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Pediatric Drug Policies Supporting Safe And Effective Use Of Therapeutics In Children: A Systematic Analysis

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ABSTRACT Several policies have been implemented in the US to promote the evidence-based use of therapeutics in pediatric populations. Under the Best Pharmaceuticals for Children Act of 2002 and the Pediatric Research Equity Act of 2003, the Food and Drug Administration (FDA) can request pediatric studies for new drug and biologic indications. The acts have been credited with generating pediatric information for hundreds of drugs. However, concerns have been raised that delays and noncompliance with study requests contribute to high rates of off-label and potentially unsafe or ineffective medication use in children. We used publicly available FDA documents to analyze all indications for new drugs and biologics approved by the FDA from 2002 through 2018. During this time the FDA issued 389 pediatric study requests (141 under the Best Pharmaceuticals for Children Act and 248 under the Pediatric Research Equity Act) for 274 new drugs and biologics, representing 320 indications. We found that as of December 31, 2018, fewer than a third of these study requests had been completed. Overall, 64 percent of new drug and biologic indications deemed relevant to pediatric patients lacked pediatric prescribing information at five years after FDA approval. Enforcement of pediatric drug study policies should be strengthened to reduce non-evidence-based medication use in pediatric patients.

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The development of safe and effective medications holds tremendous potential to meaningfully improve children's health. Historically, most drugs have not been developed specifically for children but have been adapted for use in pediatric patients, with clinicians extrapolating data on drug safety and efficacy from adult to pediatric populations.¹ This poses a number of challenges, as safety and efficacy profiles may differ between children and adults as a result of age-dependent differences in pharmacokinetics, pharmacodynamics, and pathophysiology.² Children treated with drugs that have not been appropriately studied in pediatric populations may be exposed to products

administered at inappropriate doses, suffer from unforeseen adverse events, or receive drugs lacking therapeutic benefit.^{3–5}

The dearth of pediatric drug development is related to a number of factors, including unique ethical and feasibility considerations when performing clinical trials in children and the perception of children as a vulnerable population requiring “protection” from research.^{5–7} The challenges of enrolling a sufficiently large study cohort and addressing multiple age groups can require considerable resources and lengthen study duration. In general, pharmaceutical companies have been reluctant to embark on costly pediatric product development programs given the reduced financial incentives related to the

small pediatric markets and the limited commercial value of pediatric versus adult products.⁵ Recognizing these barriers and the pressing need for greater pediatric drug research, during the past two decades Congress has implemented several policies to increase the study of drugs in children and promote the evidence-based use of therapeutics in pediatric populations.

The resulting policy framework primarily comprises two arms: a voluntary program under the Best Pharmaceuticals for Children Act (BPCA), passed in 2002, and its counterpart, the requirements-based Pediatric Research Equity Act (PREA), passed in 2003. Under BPCA, the Food and Drug Administration (FDA) can request (but not require) that sponsors perform specified pediatric studies for drugs and biologics that might be relevant for the treatment of a pediatric condition. These requests are issued before or after a drug has been approved, and sponsors that complete the requested studies are awarded a six-month extension of market exclusivity on their product. Notably, the commercial value of this award is limited to products that still have patent protection. Under PREA, the FDA can require sponsors to perform specific pediatric studies as part of their development plan if a drug is deemed relevant to pediatric populations. The law aimed to reduce off-label prescribing by increasing the availability of pediatric prescribing information from the time of initial market introduction, but the FDA can issue deferrals to allow for the completion of pediatric studies after a drug is approved.

These policies have been credited with generating pediatric information for hundreds of drug products, thus facilitating appropriate dosing and evidence-based prescribing.¹ However, concerns have been raised regarding delays and non-compliance with pediatric study requests, both of which contribute to the ongoing high rates of off-label and potentially unsafe or ineffective use in pediatric patients.^{8,9} Although rates of off-label medication use in children have been previously assessed, limited information is available on pediatric labeling resulting from the pediatric programs.¹⁰⁻¹³ To inform actions needed to strengthen current US policies and increase pediatric drug development, we performed a systematic analysis of the application of BPCA and PREA to pediatric labeling for new drugs and biologics approved by the FDA since the inception of the pediatric programs.

Study Data And Methods

STUDY COHORT For new drugs and biologics first approved by the FDA from January 4, 2002, to December 31, 2018, we identified all product in-

dications, including indications approved subsequent to the initial product approval through the end of 2018, using the FDA's online database of approved products.¹⁴ The start date was chosen on the basis of the BPCA implementation date. Study requests issued under BPCA and PREA were identified through FDA databases and drug approval letters and review documents.^{14,15} Pediatric study requests include requests for pharmacokinetic, safety, efficacy, and observational studies. Although juvenile animal studies can be requested under PREA, we did not include these in our analysis. And although PREA requirements apply to new active ingredients, indications, dosage forms, dosing regimens, or routes of administration, we only studied requirements for new active ingredients and indications. Indications are exempt from PREA requirements if an indication has been granted orphan designation, meaning that a drug is intended to treat a rare disease or condition as designated under the Orphan Drug Act. Requirements can also be waived in certain cases, such as when an indication applies to a condition occurring primarily in adults. When we found multiple pediatric studies required under PREA for the same indication, we considered them to be a single PREA request for that indication. The final study cohort consisted of all indications with at least one pediatric study request issued under BPCA or PREA.

DATA EXTRACTION AND CLASSIFICATION For each product indication with a pediatric study request, we determined whether and when the study request was fulfilled. For studies performed under BPCA, data were extracted from a list maintained by the FDA of drugs with completed BPCA study requests.¹⁶ Information on pediatric studies conducted under PREA was obtained from FDA letters outlining the required pediatric studies and confirming completion of required pediatric studies, as well as through the FDA's database on postmarketing requirements.¹⁷ In calculating the time to fulfillment for each study request, we used the FDA approval date as the start date.

For each indication in our study cohort, we reviewed the FDA product label for availability of any pediatric safety or efficacy data, noting the age group to which information pertained and the date of inclusion. Under both BPCA and PREA, sponsors are required to add information from completed studies to the product label, irrespective of the findings with regard to therapeutic benefit. In reviewing product labels, we examined the "Indications and Usage," "Dosage and Administration," and "Pediatric Use" sections of the labels to identify pediatric-specific indications; pediatric-specific dosage guidance;

or results from pediatric pharmacokinetic/pharmacodynamic, safety, or efficacy studies. We reviewed initial labels as well as all revisions to labels through December 31, 2018, to capture both pediatric information available at the time of approval and data added after market availability as pediatric studies were completed. Pediatric information was classified as pertaining to neonates (less than 1 month), infants (1–23 months), children (2–11 years), or adolescents (12–17 years). Product indications were categorized by active ingredient in therapeutic classes, using Anatomical Therapeutic Chemical classification system codes.¹⁸

STATISTICAL ANALYSIS We performed descriptive statistics to describe the proportion of drug indications with completed FDA-requested pediatric studies and with pediatric labeling information at the time of approval and as of December 31, 2018. Median time to fulfillment of pediatric study requests and to the addition of pediatric labeling data after product approval was calculated with interquartile ranges for indications with completed study requests and with available pediatric labeling data, respectively. We further assessed the time to these outcomes using Kaplan-Meier curves with data through December 31, 2018. Analyses were conducted for BPCA and PREA both individually and in combination, as well as stratified by pediatric age groups and therapeutic classes. We assessed changes in time to addition of pediatric labeling data over the study period using a Cox model. All analyses were performed using Stata, version 15.0.

LIMITATIONS Our study had several limitations. First, we did not examine the content of study requests, precluding further analysis of barriers to successful completion of pediatric studies and whether pediatric drug policies might address them. Second, we did not examine which age groups were included in each study request or whether the pediatric labeling information provided complete safety and efficacy information for each of the age groups considered. Third, we did not assess the scope of the policies, including the impact of the exclusion of orphan indications under PREA on pediatric prescribing information for drugs and biologics with orphan indications. Finally, BPCA has been invoked to request pediatric data on drugs and biologics approved before 2002, but we examined only new drug and biologic approvals starting after its implementation in 2002.

Study Results

The FDA issued 389 pediatric study requests for 274 new drugs and biologics, representing a total of 320 indications approved from 2002 to 2018.

There were 141 requests under BPCA and 248 under PREA (exhibit 1). The total number of indications approved by the FDA over this period was 775 (data not shown), indicating that 41.3 percent (320 of 775 approved indications) were identified as relevant to pediatric patients and in need of pediatric prescribing information.

FULFILLMENT OF PEDIATRIC STUDY REQUESTS

As of December 31, 2018, 34.8 percent of BPCA requests (49 of 141) and 29.0 percent of PREA requests (72 of 248) had been fulfilled. The median time to fulfillment of pediatric study requests conducted under BPCA was 6.7 years (interquartile range: 4.7, 10.7); it was 4.1 years (IQR, 0.0, 6.1) for those completed under PREA. Exhibit 2 illustrates the time from approval of an indication to the completion of pediatric studies under BPCA and PREA, indicating that at five years after approval, the rates of completion of BPCA and PREA requests were 13.4 percent and 22.7 percent, respectively.

Overall, with a median follow-up of 6.5 years (IQR: 3.5, 11.3), as of December 31, 2018, 31.1 percent of pediatric study requests (121 of 389; data not shown) had been fulfilled for 32.5 percent of indications (104 of 320). The median time to fulfillment was 4.5 years (IQR: 0.4, 7.5) (exhibit 1).

ADDITION OF PEDIATRIC INFORMATION TO

PRODUCT LABELS Pediatric prescribing information was available at the time of approval for 15.6 percent of indications (22 of 141) with BPCA requests and 22.6 percent of indications (56 of 248) with PREA requests (exhibit 1). For indications receiving pediatric data after approval, the median time between approval and addition of any pediatric prescribing information was 5.9 years (IQR: 4.2, 8.3) for indications with BPCA study requests and 4.6 years (IQR: 2.7, 7.8) for those with PREA requests (exhibit 1).

Examining these programs in combination, at the time of approval, 21.6 percent (69 of 320) of indications for new drugs and biologics included any pediatric safety or efficacy information in the FDA label, increasing to 46.6 percent (149 of 320) over the study period (exhibit 1). In all, 63.8 percent of drug and biologic indications with pediatric study requests were marketed for at least five years without any pediatric safety or efficacy labeling information (exhibit 2). There was no difference in the time to addition of pediatric information based on year of approval (see the online appendix).¹⁹

The availability of pediatric product labeling was lowest for neonates, increasing from 3.4 percent at the time of approval to 16.1 percent at five years postapproval. Adolescents and children had the highest rates of available pediatric safety and efficacy information throughout the study

EXHIBIT 1

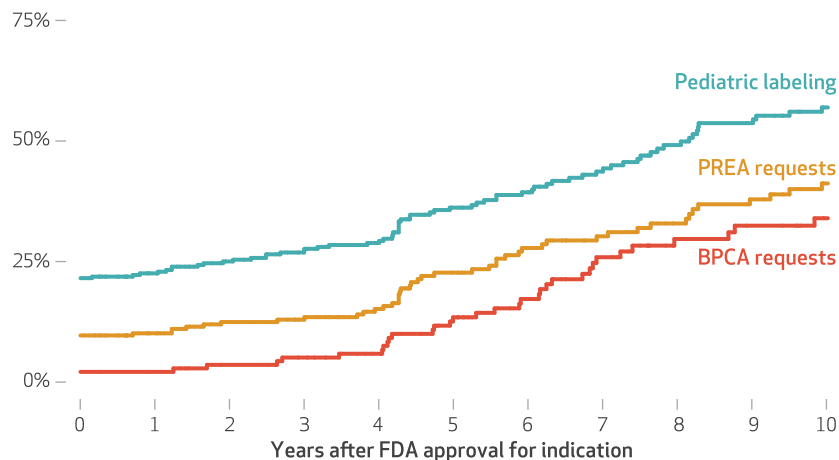
Pediatric study requests and addition of pediatric age-specific information to prescription labels for drugs and biologics for indications approved by the Food and Drug Administration (FDA) from 2002 to 2018, by relevant legislation

	Indications with a pediatric study request issued under an FDA pediatric program				Total indications with any pediatric study request	
	BPCA		PREA		No.	% or IQR
	No.	% or IQR	No.	% or IQR		
STUDY REQUESTS ^a						
Request fulfilled at time of approval (%)	3	2.1	24	9.7	26	8.1
Request fulfilled as of December 31, 2018 (%)	49	34.8	72	29.0	104	32.5
Median years from indication approval to request fulfillment (IQR)	6.7	(4.7, 10.7)	4.1	(0.0, 6.1)	4.5	(0.4, 7.5)
LABELING INFORMATION						
Any pediatric prescribing information at time of approval (%)	22	15.6	56	22.6	69	21.6
Any pediatric prescribing information as of December 31, 2018 (%)	71	50.4	112	45.2	149	46.6
Median years to addition of prescribing information (IQR)	5.9	(4.2, 8.3)	4.6	(2.7, 7.8)	5.6	(3.9, 8.2)
Age groups with prescribing information added as of December 31, 2018 (%)						
Adolescent (12–17 years)	67	47.5	108	43.5	143	44.7
Child (2–11 years)	59	41.8	86	34.7	121	37.8
Infant (1–23 months)	25	17.7	37	14.9	54	16.9
Neonate (<1 month)	9	6.4	20	8.1	26	8.1

SOURCE Authors' analysis of information in FDA documents and drug labels. **NOTES** The total number of indications with a study request is less than the sum of the indications with a study request under the individual programs because both programs can issue a pediatric study request for the same product indication. When more than one study request was fulfilled, the study request with the shortest time to fulfillment was considered. Calculations of median time to the addition of prescribing information were limited to indications with information added after approval. ^aA total of 320 indications were approved from 2002 to 2018. There were 141 requests under the Best Pharmaceuticals for Children Act (BPCA) and 248 under the Pediatric Research Equity Act (PREA).

EXHIBIT 2

Percent of fulfilled requests to study pediatric indications and percent of indications with pediatric age-specific information added to prescription labels, by relevant legislation and years since Food and Drug Administration (FDA) approval



SOURCE Authors' analysis of information in FDA documents and drug labels. **NOTES** Time from FDA approval to the fulfillment of pediatric study requests, stratified by relevant legislation, and time to the addition of pediatric labeling information for all drug and biologic indications with a pediatric study request. PREA is Pediatric Research Equity Act. BPCA is Best Pharmaceuticals for Children Act.

period (exhibit 3). For adolescents, 13.8 percent of indications included any pediatric labeling at the time of approval, increasing to 30.4 percent at five years postapproval.

The availability of pediatric prescribing information varied widely for indications across therapeutic classes (exhibit 4). The therapeutic classes with the highest number of indications associated with pediatric study requests were antineoplastic and immunomodulating agents (65 indications), anti-infectives for systemic use (59 indications), and nervous system agents (56 indications). The rates of pediatric labeling for these therapeutic classes were 38.5 percent, 47.5 percent, and 51.8 percent, respectively.

Discussion

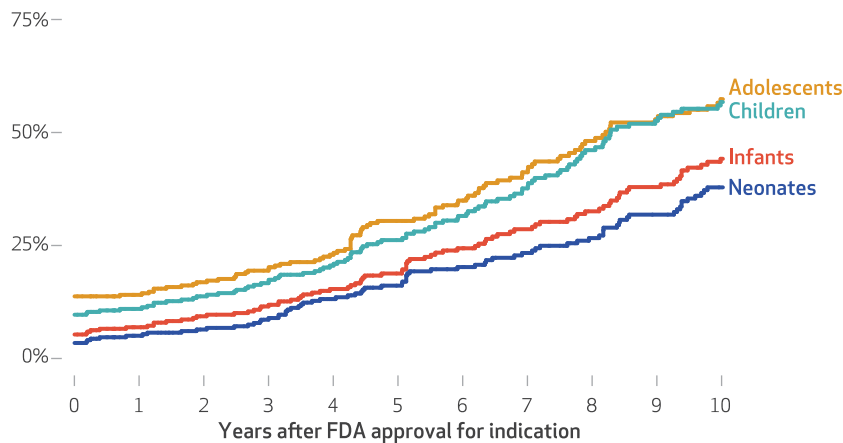
Our study provides a comprehensive assessment of the primary US pediatric drug policies implemented to promote drug research and labeling for children. The results indicate that completion of requested pediatric studies is often slow, resulting in prolonged periods of potential off-label use for a large proportion of drugs and biologics deemed relevant to pediatric patients. In all, 63.8 percent of therapeutic indications with FDA-requested pediatric studies lacked any pediatric safety or efficacy prescribing infor-

mation at five years after FDA approval.

BPCA currently contributes a small proportion of pediatric labeling changes, with a prior analysis reporting that just 9.5 percent of pediatric labeling additions were attributed solely to BPCA during the period 2014–18.⁹ Our findings indicate that the majority of requests issued under BPCA remain unfulfilled, and for those that are addressed by sponsors, the time between approval and completion of pediatric assessments is nearly seven years. The high rate of noncompletion may be related to variability in the value of the six-month exclusivity period.²⁰ Of note, BPCA provides a mechanism to facilitate the pediatric study of drugs that are already marketed, whereas PREA requirements are applied to products in development and under review by the FDA. Under BPCA, there is also a process to support the study of off-patent medications to which the six-month exclusivity incentive would not apply. To promote pediatric study of these products, BPCA authorized the Eunice Kennedy Shriver National Institute of Child Health and Human Development to establish and fund the Pediatric Trials Network, which conducts BPCA-requested pediatric trials specifically for drugs that no longer have patent protection.^{21,22} To

EXHIBIT 3

Addition of pediatric age-specific information to prescription labels, by years since Food and Drug Administration (FDA) approval



SOURCE Authors' analysis of information in FDA documents and drug labels. **NOTES** Time from FDA approval to the addition of pediatric labeling information, stratified by age group. The percentage of indications with available pediatric prescribing information is higher than the percentage of study requests completed because certain pediatric prescribing information may be provided unrelated to FDA study requests. Pediatric labeling was classified as pertaining to neonates (less than 1 month), infants (1–23 months), children (2–11 years), or adolescents (12–17 years).

EXHIBIT 4

Pediatric study requests and addition of pediatric age-specific information to prescription labels for drugs and biologics, by relevant legislation and therapeutic class

Therapeutic classes	Indications with a BPCA study request (n = 141)		Indications with a PREA study request (n = 248)		Total indications with any pediatric study request (N = 320)	
	No.	Any pediatric prescribing information	No.	Any pediatric prescribing information	No.	Any pediatric prescribing information
Antineoplastic and immunomodulating agents	40	47.5%	29	31.0%	65	38.5%
Anti-infectives for systemic use	23	65.2	56	46.4	59	47.5
Nervous system	29	55.2	46	50.0	56	51.8
Alimentary tract and metabolism	13	23.1	40	17.5	44	32.7
Blood and blood forming organs	6	50.0	12	41.7	16	43.8
Cardiovascular system	11	36.4	9	22.2	16	25.0
Various	2	50.0	15	66.7	16	68.7
Dermatologicals	3	66.7	15	86.6	15	86.7
Genitourinary system and sex hormones	6	16.7	9	44.4	11	45.4
Respiratory system	3	100.0	6	100.0	8	100.0
Sensory organs	2	100.0	5	100.0	5	100.0
Systemic hormonal preparations excluding sex hormones and insulins	3	66.7	1	0.0	4	50.0
Antiparasitic products, insecticides and repellants	0	0.0	3	66.7	3	66.7
Musculoskeletal system	0	0.0	2	0.0	2	0.0

SOURCE Authors' analysis of information in Food and Drug Administration documents and drug labels. **NOTES** Availability of any prescribing information is current as of December 31, 2018. The total number of indications with a study request is less than the sum of the indications with a study request under the individual programs, because both programs can issue a pediatric study request for the same product indication. BPCA is Best Pharmaceuticals for Children Act. PREA is Pediatric Research Equity Act.

date, the Pediatric Trials Network has submitted data to the FDA for twenty-one off-patent drugs, six of which have resulted in pediatric labeling changes.^{23,24} This feature of the BPCA program represents a critical component to complement other policies addressing the pediatric study of new drugs and biologics.

Because the majority of pediatric study requests are issued under PREA, measures providing the FDA with additional tools to ensure timely completion of PREA studies may have the most impact on pediatric drug development. Although PREA was implemented specifically to reduce the postapproval evidence gap in pediatric use, we found that fewer than a quarter of indications with PREA requests included pediatric labeling information at the time of approval. Fulfillment of study requests continued after approval, but by five years only 40 percent of indications with a PREA request included pediatric labeling information. Consistent with our findings, a previous study examining studies requested under PREA for new approvals issued between 2007 and 2014 found that only 41.2 percent of drug labels included pediatric information after a median follow-up of 6.8 years.⁸

The current penalty for sponsors that do not meet PREA requirement deadlines is a noncompliance letter issued and publicly posted by the FDA. Additional means of increasing completion of pediatric studies before the market availability of drugs and biologics could be considered. The deadline for developing pediatric study plans under PREA is at the end of Phase II clinical trials, which might not always provide sufficient time to complete requested studies by the time of approval. The FDA could encourage sponsors to enroll adolescents in adult-only studies, and even to start pediatric studies in parallel to adult studies whenever feasible. Identifying high-priority drugs, such as those relevant to conditions with limited therapeutic options or high disease prevalence, could also inform the allocation of incentives (for example, tax credits) or input from the FDA's Pediatric Review Committee to support efficient enrollment and timely comple-

tion of pediatric studies for these products.

Under the Food and Drug Administration Amendments Act of 2007, the FDA is required to track and report certain information to assess the outcomes of the pediatric policies. This includes posting on the FDA website the total number of pediatric studies conducted and the labeling changes made as a result of studies conducted under BPCA and PREA. The FDA is also required to report annually, in aggregate, the number of study requests completed, the number of deferrals granted under PREA, and the status of ongoing pediatric studies.²⁵ Although these reports are useful in providing an overview of activities specific to BPCA and PREA, they do not enable easy assessment of the overarching intent of these policies, which was to increase the number of drugs and biologics approved with pediatric prescribing information, including for the youngest pediatric patients. Monitoring the specific drugs and biologics that are approved and marketed with appropriate pediatric information is a key outcome that should be made readily available. Similarly, longitudinal data on pediatric study requirements, study progress, and pediatric labeling changes should be tracked and ideally published in a unified public database at the level of individual products and for specific age groups.

Conclusion

Under current pediatric policies in the US, many drugs and biologics relevant to pediatric populations continue to reach patients without adequate pediatric prescribing information. Policies could be strengthened to increase the number of requests fulfilled under BPCA, especially for off-patent products, and to ensure timely completion of study requests issued under PREA. In addition, to better monitor progress under the pediatric programs, the FDA should consider alternative reporting approaches that enable the efficient assessment of the availability of pediatric prescribing information for drugs and biologics, including for specific age groups. ■

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NOTES

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