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Clinical trials of drugs in the pediatric population

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Abstract

This paper reviews current trends in pediatric clinical trials conducted for drugs in the United States. There are many known challenges in conducting clinical trials in the pediatric population, including the lack of available patients and financial incentives, among others. 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 in determining whether pediatric clinical trials are conducted for a given medication. 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 and the severity of the disease. While not ideal, we propose that adopting alternative clinical protocols suited for a limited cohort as well as using relevant biomarkers and the quality of life (QOL) as primary clinical endpoints may encourage and expedite clinical trials in pediatric patients. FDA guidance on efficacy age-agnostic scientific and technological platforms may incentivize expanding the use of approved drugs in pediatric patients with only pharmacokinetic supporting data. In addition, instituting a requirement to report off-label (pediatric) 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, Food and Drug Administration, Pharmaceutical industry, Alternative clinical protocols, Orphan drugs, Clinical end point

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1. Introduction

A substantial number of the medicines administered to pediatric patients (up to 18 years old) constitute off-label uses of the medications (1-3). 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 children tend to be healthier than adults, when they get sick, they often have different needs and react differently to medication than adults (4). A common misconception that many people share is that children are tiny adults and can take the same (reduced dosage) medications for the same or even just similar illnesses (5). 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 mis-dosed with a medication for off-label use (6). Off-label uses put vulnerable pediatric patients at an increased risk because they can result in unforeseen adverse drug reactions (7). 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 (8). Under the Pediatric Exclusivity Provision, a drug manufacturer that conducts pediatric clinical trials and meets certain requirements set by the United States Food and Drug Administration (FDA) is entitled to add an additional 6 months of exclusivity to its patents that cover the drug (8). 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 improving, are still lacking (9, 10). 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 (10).

Many potential reasons may account for the lack of sufficient pediatric clinical trials (11, 12). For example, there may be ethical issues associated with clinical testing of the pediatric population (13). The pediatric patient population may be small in number, which can increase the difficulty of conducting a randomized clinical trial (14). For some uncommon conditions, there may not be enough financial incentive for pharmaceutical companies to develop and/or market a drug for pediatric use (15).

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 these 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 measure 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. Methods

For this review, we obtained the prescribing information of the drugs we analyzed from the FDA database, Drugs@FDA, which is a public database that allows a user to search 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 subsequently, updated labels are approved for such drugs, which include recently 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 measure 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 (16). 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, ~ 66% of the top 30 selling drugs we reviewed included 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 (16). Our rationale was that if annual sales 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, ~ 60% included pediatric clinical trial information, which was not significantly different from the ~ 66%

observed for the top 30 bestselling drugs as shown in Figure 1. 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 was no significant 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 concluded that the annual sale of a drug did not appear to be a determining factor for whether the pharmaceutical industry conducted pediatric clinical trials for that drug.

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

2.1. *Small molecule drugs vs. Biologics*

Next, we evaluated whether the prevalence of a pediatric clinical trial for a drug correlated with whether the drug was a small molecule drug (with a molecular weight < 1,000 Da) or another type of drug, such as a peptide, antibody, vaccine, nucleic acid, polysaccharide, etc. (collectively termed "biologics" herein).

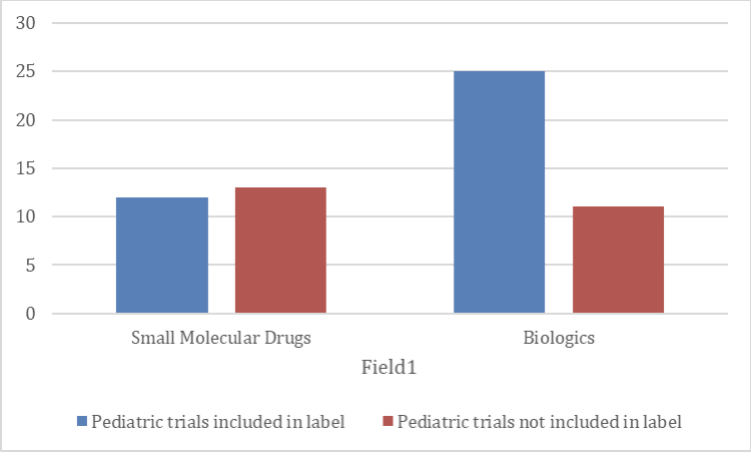

Figure 2. Prevalence of pediatric trials in small molecule drugs and biologics

Our results, shown in Figure 2, indicate that a larger number of pediatric clinical trials were conducted for biologics. ~ 70% of the biologics we analyzed had pediatric trial information on their approved labels as compared to < 50% of the approved labels for small molecule drugs. These results suggested that there may be more incentives for a pediatric clinical trial to be performed for a biological drug than for a small molecule drug.

2.2. *Disease area categories*

Next, we reviewed whether pediatric clinical trials were 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 contained pediatric clinical trial information listed in their labels, either as of the initial approval or a revised label subsequent to the initial approval, are presented in italicized format in Table 1, whereas those that did not are not italicized.

Table 1. Pediatric clinical trials for drugs in different disease areas

Oncology	**Cardio-vascular disease**	**Diabetes**	**Immunology**	**Infectious disease**	**Ophthalmology**	**Genetic disease**	**Neurology**	**Rare diseases**
Keytruda®	Eliquis®	Ozempic®	*Humira*®	*Biktarvy*®	*Eylea*®	*Trikafta*®	Ocrevus®	*Myozyme*®
Opdivo®	*Xarelto*®	Jardiance®	*Dupixent*®	*Comirnaty*®	Vabysmo®	*Spinraza*®	*Botox*®	*Advate*®
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®								

As shown in Table 1, all the evaluated drugs for treating rare diseases and genetic diseases were 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 ~ 70% of the drugs having pediatric clinical trial information in their prescribing information. ~ 60% of the considered drugs for treating cardiovascular disease or diabetes also had 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 < 40%. These results

suggested that the disease that a drug treats was a better indicator of whether a pediatric clinical trial was conducted for a drug than the annual sales of the drug. Our review also found that the highest percentages of drugs that contained pediatric clinical trial support in their labels were 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.

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 (17). 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 (18). However, late-onset Pompe disease can affect both children and adults (18). 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 have 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 (19). Haemophilia A can manifest in children at a young age (20). 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 (19). 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 (21). Haemophilia B is an inherited genetic disease that causes blood clotting factor IX deficiencies and can cause excessive bleeding in childhood (21, 22). 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 (21). Lastly, Cerezyme® is an analogue of the human enzyme β-glucocerebrosidase approved for treating Gaucher's disease in adults and pediatric patients 2 years or older (23). Gaucher's disease is a genetic disorder in which glucosylceramide accumulates in patients due to a deficiency of β-glucocerebrosidase activity (23, 24). Gaucher's disease, depending on the different types, can have symptoms occurring early in life and even in adulthood and can cause mortality in children at an early age (24). 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, as well as postmarketing experience in pediatric patients as young as 2 years old (23). In this group of approved drugs, a similar efficacy of the drugs in the pediatric patients can be expected from studies in their adult counterparts due to the same mechanism of action. 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.

Similar to 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 Cystic Fibrosis Transmembrane Receptor (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 (25). Symptoms of cystic fibrosis may appear in infancy, childhood, or adulthood (26). The pediatric use of Trikafta® was based on well controlled clinical trials in the pediatric population (25). 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 (27). Spinraza® is designed to treat SMA caused by mutations in chromosome 5q that lead to SMN protein deficiency (27). The onset of SMA can range from before birth to adulthood (28). Safety and effectiveness of Spinraza® in the pediatric population were established in clinical studies (27). Takhzryo® is a plasma kallikrein inhibitor indicated for the prevention of hereditary angioedema (HAE) in adult and pediatric patients 2 years and older (29). Onset of HAE can vary, typically from childhood to age 20 (30). 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 (29). 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 (31). XLH is caused by excess FGF23, which suppresses renal tubular phosphate reabsorption and the renal production of 1,25 dihydroxy vitamin D (31). Although typically a childhood condition, XLH can continue to progress into adulthood (32). The pediatric approval of Crysvita® was based on open label studies in patients 1 year and older (31).

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) (33). Eylea®'s prescribing information indicates that two clinical studies were conducted for pre-term infants with ROP (33). The two drugs that do not have associated pediatric clinical trials is because they treat conditions that occur in the geriatric population. Both these drugs; Vabysmo® and Lucentis®; are approved for treating age-related macular degeneration, a condition typically occurring in the geriatric patient population (34, 35). Like Eylea®, Vabysmo® is also approved for treating DME, which, although rare, can also occur in the pediatric population (36). 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 (37). Overall, the data suggests that a reason 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 (38). Invega Sustenna® is approved for schizophrenia in adults, and Vraylar® is approved for treating schizophrenia and bipolar disorders (39). Childhood schizophrenia is an uncommon but severe mental disorder (40). Bipolar disorders can also occur in children but are rare (41). Conversely, other approved indications for the drugs in the neurology disease area frequently occur in children, however, they 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 (42). According to one report, about 10% of children experience migraines, and migraines may affect children differently from adults (43). 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 approved for treating indications that rarely occur in children. For example, Xtandi® and Zytiga® are indicated for treating prostate cancer (44). Darzalex® is approved for treating adult patients with multiple myeloma, but no safety and efficacy have been established for treating pediatric patients (45). Multiple myeloma is very rare in the pediatric population, with only about 30 cases reported in the literature for patients under age 18 (46). Revlimid® is approved for a variety of indications, including multiple myeloma, transfusion-dependent anemia, mantle cell lymphoma, follicular lymphoma, and marginal zone lymphoma (47). 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 (48). For example, marginal zone lymphoma primarily occurs in older patients from 55-65 years old and is extremely rare in children (49). Tagrisso® is approved for treating non-small cell lung cancer, which is also extremely rare in the pediatric population (50,51). 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 for 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.

2.3. *Rare diseases*

Our initial results prompted us to investigate 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 (52). 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 (53). Further, out of the 407 rare diseases, 136 (or 33.4%) received pediatric approval (53). This 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 were relevant to children. In the 2019 FDA's report to congress, although for a different sample size (between April 1, 1999 and August 31, 2018), the FDA determined that only ~ 64% of the orphan drugs approved may be related to children, and ~ 36% of the approvals do not contain complete pediatric information (54). Nevertheless, Kakkilaya *et al.* did find that the percentages of drug approvals supported with pediatric studies for rare diseases were higher than for those approved for non-orphan diseases (53). This result was 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 ratio is similar to the 33.4% observed by Kakkilaya *et al.* (53). The majority of these pediatric approvals were indicated for both pediatric and adult populations, except five, which were only approved for the pediatric population. Not surprisingly, these five pediatric-only approvals are for diseases that typically only occur in the pediatric population.

Additionally, we reviewed the recently approved drugs for rare diseases that were not approved for pediatric uses. Here, the rarity of diseases in the pediatric population also appeared to be the main reason that no clinical trials were conducted. An example is Calquence®, which was approved in January 2025 for the treatment of mantle cell lymphoma (55). Mantle cell lymphoma is a cancer mainly affecting middle age to old adults and not reported in pediatric population (56). The same is true in the case for the drug, Attruby®, approved in November 2024 for treating transthyretin amyloidosis (57). Amyloidosis in children was reported as extremely rare, and transthyretin amyloidosis; rarer still (58).

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.

2.4. *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 conventional 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 (59). 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 (60), and then to 12 to 15 years (61). Children of 5-11 years old were then studied in clinical trials (62). Eventually, the vaccine was authorized for use in all age groups from 6 months and above (62). 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 humans.

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 (63). 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 (64). Casgevy® is another breakthrough gene therapy indicated for treating sickle cell disease in patients 12 years and older (65). 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 (65). 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. This sample size is typically too small for traditional clinical trials (65). 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, 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 exercised in this regard, since it has been reported that signaling pathways can be altered with age (66), hence drugs targeting those pathways or their products or their perturbations will probably not be age-agnostic. In summary, limited data on new classes of therapeutics suggest that the pharmaceutical industry is ready to adopt new technologies in the pediatric population.

3. Discussion

The results of our review suggest that a pharmaceutical company's decision with respect to whether to conduct a pediatric clinical trial for a New Chemical Entity (NCE) or 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, pharmaceutical companies, the scientific and regulatory agencies should 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 (67). Subsequently, Keytruda® has also been approved for many different adult cancers (68). 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) (69). According to the label of Keytruda®, clinical trials were conducted for patients with advanced melanoma, lymphoma, or PD-L1 positive solid tumors (69). 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. In such cases, the FDA is more likely to, and perhaps should, accept disease severity or modification clinical marker, QOL (Quality Of Life) improvements instead of Overall Survival (OS) clinical end points. 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 (70).

As a second alternative, the government can impose a requirement 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 doctors when treating patients with similar conditions.

In addition, from a policy perspective, 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.

4. 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, pharmaceutical companies can be given leeway to adopt alternative clinical protocols suited for a limited cohort in rare pediatric diseases. The use of relevant biomarkers and the quality of life (QOL) improvement as primary clinical endpoints – as opposed to Overall Survival (OS) - may encourage and expedite clinical trials in pediatric patients. FDA guidance on age-agnostic scientific and technological platforms may incentivize expanding the use of approved drugs in pediatric patients with only pharmacokinetic supporting data. Requiring physicians to submit off-label (pediatric) use information to a centralized database, may provide valuable information for physicians to use relevant medications for treating pediatric patients with such diseases.

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