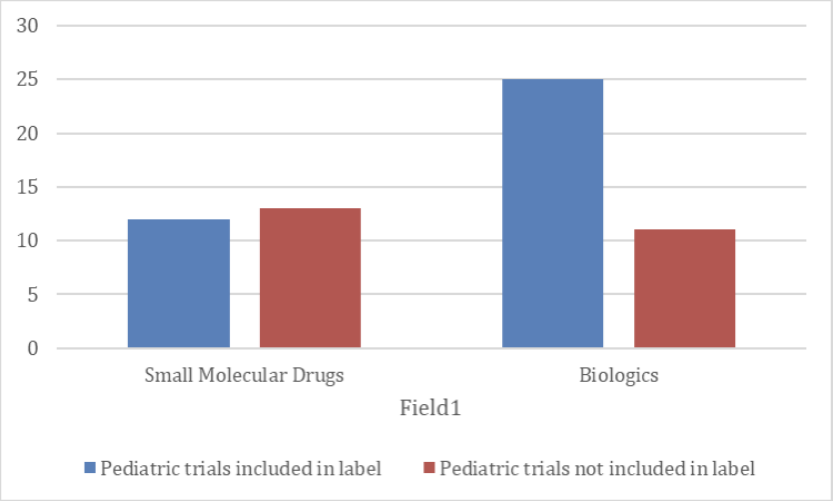
Revised to provide a rationale to address the reviewer's comment #2.
Author
(no date)

Figure 1. Comparison of prevalence of pediatric trials in top-selling drugs and others

3. Small molecular Drugs vs. Biologicals

Next, we evaluated whether the prevalence of a pediatric clinical trial for a drug correlates with whether the drug is a small molecule drug (with a molecular weight less than 1,000 Da) or another type of drug, such as a peptide, antibody, vaccine, nucleic acid, polysaccharide, etc. (collectively termed "biologics" herein). Our results, shown in Figure 2 below, indicate that more pediatric clinical trials were conducted for biologics. About 70% of the biologics we analyzed have pediatric trial information on their approved labels as compared to less than 50% of the approved labels for small molecule drugs. These results suggest that there may be more incentives for a pediatric clinical trial to be performed for a biological drug than for a small molecule drug.

Figure 2. Prevalence of pediatric trials in small molecular drugs and biologics



4. Disease Area Categories

Next, we reviewed whether pediatric clinical trials are more frequently conducted in particular disease areas. We categorized the drugs based on their use in nine different disease areas: oncology, cardiovascular, diabetes, immunology, infectious disease, ophthalmology, genetic disease, neurology, and rare diseases. Drugs that contain pediatric clinical trial information listed in their labels, either as of the initial approval or a revised label subsequent to the initial approval, are italicized in Table 1, whereas those that do not are not italicized. As reflected in Table 1, all the evaluated drugs for treating rare diseases and genetic diseases have been clinically tested in pediatric populations. The majority of the considered drugs for treating infectious disease and immunology were also clinically tested in pediatric patients, with about 70% of the drugs having pediatric clinical trial information in their prescribing information. About 60% of the considered drugs for treating cardiovascular disease or diabetes also have pediatric clinical trial information on their approved labels. However, for the drugs considered for treating ophthalmology, neurology, and oncology, the prevalence of pediatric clinical trial information in their labels dropped to about 40% or below. These results suggest that the disease that a drug treats is a better indicator of whether a pediatric clinical trial is conducted for a drug than the annual sale of the drug. Our review also found that the highest percentages of drugs that contain pediatric clinical trial support in their labels are found in the disease areas of genetic, rare, infectious, and immunology-related diseases. Perhaps not coincidentally, the drugs approved in these disease areas were also more frequently found to be biological drugs rather than small molecule drugs. For example, all drugs listed in Table 1 under the column "rare diseases" are biological drugs.

Clarified and confirmed per the reviewer's comment #9.
Author
(no date)

Table 1. Pediatric Clinical Trials for Drugs in Different Disease Areas

Oncology	**Cardiovascular disease**	**Diabetes**	**Immunology**	**Infectious disease**	**Ophthalmology**	**Genetic disease**	**Neurology**	**Rare diseases**
Keytruda®	Eliquis®	Ozempic®	*Humira*®	*Biktarvy*®	*Eylea*®	*Trikafta*®	Ocrevus®	*Myozyme*®
Opdivo	*Xarelto*®	Jardia	*Dupixent*®	*Comirna*	Vabysmo®	*Spinraz*	*Botox*®	*Advate*®

®		nce®		*ty*®		*a*®		
Darzalex®	*Entresto*®	*Trulicity*®	*Stelara*®	*Gardasil*®	Lucentis®	*Takhzryo*®	*Vyvanse*®	*Kogenate*®
Imbruvica®	Opsumit®	*Insulin*®	Skyrizi®	*Prevnar*® *Family*		*Crysvita*®	Invega Sustenna®	*Alprolix*®
Revlimid®	*Repatha*®	*Farxiga*®	Entyvio®	*Shingrix*®			*Vraylar*®	*Cerezyme*®
Xtandi®		Mounjaro®	*CoSentry*®	*Vemlidy*®			*Epidiolex*®	
Tagrisso®		Humulin®	*Synagis*®	Cabenuva®			Concerta®	
Zytiga®							Ubrelvy®	
Libtayo®							Avonex®	
Adcetris®								

Since significant differences were observed between the considered disease areas, we then evaluated whether the FDA approves a drug with or without a pediatric clinical trial based on the prevalence of the indication treated by the drug in pediatric populations.

In this regard, we first reviewed the drugs listed in Table 1 approved for treating diseases under the column "rare diseases", which all coincidentally happened to be genetic diseases. Not surprisingly, the indications approved for the drugs under this disease area were generally found in children who inherited a particular genetic defect. For example, Myozyme®, an analog of alpha-glucosidase, is approved as an enzyme replacement therapy (ERT) for the treatment of Pompe disease (11a). Pompe disease patients are primarily children, with the infantile-onset occurring within the first few months of life and is characterized by its lack of alpha-glucosidase (11b). However, late-onset Pompe disease can affect both children and adults (11b). Myozyme® approval was based on the improved ventilator-free survival in patients with infantile-onset Pompe disease as compared to an untreated historical control, whereas patients with other forms of Pompe disease, such as the late-onset Pompe disease has not been adequately studied to assure safety and efficacy. Thus, in a way, the older adult population may use Myozyme® off-label based on pediatric clinical information. Similarly, Advate® and Kogenate® are both a recombinant antihemophilic factor, approved for treating Haemophilia A, which is an inherited genetic disease that causes deficiencies in blood clotting factor VIII, in adults and children(12a). Haemophilia A can manifest in children at a young age (12b). It was clinically shown that children have a higher Factor VIII clearance, although in a different study, the efficacy of the drugs was shown to be similar among adults and the pediatric population (12a). The pharmacokinetic difference observed in the pediatric and adult population for these drugs further demonstrates the importance of having clinical information in the FDA approved labels, which can prevent incorrect and potentially detrimental treatment in the pediatric population. Alprolix® is a recombinant coagulation Factor IX fusion protein consisting of the human coagulation Factor IX sequence covalently linked to the Fc

Upon review, we found that all drugs in Table 1 under rare diseases or genetic diseases were approved for use in both adults and pediatric populations. Thus, the reviewer's concern (comments # 4-6) should be resolved. Also, added more details in the description section on these drugs and a Rare disease section below to address the reviewer's comments.
Author
(no date)

domain of human immunoglobulin G1 (IgG1), approved for treating Haemophilia B (Christmas disease) in adults and children (13a) Haemophilia B is an inherited genetic disease that causes blood clotting factor IX deficiencies and can cause excessive bleeding in childhood (13a, 13b). The pediatric approval of Alprolix® was based on clinical studies from adults and children from 12-17 years old and from 1-11 year old (13a) Lastly, Cerezyme® is an analogue of the human enzyme b-glucocerebrosidase approved for treating Gaucher's disease in adults and pediatric patients 2 years or older (14a) Gaucher's disease is a genetic disorder in which glucosylceramide accumulates in patients due to a deficiency of β-glucocerebrosidase activity (14a, 14b). Gaucher's disease, depending on the different types, can have symptoms occurring early in life and even in adulthood and can cause children to die at an early age (14b). The pediatric approval of Cerezyme® was based on well-controlled studies in adults and pediatric patients of 12 years and older, and additional data from the medical literature and postmarketing experience in pediatric patients as young as 2 years old (14a). In this group of approved drugs, the efficacy of the drugs in the pediatric patients can be expected from studies in their adult counterparts due to the same mechanism of actions. However, the difference in pharmacokinetics in adults and pediatric patients still demands clinical information to ensure that the dose used for treating pediatric patients is safe and efficacious.

Like rare diseases, the indications approved for the drugs under the column "genetic disease" were generally found in children with a particular genetic defect/mutation. For example, Trikafta®, a fixed combination of elexacaftor, tezacaftor, and ivacaftor, which are CFTR modulators, is approved for the treatment of cystic fibrosis for adults and pediatric patients aged 2 years or older with certain mutations in the *CFTR* gene (15). Symptoms of cystic fibrosis may appear in infancy, childhood, or adulthood (16). The pediatric use of Trikafta® was based on well controlled clinical trials in the pediatric population (15). Similarly, Spinraza® is a survival motor neuron-2 (SMN2)-directed antisense oligonucleotide indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients (17). Spinraza® is designed to treat SMA caused by mutations in chromosome 5q that lead to SMN protein deficiency (17). The onset of SMA can range from before birth to adulthood (18). Safety and effectiveness of Spinraza® in the pediatric population were established in clinical studies (17). Takhzryo® is a plasma kallikrein inhibitor indicated for the prevention of hereditary angioedema (HAE) in adult and pediatric patients 2 years and older (19). Onset of HAE can vary, typically from childhood to age 20 (20). The pediatric approval of Takhzryo® was based on subgroup studies of patients of 12 years and older in clinical studies that also included adult patients, and an extrapolation to patients of 2 to 12 years old based on pharmacokinetic studies (19). Lastly, Crysvita® is a fibroblast growth factor 23 (FGF23) blocking antibody indicated for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients 1 year of age and older (21). XLH is caused by excess FGF23, which suppresses renal tubular phosphate reabsorption and the renal production of 1,25 dihydroxy vitamin D (21). Although typically a childhood condition, XLH can continue to progress into adulthood (22). The pediatric approval of Crysvita® was based on open label studies in patients 1 year and older (21).

We then reviewed the drugs listed in Table 1 that are approved for treating the disease areas of ophthalmology, neurology, and oncology and were observed during our review to have the lowest percentage of approved drugs that are supported by pediatric clinical trials in their labels. In ophthalmology, Eylea® was the only drug with pediatric clinical trial support included in its label. Eylea® is approved for wet age-related macular degeneration, Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), Diabetic Retinopathy (DR), and Retinopathy of Prematurity (ROP) (23). Eylea®'s prescribing information indicates that two clinical studies were conducted for pre-term infants with ROP (23). The two drugs that do not have pediatric clinical trials may be easily understood, as both Vabysmo® and Lucentis® are approved for treating age-related

macular degeneration, a condition typically occurring in the geriatric patient population (24a, 24b). Like Eylea®, Vabysmo® is also approved for treating DME, which, although rare, can also occur in the pediatric population (25). The pediatric clinical trial conducted for Eylea® relates to treating ROP, not DME. A pediatric clinical trial was also not conducted for the use of Eylea® in treating RVO, which may potentially occur in the pediatric population (26). Overall, the data suggests that pediatric clinical trials are not conducted for some of the ophthalmology diseases may be due to the rarity of the disease in children. It is, however, interesting to see that the same drug can have uses in both adult and pediatric populations for different indications, and depending on the drug developer, the drug may or may not be extended to a pediatric indication.

In the neurology disease area, however, there does not appear to be a clear trend. As one might expect, some drugs that do not have pediatric clinical trial information in their label are approved for indications that are less likely to occur in the pediatric population. For example, Ocrevus® and Avonex® are both approved for treating multiple sclerosis (MS), which is a condition that rarely affects children, who only account for about 5% of the total MS patient population (27). Invega Sustenna® is approved for schizophrenia in adults, and Vraylar® is approved for treating schizophrenia and bipolar disorders (28a). Childhood schizophrenia is an uncommon but severe mental disorder (28b). Bipolar disorders can also occur in children but are rare (28c). Conversely, other approved indications for the drugs in the neurology disease area frequently occur in children but do not include pediatric clinical trial information in their labels. For example, Ubrelvy® is approved for treating migraines with or without aura in adults, but no pediatric clinical trial has been conducted as of now (29a). According to one report, about 10% of children experience migraines, and migraines may affect children differently from adults (29b). Overall, the results show that the rarity of the disease alone does not determine whether a pharmaceutical company conducts a pediatric clinical trial in the neurology disease area.

Lastly, we reviewed the drugs in the oncology disease area that do not have pediatric clinical trial support in their labels. Pediatric cancer is, in general, rare. As discussed below, the approved oncology drugs in Table 1 that do not have pediatric clinical trial information are generally approved for treating indications that rarely occur in children. For example, Xtandi® and Zytiga® are indicated for treating prostate cancer (30). Darzalex® is approved for treating adult patients with multiple myeloma, but no safety and efficacy have been established for treating pediatric patients (31a). Multiple myeloma is very rare in the pediatric population, with only about 30 cases reported in the literature for patients under age 18 (31b). Revlimid® is approved for a variety of indications, including multiple myeloma, transfusion-dependent anemia, mantle cell lymphoma, follicular lymphoma, and marginal zone lymphoma (32a). These approved indications for Revlimid® are all rare in the pediatric population; the lymphoma approved for Revlimid® is generally considered low-grade B-cell lymphoma, which increases in frequency with increasing age (32b). For example, marginal zone lymphoma is primarily occurring in older patients from 55-65 years old and is extremely rare in children (32c). Tagrisso® is approved for treating non-small cell lung cancer, which is also extremely rare in the pediatric population (33a, 33b). Libtayo® is a programmed death receptor-1 (PD-1) blocking antibody approved for treating cutaneous squamous cell carcinoma, basal cell carcinoma, and non-small cell lung cancer, all of which are rare in the pediatric population.

In summary, most of the evaluated approved drugs that do not have pediatric clinical trial information are in diseases that rarely occur in children. However, for specific indications in neurology, the rarity of diseases alone does not explain why some approved drugs do not have pediatric clinical trial support.

5. Rare Diseases

Our initial results prompted us to look into whether the FDA-approved drugs for rare diseases that can occur in the pediatric population are often supported by pediatric clinical trials. It was reported that there are about 7,000 rare diseases, 75% of which are known to affect children (34). According to a study by Kakkilaya *et al.*, from 2011 to 2023, the FDA approved 918 indications for 553 new drugs, 407 of which were rare diseases (designated as orphan drugs) and 231 labeled for pediatric use (35). Further, out of the 407 rare diseases, 136 (or 33.4%) received pediatric approval (35) The percentage of 33.4% is lower than what we would have expected. However, this is likely due to the fact that Kakkilaya *et al.* did not categorize whether all of the 407 rare diseases are relevant to children. In the 2019 FDA's report to congress, although a different sample size (between April 1, 1999 and August 31, 2018), the FDA determined that only about 64% of the orphan drugs approved may be related to children, and about 36% of the approvals do not contain complete pediatric information (36). Nevertheless, Kakkilaya *et al.* did find that the percentages of drug approvals supported with pediatric studies for rare diseases were higher than those approved for non-orphan diseases (35). This result is consistent with our findings that drug approval for rare diseases in the top 200 best-selling drugs we reviewed is more likely to include pediatric clinical trial information.

To understand the more recent trend in pediatric approvals for rare diseases, we searched the FDA's orphan drug designations and approvals database for the period between January 1, 2024, and February 17, 2025, at https://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm. During this time, there were 37 pediatric approvals for rare diseases out of a total of 87 orphan drug approvals, thus representing 42.5% of all orphan drug approvals. This rate is similar to the 33.4% observed by Kakkilaya *et al.* (35). The majority of these pediatric approvals are indicated for both pediatric and adult populations, except five of them are only approved for the pediatric population. Not surprisingly, these five pediatric-only approvals are for diseases that typically only concern the pediatric population.

Additionally, we reviewed the recently approved drugs for rare diseases that are not approved for pediatric uses. Here, the rarity of diseases in the pediatric population also appears to be the main reason that no clinical trials were conducted. For example, CALQUENCE, which was approved in January 2025 for the treatment of mantle cell lymphoma (37). Mantle cell lymphoma is a cancer mainly affecting middle age to old adults and not reported in pediatric population (38). The same is true in the case for the drug, Attruby, approved in November 2024 for treating transthyretin amyloidosis (39). Amyloidosis in children was reported as extremely rare and not reported for the specifically approved transthyretin amyloidosis (40).

In summary, many drugs containing information about pediatric use are approved for rare diseases. Spot checking drugs approved for the rare diseases recently also suggests that the rarity of diseases in pediatric population is the main reason that some of the approved drugs do not include pediatric clinical information. Drugs approved for rare diseases only represent a small fraction of all rare diseases, most of which concern the pediatric population. Further efforts and/or incentives are still needed for the pharmaceutical industry to conduct further clinical research in these rare diseases.

Added this new section to address the reviewer's comments #4-6.
Author
(no date)

6. New Technology

We also analyzed the FDA-approved drugs that use new technologies and are approved for use in the pediatric population. In recent years, emerging classes of medications and treatments have become available, which may offer significant advantages to traditional drugs. These new technologies include, for example, mRNA vaccines, gene therapies, and cell therapies. As with any other new technologies, we expect that the adoption will be slow. As such, our initial thoughts are that drugs using these new

technologies will be first approved in adults and gradually expanded to the pediatric population, if at all.

The mRNA vaccine approval for COVID-19 is an example of how the pharmaceutical industry expands adult uses to the pediatric population. During the pandemic, mRNA vaccines were first approved for use in adult population under emergency use authorizations (41). The initial clinical trials were not conducted in the pediatric population. Subsequently, clinical trials were gradually expanded to adolescent populations of 16 years or older (42a), and then to 12 to 15 years (42b). Children of 5-11 years old were then studied in clinical trials (42c). Eventually, the vaccine was authorized for use in all age groups from 6 months and above (42c). Although the pandemic may have accelerated the use of such new technologies in the pediatric population, the pharmaceutical industry did follow a gradual course to slowly expand the clinical studies to the pediatric population, perhaps partially because this represents the first mRNA drug ever used in human.

Cell therapies and gene therapies have been shown to be promising in treating certain genetic diseases. In this category, many of the approved products include pediatric support. For example, KYMRIAH® is a CAR-T therapy approved for use in patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia, targeting specifically CD19 (43). ELEVIDYS is an adeno-associated virus vector-based gene therapy for treating Duchenne muscular dystrophy (DMD) in patients of 4 years or older who have a confirmed mutation in the DMD gene (44). CASGEVY is another breakthrough gene therapy indicated for treating sickle cell disease in patients 12 years and older (45). CASGEVY is based on autologous CD34+ HSCs edited by CRISPR/Cas9-technology to increase fetal hemoglobin (HbF) protein production, which reduces intracellular hemoglobin S concentration, preventing the red blood cells from sickling (45) It is interesting to note that the CASGEVY approval for pediatric population was based on a clinical study with 12 patients aged 12 to less than 18 years. The sample size is typically too small for traditional therapy (45). However, in these types of gene editing based therapy, which uses autologous cells, the limited sample size may nonetheless support the efficacy and its use for other similarly situated patients.
In summary, limited data on new classes of therapeutics suggest that the pharmaceutical industry is ready to adopt new technologies to the pediatric population.

Added this section in view of the reviewer's comment #10
Author
(no date)

7. Discussions and Conclusions

The results of our review suggest that a pharmaceutical company's decision with respect to whether to conduct a pediatric clinical trial for an approved drug depends on numerous factors, among which the rarity of occurrence of the disease to be treated in the pediatric population is a predominant consideration. The majority of the labels for the drugs that we reviewed have pediatric clinical trial information, with the exception of those drugs that are approved for indications that are not common in the pediatric population.

However, the rarity of the occurrence of a disease in the pediatric population is a relative term. For example, for multiple sclerosis (MS), children are estimated to make up only about 5% of the total patient population. However, the total MS patient population is estimated to be nearly 1 million in the United States, which means that close to 50,000 pediatric patients have multiple sclerosis in the U.S. alone. Clearly, without sufficient pediatric clinical trials for such a patient population, these children will be treated only on an off-label basis.

Furthermore, some diseases, while rare, are still serious and life-threatening for pediatric patients. For example, cancer in children is, in general, rare but can affect those children having cancer and their

families significantly regardless of the rarity of their occurrence. Without sufficient clinical information, these children may not receive proper treatment. For these rare pediatric indications, perhaps conducting randomized clinical trials is impractical for pharmaceutical companies due to the limited availability of patients to participate in such trials. For these indications, one can only hope that pharmaceutical companies, the scientific and regulatory agencies work together to develop better mechanisms and incentives to ensure that drugs are developed to treat these rare conditions and that children with these rare conditions receive an informed treatment that takes into consideration pediatric clinical trial information and the best available treatment options.

One encouraging sign is that pharmaceutical companies are conducting pediatric clinical trials to expand the initial approval of their drugs in adults to include pediatric patients, and pharmaceutical companies are also conducting pediatric clinical trials to treat indications that are unique to children. For example, Keytruda® was initially approved in 2014 for treating unresectable or metastatic melanoma with no safety or efficacy studies on pediatric use (46a). Subsequently, Keytruda® has also been approved for many different adult cancers (46b). Merck, the manufacturer of Keytruda®, has conducted further clinical trials that have supported the expansion of the approved indications of Keytruda® to include the treatment of pediatric patients with classical Hodgkin Lymphoma (cHL), Primary Mediastinal Large B-cell lymphoma (PMBCL), Microsatellite Instability-High or Mismatch Repair Deficient Cancer (MSI-H Cancer), Merkel Cell Carcinoma (MCC), or Tumor Mutational Burden-High (TMB-H) Cancer (TMB-H Cancer) (46c). According to the label of Keytruda®, clinical trials were conducted for patients with advanced melanoma, lymphoma, or PD-L1 positive solid tumors (46c). Although the Keytruda® label does not indicate that children with other types of pediatric cancers can be treated with Keytruda®, for which their adult counterpart has been approved, the inclusion of some pediatric clinical information for which Keytruda® has been tested may, nevertheless, provide valuable information for doctors when deciding whether and how to treat a child with rare cancer with Keytruda®, even if off label.

However, the Keytruda® example is not generally applicable to all other drugs, and there are still gaps due to the rarity of certain diseases in pediatric populations. Further incentives or requirements from the government will not close the gaps for such diseases because it may be impossible or impractical to conduct pediatric clinical trials due to the limited number of patients. For such situations, we propose two alternatives to conventional pediatric clinical trials, which may provide useful information for treating physicians when using a drug off-label. The first alternative is to adopt alternative clinical protocols suited for a limited cohort when running pediatric clinical trials, such as by not requiring double-blind trials. A double-blind or well-controlled clinical trial in such situations can be nearly impossible due to a limited patient pool. On this approach, we are also encouraged to observe that the FDA under certain circumstances accepted clinical studies or information without randomized clinical trials as supporting the pediatric use of a drug. As discussed above, open label studies, subgroup analysis, extrapolations based on pharmacokinetic studies, medical literature, and post-marketing experience, etc., have all been used to support pediatric use of the approved drugs. As a second alternative, the government can impose a duty for a physician treating a pediatric patient off-label to submit relevant safety and efficacy information to a centralized database. Even though not ideal, such a centralized database would provide at least some information that can guide future doctors when treating patients with similar conditions.

Revised per the reviewer's comment #8.
Author
(no date)

In addition, from a policy perspective, which is not the focus of this paper, the authors suggest that pharmaceutical companies and/or other interest groups collaborate with startup companies that are researching pediatric diseases to expedite clinical trials on such pediatric diseases and together control

the cost of the ultimate approved drugs. After all, many rare diseases affecting children still have no FDA approved drugs as treatment options.

In conclusion, while pharmaceutical companies have conducted pediatric clinical trials, gaps exist. For rare conditions in children, doctors still have limited information to make informed treatment decisions. Conducting pediatric trials for some indications while expanding a drug's approval to other conditions that affect a significant number of children, although not a complete solution, can provide lifesaving information for doctors to use off-label drugs more safely in children. Alternatively, the government can also adopt alternative clinical protocols suited for a limited cohort in rare pediatric diseases or demand physicians to submit off-label use information to a centralized database, which should also provide valuable information for doctors.

Added based on the reviewer's suggestion. However, since this paper is not focused on the perspective of controlling drug price, we believe it is not necessary to include a detailed discussion.
Author
(no date)

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Added new references

Author
(no date)

Thank you for addressing my comments. I still have some outstanding challenges regarding this manuscript.

1.Can you change the title to “Clinical trials of drugs in the pediatric population”, or something that reflects that the drug need not have been approved by the FDA when such clinical trials were performed; i.e. the trial was for a new chemical entity (NCE), not yet approved by the FDA for pediatric OR adult populations.

2.Mention somewhere (context related) in the manuscript that “…..if the drug discovery/delivery platform is age-agnostic, there will be more pediatric clincal trials related to that drug(s), since they can be put to use in the adult population as well (even if for a different indication). or vice-versa (i.e. if the platform is successful in clinical trails in adult patients, it stands a good chance of being successful in pediatric patients as well). Examples of such platforms include vector/gene delivery, targeting splicing factors, exon skipping, PROTACs (molecular glue), CAR-T cells, mRNA vaccines, etc. Signaling pathways can be altered with age (see reference below), hence targeting those pathways or their products or their perturbations will not be age-agnostic….”

3.Mention somewhere (context related) in the manuscript that the likelihood of death of permanent disability occuring within < 5 years of age (muscular dystrophy or Spinal Muscle Atrophy…etc.) increases the chances of clinical pediatric drug investigation since this is where the FDA may accept clinical marker improvements which may not necessarily have translated into QOL (quality of life) improvements. For example, Elevidys, Serepta Therapeutics (priced at $3.2 million for a one time treatment) for DMD was approved despite failing the primary endpoint
ref: https://medcitynews.com/2024/06/sarepta-gene-therapy-duchenne-muscular-dystrophy-fda-approval-peter-marks-elevidys-srpt/

4.Mention somewhere in the manuscript that " policies that dis-incentivize big pharma from buying out startups’ that are researching pediatric diseases may lead to more of such clinical trials being performed faster. This will increase the likelihood that the resultant drugs (if approvable) are cheaper.

If you incorporate these points (which were also a part of the initial review) into the manucript, its already large value-added contribution, should significantly increase.

Clinical Trials of Drugs in the Pediatric Population

Michelle Z Liu[2], Kenley K. Hoover[2]

Revise the title per the reviewer's comment #1
Author
(no date)

Abstract

This paper reviews current trends in pediatric clinical trials conducted for marketed drugs in the United States. There are many known difficulties in conducting clinical trials in the pediatric population, including the lack of available patients, financial incentives, etc. In this paper, we found that the majority of marketed drugs are also approved in the United States for pediatric patients, which indicates that various government incentives and/or requirements are effective in encouraging pharmaceutical companies to conduct pediatric clinical trials. However, a gap still exists for some pediatric diseases. Based on our review, the rarity of diseases in the pediatric population is one of the main factors determining whether a medication is supported by pediatric clinical trials. For these diseases, further government incentives and requirements are unlikely to be effective in promoting pediatric clinical trials because of the inherent difficulties associated with the limited number of patients. While not ideal, we propose that adopting alternative clinical protocols suited for a limited cohort and/or imposing a duty to report off-label use to a centralized database may provide valuable information for physicians to use relevant medications for treating pediatric patients with such diseases.

Keywords

Pediatric Clinical Trials, Rare Disease, Off-label Use, Pediatric Exclusivity, Pediatric Research Equity Act

1. Introduction

A substantial number of the medicines administered to pediatric patients (up to 18 years old) constitute off-label uses of the medications (1a, 1b, 1c). That is, pediatric patients are given a drug to treat a disease or condition for which the drug has not been approved in children. While kids tend to be healthier than adults, when they get sick, they often have different needs and react differently to medications than adults (2). A common misconception that many people share is that kids are tiny adults and can take the same medications for the same or even just similar illnesses (3). Reducing the dosing amount of a corresponding medication approved for adults might, in some cases, be suitable for treating some pediatric patients and conditions. However, without supporting research and information gleaned from pediatric clinical trials, it is difficult to predict how a child will respond when underdosed with a medication for off-label use (4a). Off-label uses put vulnerable pediatric patients at an increased risk because they can result in unforeseen adverse drug reactions (4b). In 1994, the United States implemented the Pediatric Exclusivity Provision in an effort to encourage pediatric drug development and to address issues of inadequate pediatric clinical testing, drug labeling, treatment information, and regulation in general (5). Under the Pediatric Exclusivity Provision, a drug manufacturer that conducts pediatric clinical trials and meets certain requirements set by the government is entitled to add an additional 6 months of exclusivity to its patents that cover the drug (5). The United States government's efforts to encourage and regulate pediatric drug development were furthered in 2003, with the passing of the Pediatric Research Equity Act that gives the FDA the authority to require drug manufacturers to study their products in pediatric populations if the drugs are likely to be used in children, ensuring that medications are safe and effective for younger patients. Unfortunately, despite the incentives and requirements provided by the government, pediatric clinical trials, although

2 Corresponding author: Michelle Liu, Thomas S. Wootton High School, 2100 Wootton Pkwy, Rockville, MD 20850
[2]Kenley K. Hoover, Nixon & Vanderhye PC, 901 N Glebe Rd #1100, Arlington, VA 22203

improving, are still lacking (6a, 6b). In fact, it was found that between 2007 and 2011, for the five conditions with the highest disease burden among children, only 12% of clinical trials registered were pediatric trials, whereas 60% of the disease burden was attributed to children (6b).

Many potential reasons may account for the lack of sufficient pediatric clinical trials (7a, 7b). For example, there may be ethical issues associated with clinical testing of the pediatric population (7c). The pediatric patient population may be small in number, which can increase the difficulty of conducting a randomized clinical trial (8). And for some uncommon conditions, there may not be enough financial incentive for pharmaceutical companies to develop and/or market a drug for pediatric use (9).

In this paper, we review the current trends in pediatric clinical trials conducted for marketed drugs in the United States in an attempt to understand some of the driving forces that influence a pharmaceutical company's decision regarding whether or not to conduct a pediatric clinical trial for a drug, either as a new drug or for an already approved drug. We first review the prescribing information for some of the top-selling drugs to identify whether any pediatric clinical studies have been conducted for the drugs. We then analyze the types of drugs that are more likely to have support from pediatric clinical studies, and if an adult version of the drugs is approved first, we analyze the time lag between the initial approvals of the drugs for adults and their later approval for treating pediatric patients. We also reviewed the more recently approved drugs for rare disease indications and those using new technologies to understand whether the pediatric population is sufficiently represented in these drug approvals. Lastly, we summarize the trends we identify and provide our point of view to rationalize the trends and our conclusions.

2. Our Methodology

For this review, we obtained the prescribing information of the drugs we analyzed from the United States Food and Drug Administration's (FDA) database, Drugs@FDA, which is a public database that allows a user to search for and obtain information for an FDA-approved drug at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm. The Drugs@FDA database includes the FDA's approval history for approved drugs and includes the different versions, if any, of FDA-approved labels for such drugs. For example, for some drugs, the initially approved labels do not include pediatric clinical trial information, but afterward, updated labels are approved for such drugs, which include newly conducted pediatric clinical trial information. During our review, we analyzed the prescribing information of select best-selling drugs to determine whether they include any pediatric clinical trial information and to evaluate the lag time between the initial approval of the drug for its use in adults and the time when the first pediatric clinical trial information is included in an approved label for the drug.

We first reviewed the top 30 bestselling drugs worldwide in 2023 (10). We hypothesized that the economic incentives provided by pediatric exclusivity would be the strongest for top-selling drugs – a 6-month additional exclusivity can translate into billions of dollars of extra profit. However, to our surprise, there was no uniform inclusion of pediatric clinical trial information or data in the approved labels for these top-selling drugs. Overall, only about 66% of the top 30 selling drugs we reviewed include information on pediatric clinical trials. Our review also found that the lag time for the inclusion of pediatric clinical trial information in the label of the analyzed drugs varied greatly from 0, i.e., no lag time (Trikafta®), a few months (Farxiga®), to more than 11 years (Eylea®) from the initial approval of the drug by the FDA. Overall, this analysis did not identify any clear trend for the top 30 bestselling drugs.

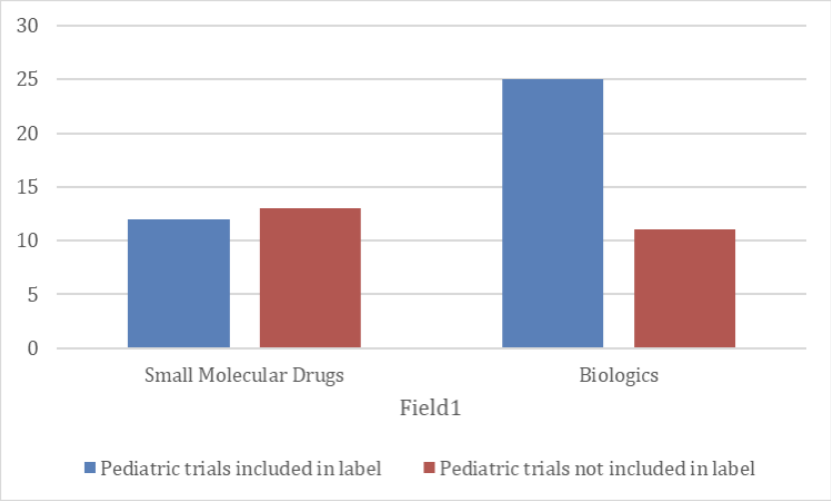
We then reviewed the prescribing information of drugs that ranked from 180-200 by sales in 2023 (10). Our rationale was that if annule sale is a determining factor, then we may expect that the chance of a drug having pediatric clinical support in the bottom 20 of bestselling drugs would be lower than that for drugs appearing on the top 30 of bestselling drugs. Among the drugs ranked from 180-200 that we analyzed, about 60% included pediatric clinical trial information, which was slightly less but very close to the 66% observed for the top 30 bestselling drugs. See, Figure 1 below. The lag time for the labels of these dozen or so drugs to include pediatric clinical information in their labels ranged from 0 to more than 11 years from the initial drug approval for adult use by the FDA. Since our review found that there is little difference between the top 30 bestselling drugs and those ranked 180-200, in terms of the inclusion of pediatric clinical trial information in their labels, we conclude that the annual sale of a drug does not appear to be a determining factor for whether the pharmaceutical industry conducts pediatric clinical trials.

Figure 1. Comparison of prevalence of pediatric trials in top-selling drugs and others

3. Small Molecule Drugs vs. Biologics

Next, we evaluated whether the prevalence of a pediatric clinical trial for a drug correlates with whether the drug is a small molecule drug (with a molecular weight less than 1,000 Da) or another type of drug, such as a peptide, antibody, vaccine, nucleic acid, polysaccharide, etc. (collectively termed "biologics" herein). Our results, shown in Figure 2 below, indicate that more pediatric clinical trials were conducted for biologics. About 70% of the biologics we analyzed have pediatric trial information on their approved labels as compared to less than 50% of the approved labels for small molecule drugs. These results suggest that there may be more incentives for a pediatric clinical trial to be performed for a biological drug than for a small molecule drug.

Figure 2. Prevalence of pediatric trials in small molecule drugs and biologics



4. Disease Area Categories

Next, we reviewed whether pediatric clinical trials are more frequently conducted in particular disease areas. We categorized the drugs based on their use in nine different disease areas: oncology, cardiovascular, diabetes, immunology, infectious disease, ophthalmology, genetic disease, neurology, and rare diseases. Drugs that contain pediatric clinical trial information listed in their labels, either as of the initial approval or a revised label subsequent to the initial approval, are italicized in Table 1, whereas those that do not are not italicized. As reflected in Table 1, all the evaluated drugs for treating rare diseases and genetic diseases have been clinically tested in pediatric populations. The majority of the considered drugs for treating infectious disease and immunology were also clinically tested in pediatric patients, with about 70% of the drugs having pediatric clinical trial information in their prescribing information. About 60% of the considered drugs for treating cardiovascular disease or diabetes also have pediatric clinical trial information on their approved labels. However, for the drugs considered for treating ophthalmology, neurology, and oncology, the prevalence of pediatric clinical trial information in their labels dropped to about 40% or below. These results suggest that the disease that a drug treats is a better indicator of whether a pediatric clinical trial is conducted for a drug than the annual sale of the drug. Our review also found that the highest percentages of drugs that contain pediatric clinical trial support in their labels are found in the disease areas of genetic, rare, infectious, and immunology-related diseases. Perhaps not coincidentally, the drugs approved in these disease areas were also more frequently found to be biological drugs rather than small molecule drugs. For example, all drugs listed in Table 1 under the column "rare diseases" are biological drugs.

Table 1. Pediatric Clinical Trials for Drugs in Different Disease Areas

Oncology	**Cardiovascular disease**	**Diabetes**	**Immunology**	**Infectious disease**	**Ophthalmology**	**Genetic disease**	**Neurology**	**Rare diseases**
Keytruda®	Eliquis®	Ozempic®	*Humira*®	*Biktarvy*®	*Eylea*®	*Trikafta*®	Ocrevus®	*Myozyme*®
Opdivo	*Xarelto*®	Jardia	*Dupixent*®	*Comirna*	Vabysmo®	*Spinraz*	*Botox*®	*Advate*®

®		nce®		*ty*®		*a*®		
Darzalex®	*Entresto*®	*Trulicity*®	*Stelara*®	*Gardasil*®	Lucentis®	*Takhzryo*®	*Vyvanse*®	*Kogenate*®
Imbruvica®	Opsumit®	*Insulin*®	Skyrizi®	*Prevnar*® *Family*		*Crysvita*®	Invega Sustenna®	*Alprolix*®
Revlimid®	*Repatha*®	*Farxiga*®	Entyvio®	*Shingrix*®			*Vraylar*®	*Cerezyme*®
Xtandi®		Mounjaro®	*CoSentry*®	*Vemlidy*®			*Epidiolex*®	
Tagrisso®		Humulin®	*Synagis*®	Cabenuva®			Concerta®	
Zytiga®							Ubrelvy®	
Libtayo®							Avonex®	
Adcetris®								

Since significant differences were observed between the considered disease areas, we then evaluated whether the FDA approves a drug with or without a pediatric clinical trial based on the prevalence of the indication treated by the drug in pediatric populations.

In this regard, we first reviewed the drugs listed in Table 1 approved for treating diseases under the column "rare diseases", which all coincidentally happened to be genetic diseases. Not surprisingly, the indications approved for the drugs under this disease area were generally found in children who inherited a particular genetic defect. For example, Myozyme®, an analog of alpha-glucosidase, is approved as an enzyme replacement therapy (ERT) for the treatment of Pompe disease (11a). Pompe disease patients are primarily children, with the infantile-onset occurring within the first few months of life and is characterized by its lack of alpha-glucosidase (11b). However, late-onset Pompe disease can affect both children and adults (11b). Myozyme® approval was based on the improved ventilator-free survival in patients with infantile-onset Pompe disease as compared to an untreated historical control, whereas patients with other forms of Pompe disease, such as the late-onset Pompe disease has not been adequately studied to assure safety and efficacy. Thus, in a way, the older adult population may use Myozyme® off-label based on pediatric clinical information. Similarly, Advate® and Kogenate® are both a recombinant antihemophilic factor, approved for treating Haemophilia A, which is an inherited genetic disease that causes deficiencies in blood clotting factor VIII, in adults and children(12a). Haemophilia A can manifest in children at a young age (12b). It was clinically shown that children have a higher Factor VIII clearance, although in a different study, the efficacy of the drugs was shown to be similar among adults and the pediatric population (12a). The pharmacokinetic difference observed in the pediatric and adult population for these drugs further demonstrates the importance of having clinical information in the FDA approved labels, which can prevent incorrect and potentially detrimental treatment in the pediatric population. Alprolix® is a recombinant coagulation Factor IX fusion protein consisting of the human coagulation Factor IX sequence covalently linked to the Fc

domain of human immunoglobulin G1 (IgG1), approved for treating Haemophilia B (Christmas disease) in adults and children (13a) Haemophilia B is an inherited genetic disease that causes blood clotting factor IX deficiencies and can cause excessive bleeding in childhood (13a, 13b). The pediatric approval of Alprolix® was based on clinical studies from adults and children from 12-17 years old and from 1-11 year old (13a) Lastly, Cerezyme® is an analogue of the human enzyme b-glucocerebrosidase approved for treating Gaucher's disease in adults and pediatric patients 2 years or older (14a) Gaucher's disease is a genetic disorder in which glucosylceramide accumulates in patients due to a deficiency of β-glucocerebrosidase activity (14a, 14b). Gaucher's disease, depending on the different types, can have symptoms occurring early in life and even in adulthood and can cause children to die at an early age (14b). The pediatric approval of Cerezyme® was based on well-controlled studies in adults and pediatric patients of 12 years and older, and additional data from the medical literature and postmarketing experience in pediatric patients as young as 2 years old (14a). In this group of approved drugs, the efficacy of the drugs in the pediatric patients can be expected from studies in their adult counterparts due to the same mechanism of actions. However, the difference in pharmacokinetics in adults and pediatric patients still demands clinical information to ensure that the dose used for treating pediatric patients is safe and efficacious.

Like rare diseases, the indications approved for the drugs under the column "genetic disease" were generally found in children with a particular genetic defect/mutation. For example, Trikafta®, a fixed combination of elexacaftor, tezacaftor, and ivacaftor, which are CFTR modulators, is approved for the treatment of cystic fibrosis for adults and pediatric patients aged 2 years or older with certain mutations in the *CFTR* gene (15). Symptoms of cystic fibrosis may appear in infancy, childhood, or adulthood (16). The pediatric use of Trikafta® was based on well controlled clinical trials in the pediatric population (15). Similarly, Spinraza® is a survival motor neuron-2 (SMN2)-directed antisense oligonucleotide indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients (17). Spinraza® is designed to treat SMA caused by mutations in chromosome 5q that lead to SMN protein deficiency (17). The onset of SMA can range from before birth to adulthood (18). Safety and effectiveness of Spinraza® in the pediatric population were established in clinical studies (17). Takhzryo® is a plasma kallikrein inhibitor indicated for the prevention of hereditary angioedema (HAE) in adult and pediatric patients 2 years and older (19). Onset of HAE can vary, typically from childhood to age 20 (20). The pediatric approval of Takhzryo® was based on subgroup studies of patients of 12 years and older in clinical studies that also included adult patients, and an extrapolation to patients of 2 to 12 years old based on pharmacokinetic studies (19). Lastly, Crysvita® is a fibroblast growth factor 23 (FGF23) blocking antibody indicated for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients 1 year of age and older (21). XLH is caused by excess FGF23, which suppresses renal tubular phosphate reabsorption and the renal production of 1,25 dihydroxy vitamin D (21). Although typically a childhood condition, XLH can continue to progress into adulthood (22). The pediatric approval of Crysvita® was based on open label studies in patients 1 year and older (21).

We then reviewed the drugs listed in Table 1 that are approved for treating the disease areas of ophthalmology, neurology, and oncology, and were observed during our review to have the lowest percentage of approved drugs that are supported by pediatric clinical trials in their labels. In ophthalmology, Eylea® was the only drug with pediatric clinical trial support included in its label. Eylea® is approved for wet age-related macular degeneration, Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), Diabetic Retinopathy (DR), and Retinopathy of Prematurity (ROP) (23). Eylea®'s prescribing information indicates that two clinical studies were conducted for pre-term infants with ROP (23). The two drugs that do not have pediatric clinical trials may be easily understood, as both Vabysmo® and Lucentis® are approved for treating age-related

macular degeneration, a condition typically occurring in the geriatric patient population (24a, 24b). Like Eylea®, Vabysmo® is also approved for treating DME, which, although rare, can also occur in the pediatric population (25). The pediatric clinical trial conducted for Eylea® relates to treating ROP, not DME. A pediatric clinical trial was also not conducted for the use of Eylea® in treating RVO, which may potentially occur in the pediatric population (26). Overall, the data suggests that pediatric clinical trials are not conducted for some of the ophthalmology diseases may be due to the rarity of the disease in children. It is, however, interesting to see that the same drug can have uses in both adult and pediatric populations for different indications, and depending on the drug developer, the drug may or may not be extended to a pediatric indication.

In the neurology disease area, however, there does not appear to be a clear trend. As one might expect, some drugs that do not have pediatric clinical trial information on their label are approved for indications that are less likely to occur in the pediatric population. For example, Ocrevus® and Avonex® are both approved for treating multiple sclerosis (MS), which is a condition that rarely affects children, who only account for about 5% of the total MS patient population (27). Invega Sustenna® is approved for schizophrenia in adults, and Vraylar® is approved for treating schizophrenia and bipolar disorders (28a). Childhood schizophrenia is an uncommon but severe mental disorder (28b). Bipolar disorders can also occur in children but are rare (28c). Conversely, other approved indications for the drugs in the neurology disease area frequently occur in children but do not include pediatric clinical trial information in their labels. For example, Ubrelvy® is approved for treating migraines with or without aura in adults, but no pediatric clinical trial has been conducted as of now (29a). According to one report, about 10% of children experience migraines, and migraines may affect children differently from adults (29b). Overall, the results show that the rarity of the disease alone does not determine whether a pharmaceutical company conducts a pediatric clinical trial in the neurology disease area.

Lastly, we reviewed the drugs in the oncology disease area that do not have pediatric clinical trial support in their labels. Pediatric cancer is, in general, rare. As discussed below, the approved oncology drugs in Table 1 that do not have pediatric clinical trial information are generally approved for treating indications that rarely occur in children. For example, Xtandi® and Zytiga® are indicated for treating prostate cancer (30). Darzalex® is approved for treating adult patients with multiple myeloma, but no safety and efficacy have been established for treating pediatric patients (31a). Multiple myeloma is very rare in the pediatric population, with only about 30 cases reported in the literature for patients under age 18 (31b). Revlimid® is approved for a variety of indications, including multiple myeloma, transfusion-dependent anemia, mantle cell lymphoma, follicular lymphoma, and marginal zone lymphoma (32a). These approved indications for Revlimid® are all rare in the pediatric population; the lymphoma approved for Revlimid® is generally considered low-grade B-cell lymphoma, which increases in frequency with increasing age (32b). For example, marginal zone lymphoma is primarily occurring in older patients from 55-65 years old and is extremely rare in children (32c). Tagrisso® is approved for treating non-small cell lung cancer, which is also extremely rare in the pediatric population (33a, 33b). Libtayo® is a programmed death receptor-1 (PD-1) blocking antibody approved for treating cutaneous squamous cell carcinoma, basal cell carcinoma, and non-small cell lung cancer, all of which are rare in the pediatric population.

In summary, most of the evaluated approved drugs that do not have pediatric clinical trial information are in diseases that rarely occur in children. However, for specific indications in neurology, the rarity of diseases alone does not explain why some approved drugs do not have pediatric clinical trial support.

5. Rare Diseases

Our initial results prompted us to look into whether the FDA-approved drugs for rare diseases that can occur in the pediatric population are often supported by pediatric clinical trials. It was reported that there are about 7,000 rare diseases, 75% of which are known to affect children (34). According to a study by Kakkilaya *et al.*, from 2011 to 2023, the FDA approved 918 indications for 553 new drugs, 407 of which were rare diseases (designated as orphan drugs) and 231 labeled for pediatric use (35). Further, out of the 407 rare diseases, 136 (or 33.4%) received pediatric approval (35) The percentage of 33.4% is lower than what we would have expected. However, this is likely due to the fact that Kakkilaya *et al.* did not categorize whether all of the 407 rare diseases are relevant to children. In the 2019 FDA's report to congress, although a different sample size (between April 1, 1999 and August 31, 2018), the FDA determined that only about 64% of the orphan drugs approved may be related to children, and about 36% of the approvals do not contain complete pediatric information (36). Nevertheless, Kakkilaya *et al.* did find that the percentages of drug approvals supported with pediatric studies for rare diseases were higher than those approved for non-orphan diseases (35). This result is consistent with our findings that drug approval for rare diseases in the top 200 best-selling drugs we reviewed is more likely to include pediatric clinical trial information.

To understand the more recent trend in pediatric approvals for rare diseases, we searched the FDA's orphan drug designations and approvals database for the period between January 1, 2024, and February 17, 2025, at https://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm. During this time, there were 37 pediatric approvals for rare diseases out of a total of 87 orphan drug approvals, thus representing 42.5% of all orphan drug approvals. This rate is similar to the 33.4% observed by Kakkilaya *et al.* (35). The majority of these pediatric approvals are indicated for both pediatric and adult populations, except five of them are only approved for the pediatric population. Not surprisingly, these five pediatric-only approvals are for diseases that typically only concern the pediatric population.

Additionally, we reviewed the recently approved drugs for rare diseases that are not approved for pediatric uses. Here, the rarity of diseases in the pediatric population also appears to be the main reason that no clinical trials were conducted. For example, CALQUENCE, which was approved in January 2025 for the treatment of mantle cell lymphoma (37). Mantle cell lymphoma is a cancer mainly affecting middle age to old adults and not reported in pediatric population (38). The same is true in the case for the drug, Attruby, approved in November 2024 for treating transthyretin amyloidosis (39). Amyloidosis in children was reported as extremely rare and not reported for the specifically approved transthyretin amyloidosis (40).

In summary, many drugs containing information about pediatric use are approved for rare diseases. Spot checking drugs approved for the rare diseases recently also suggests that the rarity of diseases in pediatric population is the main reason that some of the approved drugs do not include pediatric clinical information. Drugs approved for rare diseases only represent a small fraction of all rare diseases, most of which concern the pediatric population. Further efforts and/or incentives are still needed for the pharmaceutical industry to conduct further clinical research in these rare diseases.

6. New Technology

We also analyzed the FDA-approved drugs that use new technologies and are approved for use in the pediatric population. In recent years, emerging classes of medications and treatments have become available, which may offer significant advantages to traditional drugs. These new technologies include, for example, mRNA vaccines, gene therapies, and cell therapies. As with any other new technologies, we expect that the adoption will be slow. As such, our initial thoughts are that drugs using these new

technologies will be first approved in adults and gradually expanded to the pediatric population, if at all.

The mRNA vaccine approval for COVID-19 is an example of how the pharmaceutical industry expands adult uses to the pediatric population. During the pandemic, mRNA vaccines were first approved for use in adult population under emergency use authorizations (41). The initial clinical trials were not conducted in the pediatric population. Subsequently, clinical trials were gradually expanded to adolescent populations of 16 years or older (42a), and then to 12 to 15 years (42b). Children of 5-11 years old were then studied in clinical trials (42c). Eventually, the vaccine was authorized for use in all age groups from 6 months and above (42c). Although the pandemic may have accelerated the use of such new technologies in the pediatric population, the pharmaceutical industry did follow a gradual course to slowly expand the clinical studies to the pediatric population, perhaps partially because this represents the first mRNA drug ever used in human.

Cell therapies and gene therapies have been shown to be promising in treating certain genetic diseases. In this category, many of the approved products include pediatric support. For example, KYMRIAH® is a CAR-T therapy approved for use in patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia, targeting specifically CD19 (43). ELEVIDYS is an adeno-associated virus vector-based gene therapy for treating Duchenne muscular dystrophy (DMD) in patients of 4 years or older who have a confirmed mutation in the DMD gene (44). CASGEVY is another breakthrough gene therapy indicated for treating sickle cell disease in patients 12 years and older (45). CASGEVY is based on autologous CD34+ HSCs edited by CRISPR/Cas9-technology to increase fetal hemoglobin (HbF) protein production, which reduces intracellular hemoglobin S concentration, preventing the red blood cells from sickling (45) It is interesting to note that the CASGEVY approval for pediatric population was based on a clinical study with 12 patients aged 12 to less than 18 years. The sample size is typically too small for traditional therapy (45). However, in these types of gene editing based therapy, which uses autologous cells, the limited sample size may nonetheless support the efficacy and its use for other similarly situated patients.

In addition, new drug discovery/delivery platforms are being used in drug discovery and development, which include, for example, vector/gene delivery, targeting splicing factors, exon skipping, PROTACs (molecular glue), CAR-T cells, mRNA vaccines, etc. If a drug discovery/delivery platform is age-agnostic, we expect that there will be more pediatric clinical trials related to that drug(s), since they can be put to use in the adult population as well (even if for a different indication) and vice-versa, i.e. if the platform is successful in clinical trials in adult patients, it stands a good chance of being successful in pediatric patients as well. However, caution should be taken as it has been reported that signaling pathways can be altered with age (46), hence targeting those pathways or their products or their perturbations will not be age-agnostic.

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In summary, limited data on new classes of therapeutics suggest that the pharmaceutical industry is ready to adopt new technologies to the pediatric population.

7. Discussions and Conclusions

The results of our review suggest that a pharmaceutical company's decision with respect to whether to conduct a pediatric clinical trial for an approved drug depends on numerous factors, among which the rarity of occurrence of the disease to be treated in the pediatric population is a predominant consideration. The majority of the labels for the drugs that we reviewed have pediatric clinical trial

information, with the exception of those drugs that are approved for indications that are not common in the pediatric population.

However, the rarity of the occurrence of a disease in the pediatric population is a relative term. For example, for multiple sclerosis (MS), children are estimated to make up only about 5% of the total patient population. However, the total MS patient population is estimated to be nearly 1 million in the United States, which means that close to 50,000 pediatric patients have multiple sclerosis in the U.S. alone. Clearly, without sufficient pediatric clinical trials for such a patient population, these children will be treated only on an off-label basis.

Furthermore, some diseases, while rare, are still serious and life-threatening for pediatric patients. For example, cancer in children is, in general, rare but can affect those children having cancer and their families significantly regardless of the rarity of their occurrence. Without sufficient clinical information, these children may not receive proper treatment. For these rare pediatric indications, perhaps conducting randomized clinical trials is impractical for pharmaceutical companies due to the limited availability of patients to participate in such trials. For these indications, one can only hope that pharmaceutical companies, the scientific and regulatory agencies work together to develop better mechanisms and incentives to ensure that drugs are developed to treat these rare conditions and that children with these rare conditions receive an informed treatment that takes into consideration pediatric clinical trial information and the best available treatment options.

One encouraging sign is that pharmaceutical companies are conducting pediatric clinical trials to expand the initial approval of their drugs in adults to include pediatric patients, and pharmaceutical companies are also conducting pediatric clinical trials to treat indications that are unique to children. For example, Keytruda® was initially approved in 2014 for treating unresectable or metastatic melanoma with no safety or efficacy studies on pediatric use (47a). Subsequently, Keytruda® has also been approved for many different adult cancers (47b). Merck, the manufacturer of Keytruda®, has conducted further clinical trials that have supported the expansion of the approved indications of Keytruda® to include the treatment of pediatric patients with classical Hodgkin Lymphoma (cHL), Primary Mediastinal Large B-cell lymphoma (PMBCL), Microsatellite Instability-High or Mismatch Repair Deficient Cancer (MSI-H Cancer), Merkel Cell Carcinoma (MCC), or Tumor Mutational Burden-High (TMB-H) Cancer (TMB-H Cancer) (47c). According to the label of Keytruda®, clinical trials were conducted for patients with advanced melanoma, lymphoma, or PD-L1 positive solid tumors (47c). Although the Keytruda® label does not indicate that children with other types of pediatric cancers can be treated with Keytruda®, for which their adult counterpart has been approved, the inclusion of some pediatric clinical information for which Keytruda® has been tested may, nevertheless, provide valuable information for doctors when deciding whether and how to treat a child with rare cancer with Keytruda®, even if off label.

However, the Keytruda® example is not generally applicable to all other drugs, and there are still gaps due to the rarity of certain diseases in pediatric populations. Further incentives or requirements from the government will not close the gaps for such diseases because it may be impossible or impractical to conduct pediatric clinical trials due to the limited number of patients. For such situations, we propose two alternatives to conventional pediatric clinical trials, which may provide useful information for treating physicians when using a drug off-label.

The first alternative is to adopt alternative clinical protocols suited for a limited cohort when running pediatric clinical trials, such as by not requiring double-blind trials. A double-blind or well-controlled clinical trial in such situations can be nearly impossible due to a limited patient pool. On this approach, we are also encouraged to observe that the FDA, under certain circumstances, accepted clinical studies

or information without randomized clinical trials as supporting the pediatric use of a drug. As discussed above, open-label studies, subgroup analysis, extrapolations based on pharmacokinetic studies, medical literature, and post-marketing experience, etc., have all been used to support pediatric use of the approved drugs. Another potential way to lower the burden for pediatric clinical trials is for the FDA to accept more biomarker outcomes as clinical end points for certain diseases rather than using the ultimate treatment outcomes, which should promote more clinical trials in the pediatric population. This is especially true for diseases from which death or permanent disability can occur within < 5 years of age, such as muscular dystrophy or Spinal Muscular Atrophy, etc. In such cases, the FDA is more likely to and perhaps should accept clinical marker improvements as surrogates for QOL (quality of life) improvements, even if the clinical marker improvements do not necessarily translate into QOL improvements. For example, Elevidys, marketed by Serepta Therapeutics for DMD, priced at $3.2 million for a one-time treatment, was approved by the FDA despite failing the primary endpoint (48).

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As a second alternative, the government can impose a duty for a physician treating a pediatric patient off-label to submit relevant safety and efficacy information to a centralized database. Even though not ideal, such a centralized database would provide at least some information that can guide future doctors when treating patients with similar conditions.

In addition, from a policy perspective, which is not the focus of this paper, the authors suggest that pharmaceutical companies and/or other interest groups collaborate with startup companies that are researching pediatric diseases to expedite clinical trials on such pediatric diseases and together control the cost of the ultimate approved drugs. For example, policies that dis-incentivize big pharma from buying out startup companies that are researching pediatric diseases and then discontinuing or delaying such research may lead to more of such clinical trials being performed faster. This will increase the likelihood that the resultant drugs (if approvable) are cheaper. After all, many rare diseases affecting children still have no FDA approved drugs as treatment options.

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In conclusion, while pharmaceutical companies have conducted pediatric clinical trials, gaps exist. For rare conditions in children, doctors still have limited information to make informed treatment decisions. Conducting pediatric trials for some indications while expanding a drug's approval to other conditions that affect a significant number of children, although not a complete solution, can provide lifesaving information for doctors to use off-label drugs more safely in children. Alternatively, the government can also adopt alternative clinical protocols suited for a limited cohort in rare pediatric diseases or demand physicians to submit off-label use information to a centralized database, which should also provide valuable information for doctors.

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