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Characteristics and Changes of Pediatric Therapeutic Trials under the Best Pharmaceuticals for Children Act

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Before 1997, children were usually excluded from therapeutic trials for numerous reasons. Therefore, most drug and biological products lacked adequate pediatric information in labeling.^{1,2} The Best Pharmaceuticals for Children Act (BPCA)³ and the Pediatric Research Equity Act (PREA)⁴ use incentives and requirements, respectively, to address this gap, spurring pediatric drug research and development to inform new pediatric drug labeling by allowing the US Food and Drug Administration (FDA) to request and require studies. As a result of these legislative initiatives, as of September 2016, more than 650 products have had new pediatric information added to labeling.

This article focuses on the BPCA incentive program. For this process, the FDA requests that the drug company perform a pediatric clinical trial program for a specific drug moiety, that is, the molecule responsible for the physiological or pharmacologic action of the drug substance.⁵ The document requesting the pediatric clinical trials is known as a Written Request (WR). The WR is sent to the drug company, also known as the sponsor, which holds the rights to the drug of interest. The sponsor has the option to accept the WR or decline because performing BPCA clinical trials is completely voluntary. If the sponsor accepts the WR, they conduct the pediatric clinical trials and submit the results to the FDA. A WR may include studies for both approved and unapproved indications. In fact, BPCA permits the FDA to request all feasible pediatric studies for a given moiety, including studies in neonates when appropriate. If the studies are completed as outlined in the WR, the FDA will grant the sponsor a reward of an additional 6 months of marketing exclusivity for the entire moiety that was studied. This reward is known as the Pediatric Exclusivity. Once pediatric studies are completed and submitted to the FDA, the agency reviews the new clinical data and updates the product labeling to inform healthcare providers regarding the safe and effective use of the drug in the pediatric population.

BPCA provides the FDA with a mechanism to request pediatric studies that would not usually otherwise be performed under PREA, which is limited to the drug under review and the indication proposed in adults. BPCA permits the FDA to request sponsors to study diseases or conditions that occur only in pediatric patients, such as pediatric cancer and pediatric rare diseases, including those with Orphan Designation.⁶ If a product obtains

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Orphan Designation, the FDA cannot require studies under PREA but can request them under BPCA.

Methods

For this review, we analyzed all pediatric studies completed pursuant to BPCA that resulted in a pediatric labeling change between September 27, 2007, and September 30, 2016. Pediatric trial information was extracted from medical, clinical pharmacology, and statistical reviews posted publicly on the FDA website for BPCA trials for the defined timeframe.^{7,8} The pediatric clinical trial information can usually be found in section 5 of the Medical Officer Review entitled “Sources of Clinical Data,” and the Review can be found on the FDA website.⁹ The FDA Document Archiving, Reporting, and Regulatory Tracking System was also used if the necessary trial information was not available from the reviews posted publicly on the FDA website. Document Archiving, Reporting, and Regulatory Tracking System data are not accessible to the public because these data contain confidential commercial information.

Information collected from BPCA pediatric studies included the date of the pediatric labeling change resulting from the studies, drug name, indication studied, therapeutic category, study type and design, ages studied, number of patients, number of clinical trial sites, participating countries, and racial and ethnicity data. Analyses included (1) trial types and designs, (2) indications applicable to both adults and children, or if they exist primarily in the pediatric population, indications that pertain to rare pediatric conditions, (3) number of children analyzed, (4) age spectrum included in trials for various therapeutic categories, (5) racial and ethnicity data of patients analyzed,¹⁰ (6) countries and trial sites, and (7) trends over time. Summary statistics were compiled by pivot tables in Microsoft Excel (Microsoft, Redmond, WA).

Drugs were classified by therapeutic indication. The trial design was defined by the reviewing FDA medical officer. Some FDA reviewers provided more information than others, and there were situations where specific information could not be found in the medical officer’s review for a given drug, for example, countries where the studies were performed.

Results

Between September 2007 and September 2016, there were a total of 292 BPCA pediatric therapeutic trials involving 98 drugs (Table I). These 292 trials resulted in 107 pediatric labeling changes. By trial type, there were 151 efficacy and safety trials completed, 51 pharmacokinetic (PK)/pharmacodynamic, 66 PK and safety, and 24 safety only trials. Safety information is obtained in all trials. In terms of trial design, 70 were double blind, 181 were open label, and 41 were single blind. The number of studies performed for each drug ranged from 1 to 9 with a median of 3.

Of the 107 pediatric labeling changes, 61 (57%) had a new or expanded age group, which means that the effectiveness and safety were established for the indication studied for pediatric patients or a pediatric subpopulation. However, 48 labeling changes (45%)

resulting from these studies indicated that safety and effectiveness could not be established in pediatrics for the indication studied.^{11,12} Additional information on safety was added to 8 of the 48 labeling changes, and pediatric clinical trial information was added to all 48 labeling changes. In total, 16 of the 107 labeling changes (15%) had new or enhanced pediatric-specific safety information added to the labeling, and 5 (5%) new labeling changes had a specific dosing change or adjustment. Importantly, as of 2007, studies conducted under BPCA and PREA must include information about the pediatric studies and a statement of the FDA's determination whether or not the studies demonstrated safety or efficacy or if the studies were inconclusive in pediatric populations in the labeling.

BPCA pediatric clinical trials spanned 15 therapeutic categories and 55 clinical indications, which generally reflect the focus of the various FDA scientific review divisions. The 5 most commonly studied therapeutic categories based on safety and efficacy studies were gastrointestinal, anti-infective, psychiatry, neurology, and cardiovascular (Table II). There were 231 clinical trials (79%) in 35 conditions that occur in both adult and pediatric patients, 39 clinical trials (13%) in 13 pediatric rare disease indications, and 22 clinical trials (8%) in 7 conditions that occur primarily in pediatric patients (Table III). The latter 2 categories would typically not be studied under PREA.

More than 43 000 pediatric patients were involved in the 292 clinical trials. The total number of patients enrolled in and completing BPCA trials is not available, because these numbers were not always reported in the medical officer reviews. Therefore, our review focuses on the number of patients analyzed in the clinical trial, which is usually between total enrolled and total completing the trial. For our dataset, 42 855 patients were analyzed across all trials: 30 629 pediatric patients in 151 efficacy and safety trials, 7108 patients in 117 PK and safety trials, and 5118 patients in 24 safety trials. The largest trial was for olopatadine for seasonal allergic rhinitis, which analyzed 1188 patients.¹³

Typically, a WR specified a pediatric age range for inclusion in the pediatric clinical trials, giving the sponsor the option of enrolling patients of any age within the requested age range. In some circumstances, the minimum number of pediatric patients within an age range was specified in the WR, for example, at least 3 neonates. In general, the majority of requested pediatric studies included patients between 2 and 17 years of age. For indications such as oncology and HIV, the age span also included older adolescents and young adults, for example, 18–26 years of age. The age range requested reflects the therapeutic category and the epidemiology of the condition. For example, psychiatry trials usually requested pediatric patients 6 to 17 years of age, reflecting the epidemiology of the disease in the pediatric population. Pulmonary trials usually requested pediatric patients 1 month to 12 years of age because adolescent data are usually obtained during adult trials. Oncology had the broadest age range of 1 month to 26 years of age. The inclusion of neonates and/or pediatric patients 1 month to less than 2 years of age was more frequently requested in cardiology, analgesic/anesthesia, gastrointestinal, anti-infective, ophthalmology, pulmonology, and hematology WRs. Of note, successful enrollment of neonates occurred in only 23 of 292 clinical trials (7.9%). These 23 clinical trials involved 2800 neonates and were performed in 5 therapeutic categories, namely, cardiovascular, analgesic/anesthesia, gastrointestinal, ophthalmology, and anti-infective.

Of the 292 trials, 227 reported a breakdown of patients analyzed by race and ethnicity. White patients were the majority, with 24 089 or 69% of those reported, followed by black (6042; 17%), other (2408; 7%), Asian (1915; 6%), American Indian or Alaska Native (283; 1%), and Native Hawaiian or Pacific Islander (72; 0%). The ethnic breakdown for those reported was 3036 Hispanic or Latino patients (19%) and 13 028 non-Hispanic or Latino (81%). Some trials enrolled greater numbers of patients from certain racial groups, reflecting the disease epidemiology. For instance, black patients constituted the majority in 13 HIV trials and 2 sickle cell disease trials. Asian patients were the majority in the 3 trials for Kawasaki disease, which is most common in males of Japanese ancestry, and for 2 HIV trials conducted in Thailand.¹⁴ There was no noticeable pattern for Hispanic patient inclusion.

Clinical sites by country were documented in 143 of the 292 trials. The US was the most common host country with 124 BPCA clinical trials registering at least 1 trial site in the US (87%). The next most common host countries were Canada (33), the United Kingdom (19), Russia (19), South Africa (16), France (16), Argentina (15), and Germany (15) followed by 64 other countries. The median number of sites per trial was 20 with a range from 1 to 191. On the far end of the spectrum, 1 trial for rizatriptan for the treatment of migraines enrolled 1147 pediatric patients across 191 clinical trial sites including 134 in the U.S.¹⁵ This was the second largest study conducted under BPCA. The largest trial conducted was a safety and efficacy study of olopatadine for seasonal allergic rhinitis in 6- to 11-year-old children conducted solely in the US, with 173 clinical trial sites. The US was not represented in 19 of 143 clinical trials (13%) with country-level data.

The types and designs of trials changed over time (Table IV), with an increase in double-blind efficacy trials and safety trials. During the early period (2007–2011), there were 18 double-blind efficacy trials, 41 single-blind efficacy trials, and 7 safety trials. In subsequent years (2012–2016), there were 45 double-blind efficacy trials, no single-blind efficacy trials, and 17 safety trials.

Additional shifts over time occurred in the number of pediatric rare diseases or predominately pediatric conditions studied under BPCA. During the 2007–2011 period, 19 studies were performed for 5 rare pediatric conditions: McCune-Albright syndrome with progressive precocious puberty, Kawasaki disease, subependymal giant cell astrocytomas, solid tumors, and osteogenesis imperfecta. During this same timeframe, 9 studies were performed for 4 pediatric-specific conditions: bronchopulmonary dysplasia prevention, precocious puberty in boys, delayed puberty in boys, and tinea capitis. One hundred nineteen studies were performed for 22 conditions that occur in both adult and pediatric patients. Examples include hypertension, prophylaxis of cytomegalovirus disease, herpes simplex, varicella zoster, and adjunct to general anesthesia.

In the later years (2012–2016), 20 studies were performed for 10 rare pediatric indications: pulmonary arterial hypertension, relapsed or refractory acute leukemia, solid tumors, subependymal giant cell astrocytomas, infantile spasms, phenylketonuria, acute lymphoblastic leukemia and lymphoblastic lymphoma, Lennox Gastaut syndrome, treatment of thrombocytopenia, and vaso-occlusive crises in pediatric patients with sickle cell disease.

During this timeframe, 13 studies were performed for 3 pediatric specific indications: attention deficit hyperactivity disorder, autism spectrum disorders, and attention deficit hyperactivity disorder-induced insomnia. One hundred twelve studies were performed for 23 conditions that occur in adult and pediatric patients, including complicated intra-abdominal infections, severe pain, blepharoconjunctivitis, sedation, and ulcerative colitis.

Discussion

The BPCA incentive has provided an enormous amount of information that has improved our understanding of issues associated with pediatric therapeutic clinical trials and the products studied. During the early implementation of the pediatric therapeutic trials programs, it was reasonable to construct trials for conditions that occur in both adults and children. These trials could be required under PREA for conditions such as hypertension, seasonal allergic rhinitis, and many infectious diseases.

The scope of BPCA is broader than PREA and, thus, over time, studies conducted under BPCA have increasingly focused on rare or pediatric-specific diseases. Our analysis identified 39 clinical trials (13%) in 13 pediatric rare disease indications as well as 22 clinical trials (8%) in 7 conditions that occur primarily in pediatric patients and cannot typically be required under PREA. Of note, during the 2012–2016 timeframe, 10 pediatric rare conditions were studied under BPCA compared with 5 in the 2007–2011 timeframe. The field is now moving toward more difficult to study conditions that occur in fewer patients, such as rare or pediatric-only conditions. The challenge encountered with these conditions is that the pathophysiology is often less well-understood and pediatric validated clinical endpoints are often lacking.^{16,17}

The types and designs of trials have evolved over time as well. This is due to several factors, including the knowledge gained during previous pediatric studies and a better understanding of when to perform PK and dose-ranging studies. Presently, the FDA encourages dose-finding studies to be performed before safety and efficacy studies because of the many failed trials owing to dosing issues. Examples of failed pediatric trials include many antihypertensive trials.¹⁸ The draft FDA guidance for pediatric PK studies from 1998 stated, “Pharmacokinetic studies in the pediatric population should determine how the dosage regimen should be adjusted to achieve approximately the same level of systemic exposure that is safe and effective in adults.” Subsequently, the FDA learned that poor dose selection was a contributor for many pediatric trial failures. An updated Guidance for Industry on pediatric PK studies was issued in 2014.¹⁹ An increased use of WRs should be considered in challenging areas. BPCA provides a mechanism to request pediatric studies for unique pediatric populations and rare or orphan conditions. Studies in neonatal-specific conditions, such as pulmonary arterial hypertension, broncho-pulmonary dysplasia, necrotizing enterocolitis, retinopathy of prematurity, and neonatal sepsis, are challenges for the future. A number of products with Orphan Designation have been studied under BPCA, including (1) prasugrel for vaso-occlusive crises in sickle cell disease, (2) eltrombopag for the treatment of thrombocytopenia in patients 1 year of age and older with chronic immune (idiopathic) thrombocytopenia, (3) sapropterin dihydrochloride to reduce blood phenylalanine levels in patients with hyperphenylalaninemia owing to tetrahydrobiopterin-responsive

phenylketonuria, (4) vigabatrin for the treatment of infantile spasms, (5) rufinamide for the treatment of Lennox Gastaut syndrome, and (6) bortezomib for the treatment of acute lymphoblastic leukemia and lymphoblastic lymphoma.

The knowledge gained through the conduct of trials in pediatric patients provides an opportunity to review the approaches taken and modify them in subsequent studies. For example, after reviewing data for several antiepileptic drugs approved in the US for the treatment of partial onset seizures in children, the FDA recently concluded that extrapolation of the efficacy results from adult to pediatric patients 4 years of age and older with partial onset seizures is acceptable and that independent clinical efficacy trials in these children are not needed.²⁰ However, dosing and safety data will still need to be collected in the pediatric population.

Conclusions

Therapeutic trials in the pediatric population have resulted in pediatric labeling changes that provide essential information regarding safety, efficacy, and dosing to pediatricians and other healthcare providers. One of the challenges is to know how much of the new labeling information is translated into medical practice. The FDA does not regulate the practice of medicine and thus will not usually know if the new labeling information is being used by practitioners. Adverse event reporting to the FDA will sometimes indicate inappropriate use of a therapy. However, reports from physicians and patients are only a small component of adverse event reporting, because most are provided by the sponsors of the therapy.

BPCA has encouraged studies that have advanced knowledge on the use of therapeutics for pediatric-specific indications in pediatric populations. Modifications of investigative approaches and trial design may occur as more is learned about the pathophysiology of diseases and the response to various therapeutic interventions. There are many lessons learned from both successful and failed trials, and this information can be applied to inform development of future trials.^{12,21,22} Knowing which trials failed should help to reduce unnecessary pediatric studies and inform future pediatric studies regarding trial design, dosing, pediatric study endpoints, and methodology. Even if a trial fails to meet a predetermined statistical endpoint, there may be informative information on trial design, endpoints, and safety, which are added to labeling. The BPCA incentive can be used in conjunction with the PREA requirement to maximize pediatric drug development and is particularly important for pediatric-specific diseases.

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Glossary

BPCA	Best Pharmaceuticals for Children Act
FDA	US Food and Drug Administration

PK	Pharmacokinetic
PREA	Pediatric Research Equity Act
WR	Written Request

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Table I

Overview of pediatric clinical trials completed under BPCA 2007–2016 (n = 292)

Categories	n	
Pediatric trials completed	292	
Unique products studied	98	
Trials with racial and ethnic data	227	
Trials with clinical site data	220	
Trials with country data	228	
Resulting pediatric labeling changes	107	
Median trials per unique product	3	Range, 1–9
Median duration in days per trial	56	Range, 1–2555
Median patients analyzed per trial	80	Range, 4–1188
Median sites per trial	20	Range, 1–191
Median countries per trial	2	Range, 1–31
Most common trial type		
Efficacy/safety	151 trials	
Most common indication studied		
Schizophrenia and/or bipolar disorder; HIV	26 trials	
Most common country for clinical trial sites		
US	124 trials	1447 sites
Most common patient race		
White	24 089 patients	69%

Clinical trial type by therapeutic category 2007–2016 (n = 292)

Table II

Therapeutic categories	Efficacy/safety	PK/PD	PK/safety	Safety	No. of trials	No. of products
Gastrointestinal	25	10	11	—	46	11
Anti-infective	23	4	30	—	57	21
Psychiatry	22	7	7	11	47	10
Neurology	16	6	5	6	33	10
Oncology	13	6	2	1	22	8
Cardiovascular	13	4	1	2	20	8
Endocrine	10	3	2	—	15	9
Hematology	8	1	—	—	9	5
Pulmonary	6	2	1	2	11	5
Analgesic/anesthetic	5	4	6	1	16	3
Urology	3	2	—	—	5	2
Ophthalmology	3	—	—	1	4	3
Dermatology	2	1	—	—	3	1
Medical Imaging	2	—	1	—	3	1
Smoking cessation	—	1	—	—	1	1
Total	151	51	66	24	292	98

Table III

Top 5 indications studied in adults and pediatrics, pediatrics, and pediatric rare conditions

Top 5 indications studied	No. of studies
Indications that occur in both adults and pediatrics (n = 103)	
Schizophrenia and/or bipolar disorder	26
HIV	26
Gastroesophageal reflux	22
Migraine/migraine prophylaxis	16
Seizures	13
Indications that occur primarily in pediatrics (n = 19)	
Autism spectrum disorders	7
ADHD-induced insomnia	4
Tinea capitis	3
Kawasaki disease	3
Delayed puberty	2
Rare diseases that occur primarily in pediatrics (n = 23)	
Solid tumors (eg, Ewing sarcoma, rhabdomyosarcoma and undifferentiated sarcoma, osteosarcoma, neuroblastoma, medulloblastoma, and astrocytoma)	7
Female patients with McCune-Albright syndrome with progressive precocious puberty	5
Acute lymphoblastic leukemia and lymphoblastic lymphoma	4
Osteogenesis imperfecta	4
Kawasaki disease	3

ADHD, Attention deficit hyperactivity disorder.

Table IV

Trends in pediatric clinical trials between 2007 and 2016 (n = 292)

Study types	2007–2011 n (%)	2012–2016 n (%)	Total n (%)
Efficacy	74 (50)	77 (53)	151 (52)
Double-blind	18	45	63
Open label	19	32	51
Single-blind	37	0	37
PK	66 (45)	51 (35)	117 (40)
Double-blind	3	2	5
Open label	61	49	110
Single-blind	2	0	2
Safety	7 (5)	17 (12)	24 (8)
Double-blind	1	1	2
Open label	4	16	20
Single-blind	2	0	2
Total	147	145	292