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## Duration of Pediatric Clinical Trials Submitted to the US Food and Drug Administration

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### Abstract

**IMPORTANCE**—The increasing prevalence of pediatric chronic disease has resulted in increased exposure to long-term drug therapy in children. The duration of recently completed drug trials that support approval for drug therapy in children with chronic diseases has not been systematically evaluated. Such information is a vital first step in forming safety pharmacovigilance strategies for drugs used for long-term therapy in children.

**OBJECTIVE**—To characterize the duration of clinical trials submitted to the US Food and Drug Administration (FDA) for pediatric drug approvals, with a focus on drugs used for long-term therapy.

**DESIGN AND SETTING**—A review was performed of all safety and efficacy clinical trials conducted under the Best Pharmaceuticals for Children Act or the Pediatric Review Equity Act and submitted to the FDA from September 1, 2007, to December 31, 2014, to support the approval of drugs frequently used for long-term therapy in children. Statistical analysis was performed from July 1, 2015, to December 31, 2017.

**MAIN OUTCOMES AND MEASURES**—Maximum duration of trials submitted to support FDA approval of drugs for children.

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Author Contributions:

Dr Zimmerman had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

*Concept and design:* Zimmerman, Smith, McMahon, Murphy, McCune.

*Acquisition, analysis, or interpretation of data:* Zimmerman, Smith, Temeck, Avant, McCune. *Drafting of the manuscript:* Zimmerman, McMahon, Murphy.

*Critical revision of the manuscript for important intellectual content:* Smith, McMahon, Temeck, Avant, McCune.

*Statistical analysis:* Zimmerman.

*Administrative, technical, or material support:* Avant.

*Supervision:* Smith, McMahon, Temeck, Murphy, McCune.

Conflict of Interest Disclosures:

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Disclaimer:

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the US Food and Drug Administration.

**RESULTS**—A total of 306 trials supporting 86 drugs intended for long-term use in children were eligible for the primary analysis. The drugs most commonly evaluated were for treatment of neurologic (25 [29%]), pulmonary (16 [19%]), and anti-infective (14 [16%]) indications. The median maximum trial duration by drug was 44 weeks (minimum, 1.1 week; maximum, 364 weeks). For nearly two-thirds of the drugs (52 [61%]), the maximum trial duration was less than 52 weeks. For 10 of the drugs (12%), the maximum trial duration was 3 years or more. Maximum duration of trials did not vary by therapeutic category, minimum age of enrollment, calendar year, or legislative mandate.

**CONCLUSIONS AND RELEVANCE**—Pediatric clinical trials designed to sufficiently investigate drug safety and efficacy to support FDA approval are of relatively limited duration. Given the potential long-term exposure of patients to these drugs, the clinical community should consider whether new approaches are needed to better understand the safety associated with long-term use of these drugs.

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During the past 20 years, research has established marked differences between children and adults in drug pharmacokinetics and pharmacodynamics. If pharmacokinetics and pharmacodynamics are not adequately considered in pediatric dosing, ontogenesis of drug receptors and pathways of biotransformation can lead to therapeutic failure or drug toxic effects.<sup>1-5</sup>

Through mechanisms and incentives provided in the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA), the US government recognizes the importance of studying drug safety and efficacy within pediatric populations.<sup>1</sup> These legislative acts have had notable success, resulting thus far in more than 700 changes in US Food and Drug Administration (FDA) product labels to include pediatric information.<sup>6</sup> However, the study of drugs within pediatric populations is complex. Chronic disease is becoming more prevalent among children and often requires lifelong drug therapy.<sup>7-9</sup> Furthermore, the administration of some drugs during vulnerable periods of growth and development may have implications for the attainment of adequate growth and development among children.<sup>10-12</sup> Given the potential for long-term administration of drugs to pediatric patients, drug safety may need to be assessed for prolonged durations and during vulnerable periods of growth and development.

We have limited understanding of the current state of long-term drug safety evaluations in children. To improve our understanding, we evaluated the duration of clinical trials submitted to the FDA under BPCA and PREA, with a focus on drugs potentially administered to children with chronic health conditions. We then reviewed the literature for other studies conducted for children or adults that could provide guidance for feasibility and alternative methods for gathering data on long-term drug administration in children. Such efforts are necessary first steps toward understanding the availability of data on long-term drug safety in children.

## Methods

### Data Sources and Inclusion Criteria

We used the FDA's Document Archiving, Reporting, and Regulatory Tracking System electronic database as our data source for clinical trial submissions to the agency. Within this database, we identified all drugs submitted to and reviewed by the FDA, under BPCA and PREA, for pediatric drug approval from September 1, 2007, to December 31, 2014. Drugs that did not receive FDA approval for the intended pediatric indication were excluded. We also excluded drugs administered topically (including administration to the skin, eye, or ear) unless previous evidence suggested substantial systemic absorption. We extracted deidentified data from prospective drug trials in humans as well as FDA medical, statistical, and pharmacokinetic reviews of the primary data. This research study did not require Research Involving Human Subjects Committee review and approval because it is exempt from the requirements of 45 CFR §46.101b(4).

A committee of 4 pediatricians (K.O.Z., A.W.M., J.T., and S.M.), each with clinical and regulatory experience, characterized the potential uses of the drugs as short-term, intermediate, or long-term, based on the typical or expected clinical use in pediatric populations. The safety and efficacy data sufficient for FDA approval of a drug for its intended length of use may not include data on longer-term use. The analysis described herein focused on the trial length for drugs potentially used for the long-term medical management of children, excluding trials whose primary objective was to evaluate bioequivalence, pharmacokinetics, or a device.

Our literature review included articles referenced in Medline and PubMed as of February 12, 2018. Search terms were limited to "safety" AND the generic or brand name for the specific drug of interest OR "long-term" AND "safety" AND the generic or brand name for the specific drug of interest.

### Definitions and Outcomes

The committee defined *short-term therapy* as drugs typically administered for less than 3 months, *intermediate therapy* as drugs typically administered for 3 to 6 months, and *long-term therapy* as drugs typically administered for longer than 6 months. Drugs classified as long-term therapy were further classified as continuous or intermittent. Continuous drugs were those administered on a scheduled basis dependent on drug pharmacokinetics (ie, daily, weekly, or monthly), while intermittent drugs were those administered seasonally.

We classified drugs into the following therapeutic categories according to the primary indication or affected organ system: anti-infectives, biologics, cardiology, dermatology, endocrinology and metabolism, gastroenterology, hematology, neurology, pulmonology, and miscellaneous. The miscellaneous category included drugs for urologic indications (eg, overactive bladder) and those for ophthalmologic disease without anti-infective activity. We designated the following age groups according to the minimum age required for enrollment in each trial: infants (<1 year), children (1 to <9 years), preadolescents (9 to <12 years), and adolescents (12 to 17 years).

For our analysis, we identified all trials submitted as primary evidence for pediatric drug efficacy and safety. We defined trial duration as the sum of controlled and uncontrolled periods during which children received drug therapy. The entire duration of crossover trials and trials with cyclical drug administration, including interval periods of drug washout or time off therapy, was included. For each drug (unit of analysis), we identified the median maximum trial duration. We then compared the maximum trial duration with the study durations identified in our literature review and identified specific drugs and drug classes that might warrant further safety assessments based on available data.

## Data Collection

We collected the following information regarding each drug trial: therapeutic area, indication, clinical trial design (eg, open-label uncontrolled, randomized controlled, or long-term extension), ages studied, duration of drug receipt (weeks), year of FDA evaluation, and legislation under which the study took place (ie, BPCA or PREA). In our literature review, we extracted information regarding patient population, type and duration of evaluation, and any noted safety concerns or calls for additional long-term data in children.

## Statistical Analysis

Statistical analysis was performed from July 1, 2015, to December 31, 2017. We used standard summary statistics, including counts (with percentages) and medians (25th and 75th percentiles) to describe the study variables. We evaluated outcomes by therapeutic classification and age category, and made comparisons using a Wilcoxon rank sum test. Changes in trial duration by study year were evaluated using Kruskal-Wallis equality-of-populations rank test. We used STATA, version 14.1 (StataCorp) to perform all statistical analyses. All *P* values were from 2-sided tests and results were deemed statistically significant at *P* < .05.

## Results

We identified 201 drugs submitted for pediatric labeling during the study period. Of these, we excluded 33 drugs that were not approved, 19 vaccines, 3 drugs used for imaging studies, and 19 topical drugs. Of the remaining 127 drugs, we identified 33 that would be used for short-term indications, 5 for intermediate-length indications, and 86 drugs potentially used for long-term therapy. Pharmacokinetic trials were submitted for only 3 drugs. A total of 306 trials supporting the 86 long-term therapy drugs were eligible for our analysis (eTable in the Supplement). Of the 86 drugs, 19 (22%) were characterized as long-term intermittent and 67 (78%) as long-term continuous (Figure 1).

A total of 25 (29%) of the 86 included drugs were for neurologic indications, 16 (19%) were for pulmonary indications, and 14 (16%) were for anti-infective indications (Table 1). Trials for nearly half of the drugs (40 [47%]) were conducted in response to BPCA alone or BPCA and PREA, and the remainder were in response to PREA alone. For 24 of the drugs (28%), the minimum age of enrollment in the trials was younger than 1 year. A total of 42 drugs (49%) had trials that initiated enrollment at ages 1 to 8 years, 7 (8%) initiated enrollment at ages 9 to 11 years, and 10 (12%) initiated enrollment at ages 12 to 17 years.

The median (25th and 75th percentiles) maximum trial duration by drug was 44 weeks (12 weeks and 53 weeks). For nearly two-thirds of the drugs (52 [61%]), the duration was less than 52 weeks (<1 year) (Table 2). The longest trial duration by drug (364 weeks/7 years) investigated the safety and efficacy of a phenylalanine hydroxylase activator for children with phenylketonuria, while the shortest duration (1.1 week) investigated the efficacy and safety of montelukast for the indication of exercise-induced asthma (longer studies were done for the other pediatric indications for montelukast).

Although trial duration appeared different between therapeutic categories, the overall distributions of trial durations were statistically similar because of the wide variability in the trial lengths. For example, the median (25th and 75th percentiles) maximum duration for biologic drug trials was 132 weeks (52 weeks and 260 weeks); for cardiovascular drugs, median maximum duration was 54 weeks (53 weeks and 57 weeks;  $P = .44$ ) (Figure 2). Similarly, trial duration did not vary according to classification as a long-term intermittent or long-term continuous drug, with median (25th and 75th percentiles) maximum durations of 12 weeks (8 weeks and 52 weeks) for long-term intermittent drugs and 48 weeks (15 weeks and 58 weeks) for long-term continuous drugs ( $P = .08$ ).

Overall distribution of trial duration varied inconsistently by indication within a therapeutic category. For example, within the neurology category, drugs with a primary indication for seizures had a median (25th and 75th percentiles) maximum trial duration (139.5 weeks [242 weeks and 291 weeks]) that was statistically significantly different from those with a nonseizure indication (29 weeks [8 weeks and 48 weeks];  $P = .04$ ). However, within the pulmonary category, drugs with a primary asthma indication had a similar median (25th and 75th percentiles) maximum trial duration (34 weeks [8 weeks and 52 weeks]) compared with those without such an indication (25 weeks [14 weeks and 52 weeks];  $P = .91$ ). The FDA labels for drugs denoted as long-term continuous were each labeled for “maintenance therapy” or “for treatment of” a specified chronic condition. Labels for long-term intermittent drugs most often had specified durations of short-term use consistent with durations of clinical trials submitted to support labeling for the specified drug.

Trials enrolling participants of minimum ages of 0 (infant), 1 (child), or 12 (adolescent) years all had similar median (25th and 75th percentiles) maximum durations (infant, 42 weeks [10 weeks and 59 weeks]; child, 50 weeks [16 weeks and 54 weeks]; and adolescent, 52 weeks [12 weeks and 53 weeks]) (Figure 3). Median (25th and 75th percentiles) maximum trial duration did not vary according to whether the trial was mandated by BPCA and PREA (48 weeks [15 weeks and 100 weeks]) or PREA alone (29 weeks [10.7 weeks and 52 weeks]) ( $P = .17$ ). Furthermore, trial duration did not change significantly over time: in 2007, the median (25th and 75th percentiles) maximum duration was 52 weeks (12 weeks and 54 weeks); in 2014, this duration was 39 weeks (25 weeks and 86 weeks) ( $P = .70$ ). Approximately 35% of included drugs (30) had extension trials, most commonly occurring for neurologic drugs (14 of 25 [56%]). Only 3 of the 30 drugs (10%) with extension trials used a controlled study design.

According to our review of the literature, long-term evaluations exceeded the duration of trials submitted as primary evidence to the FDA for 69 (80%) of the 86 drugs. For 67 drugs

(78%), long-term evaluations included prospective studies, most often characterized as nonrandomized, open-label, observational studies with standardized follow-up evaluation. Children were included in evaluations for 37 (43%) of the drugs.

Several safety findings with potential long-term implications emerged from our literature review. First, although most studies did not identify substantial effects of inhaled corticosteroids on linear growth or the hypothalamic-pituitary-axis, investigators and clinicians remain concerned about this potential phenomenon and highlight a need for more prolonged evaluations, particularly at critical times of pediatric growth and development.<sup>13–18</sup> Second, proton pump inhibitors have been associated with gastric hyperplasia among those with long-term use, and existing evaluations in children are considered inadequate to rule out this adverse event.<sup>19–21</sup> Third, short-term and longer-term evaluations of stimulants have been associated with insomnia, concern for abnormal cognitive development, and impaired growth; quantification of risks are not fully elucidated.<sup>22–24</sup> Mood stabilizers and anti-psychotics have shown associations with weight gain and metabolic derangements, the long-term effects of which are unclear.<sup>25–27</sup> Omalixumab carries an FDA warning because heart and brain issues have not been ruled out with existing studies.<sup>28</sup> Finally, tenofovir may have implications for long-term renal function.<sup>29–32</sup> We did not identify substantial long-term safety concerns for other evaluated drugs or drug classes.

## Discussion

In our analysis of data submitted to the FDA from 2007 to 2014 to support pediatric indications for drugs that are commonly used for chronic conditions, we found that the median maximum trial duration by drug infrequently exceeded 1 year. Furthermore, trial duration did not notably vary with therapeutic category, minimum age of enrollment, calendar year, or legislative mandate. Review of the literature suggests that longer-term data in nonrandomized, observational studies are available for many drugs and may provide potentially important information regarding safety signals.

Admittedly, our study is limited given its purely descriptive nature. We have categorized our data to facilitate analysis, but recognize that the available data are heterogeneous with respect to the drugs evaluated, indications for therapy, study populations, and disease processes. Such categorization does not allow for evaluation of more subtle differences between trials. Finally, we have characterized drugs as long-term intermittent or long-term continuous based on clinical experience and prior documentation of long-term use of drugs even in cases for which the labeled indication may not support such use (eg, proton pump inhibitors).<sup>33</sup> We therefore acknowledge that this classification introduces some bias in our analysis. Nonetheless, our study provides important baseline information that can inform discussion regarding long-term drug safety data in children.

Our findings suggest that these pediatric studies may not provide complete safety data across all critical periods of growth and development. This observation may be important because multiple periods of critical pediatric growth and development exist, including marked deceleration in linear growth and weight gain during the first 2 years of life, and initiation of puberty around ages 11 to 13 years, accompanied by acceleration in linear growth that may



last for 3 to 4 years.<sup>34,35</sup> Although the first 3 years of life are often considered more critical than older ages for brain development, biochemical studies of brain metabolism suggest that high brain metabolic rates characteristic of early childhood may not decline to adult levels until ages 16 to 18 years, suggesting that the school-age and adolescent periods are equally critical periods of brain development.<sup>36</sup> Given this information, even the longest trial duration identified in our study (364 weeks/7 years) does not completely evaluate potential critical stages of all pediatric growth and development periods, nor does it begin to characterize the exposure associated with lifelong therapy.<sup>1</sup>

Administration of dexamethasone to premature infants provides a pertinent example in which long-term follow-up after limited administration in the neonatal period revealed important information regarding drug safety associated with exposure during critical periods of cognitive development. Extensive investigation dating to 1990 identified dexamethasone as an effective therapy for facilitation of extubation and prevention of bronchopulmonary dysplasia in premature infants.<sup>37</sup> However, in long-term follow-up studies,<sup>38</sup> investigators identified a statistically significantly increased risk of cerebral palsy among infants who received dexamethasone, compared with those who did not, with a number needed to harm of 4. Examples such as this one underscore potential issues with limited long-term data on drug safety in children.

On average, more than 1 decade elapses between initial laboratory formulation of a drug to readiness for public use in adults.<sup>39</sup> Public availability of data on drug efficacy and safety in children may require an additional 6 years.<sup>40</sup> Requiring that studies be designed to cover all the potential periods of critical development would make pediatric drug development infeasible. Furthermore, although investigators have traditionally touted the controlled clinical trial as the most rigorous source of data, multiple barriers to the conduct of clinical trials exist and may be exacerbated when clinical trials are of prolonged duration.<sup>41,42</sup> A recent investigation of more than 500 clinical trials conducted for children found that nearly 20% were discontinued early, largely owing to poor patient accrual.<sup>43</sup> Previous investigators have long documented attrition rates as high as 15% in longitudinal pediatric studies and up to 44% in some interventional studies in specific pediatric populations.<sup>44–46</sup> Furthermore, the relatively small sample sizes of pediatric trials compared with adult trials, combined with the lack of a control group in many extension trials, may raise concern about the level of evidence for safety such trials can provide.<sup>47,48</sup> Innovative approaches to acquire information on long-term drug safety in children are needed that continue to make important therapeutics available to children in a timely manner.

Multiple approaches are likely needed to obtain high-quality, long-term safety data for drugs used to treat chronic pediatric conditions. Currently, the FDA evaluates need for long-term safety assessment based on any safety concerns related to the specific effects of the drugs, the intended duration of treatment, and potential exposure during critical periods of growth and development, despite lack of conclusive evidence that all drugs used long-term in children will have specific effects on growth and development. In addition, the Food and Drug Administration Amendments Act of 2007 required increased activities for active post marketing risk identification and analysis. More importantly, it may be possible to leverage safety information from other populations, including adults and other pediatric age groups.

Our review of the literature suggests that long-term data can take many forms, ranging from open-label extension trials<sup>49-51</sup> after randomized studies, to registries<sup>52</sup> that capture data for specific disease processes, or prospective longitudinal studies<sup>53</sup> designed to answer specific scientific questions. Furthermore, with increasing administration of drugs for chronic conditions such as attention-deficit/hyperactivity disorder and asthma, we have a ready source of real-world data from which to potentially evaluate longer-term safety.<sup>54</sup>

Although we were able to identify potentially important safety signals from different data sources in the literature, each source has benefits and limitations, and our search may have introduced bias due to the nature of our study question. In general, ability to use the data in a meaningful way hinges on collecting quality data from an adequate pediatric population. To this end, the following approaches may enhance data quality: 1) use of existing literature to highlight areas for more urgent evaluation and lessons learned about specific data sources for specific drugs/drug classes; 2) collaboration between stake-holders and formation of networks for large sample sizes and acquisition of protocol-directed data collection in prospective observational studies for specific safety signals; 3) investigation of methods to decrease attrition and improve data collection in extension phases of clinical trials or other prospective evaluations; and 4) application of rigorous pharmacoepidemiologic analysis methods to existing data sources ('real-world data') and naturally occurring cohorts (eg, clinical cohorts, members of disease registries). Concerted efforts among all stakeholders will enable us to continue to advance pediatric drug development with regard to long-term pediatric drug safety while maintaining efficient and timely access to approved therapies for all children.

### Limitations

This study has some limitations. As mentioned above, our study is limited by its purely descriptive nature; the available data are heterogeneous with respect to the drugs evaluated, indications for therapy, study populations, and disease processes, which did not allow us to evaluate more subtle differences between trials. Also, our classification (long-term intermittent vs continuous) is based on experience, which may have introduced bias into our analyses.

### Conclusions

Pediatric clinical trials that are designed to sufficiently investigate drug safety and efficacy to support FDA approval are of relatively limited duration. Given the potential long-term exposure of patients to these drugs, the clinical community should consider whether new approaches are needed to better understand the safety of long-term use of these drugs.

### Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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### Key Points

**Question**

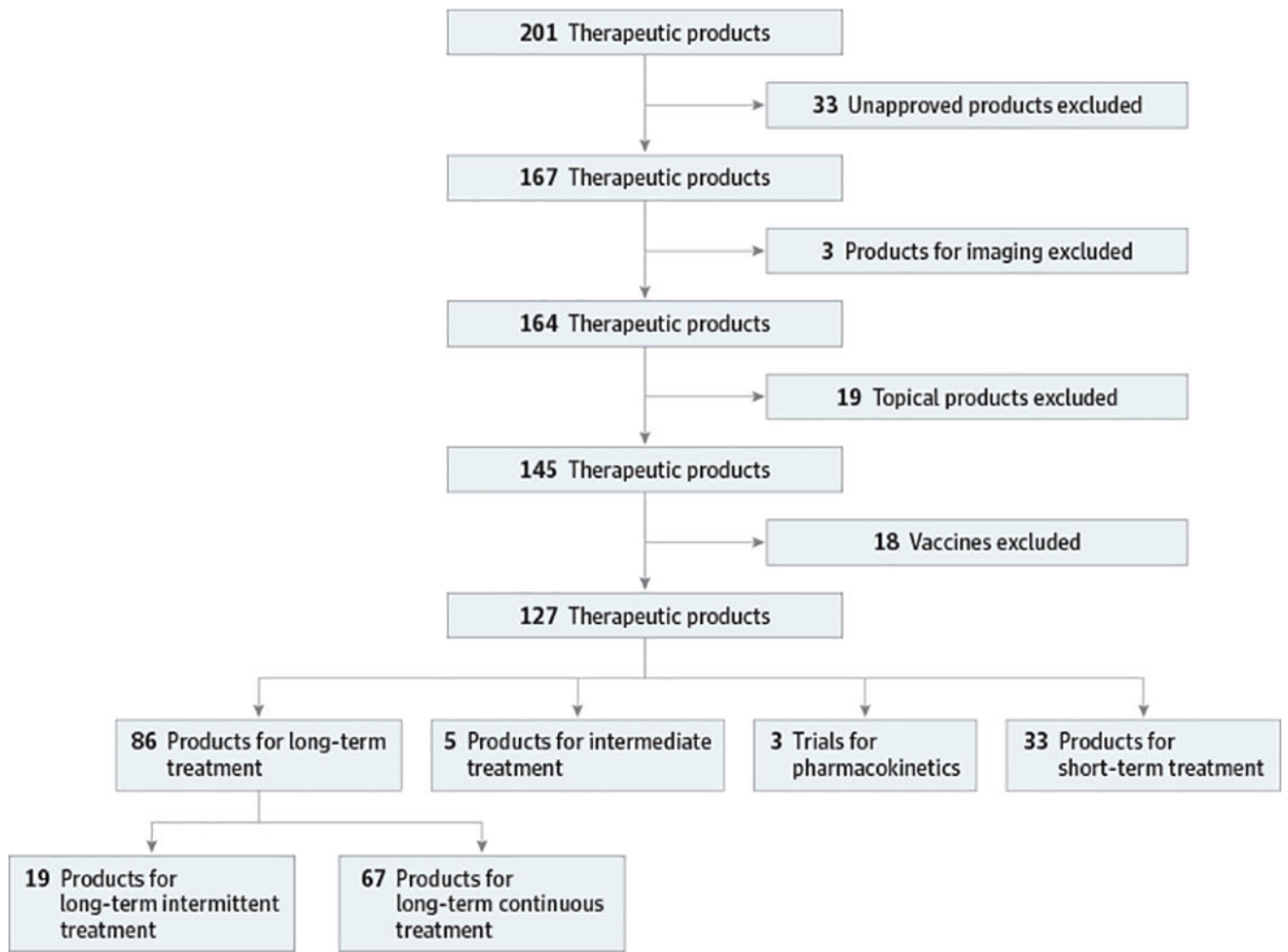
What are the durations of pediatric clinical trials recently submitted to the US Food and Drug Administration, and how can this knowledge inform discussions of safety pharmacovigilance follow-up for drugs that might be used for long-term therapy in the pediatric population?

**Findings**

This study found that nearly two-thirds of pediatric clinical trials submitted to support the approval of drugs with potential long-term use in the pediatric population are shorter than 52 weeks.

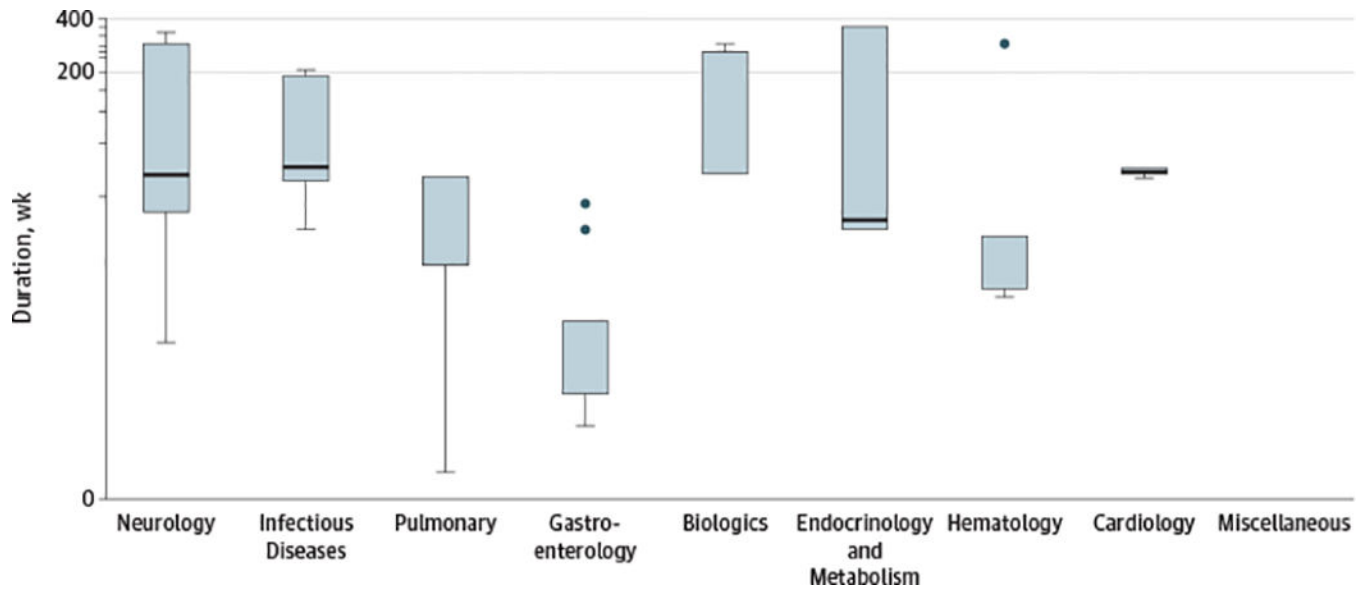
**Meaning**

Pediatric clinical trials that are sufficient to support US Food and Drug Administration drug approval may require additional strategies to ensure data availability for understanding long-term drug safety in children.



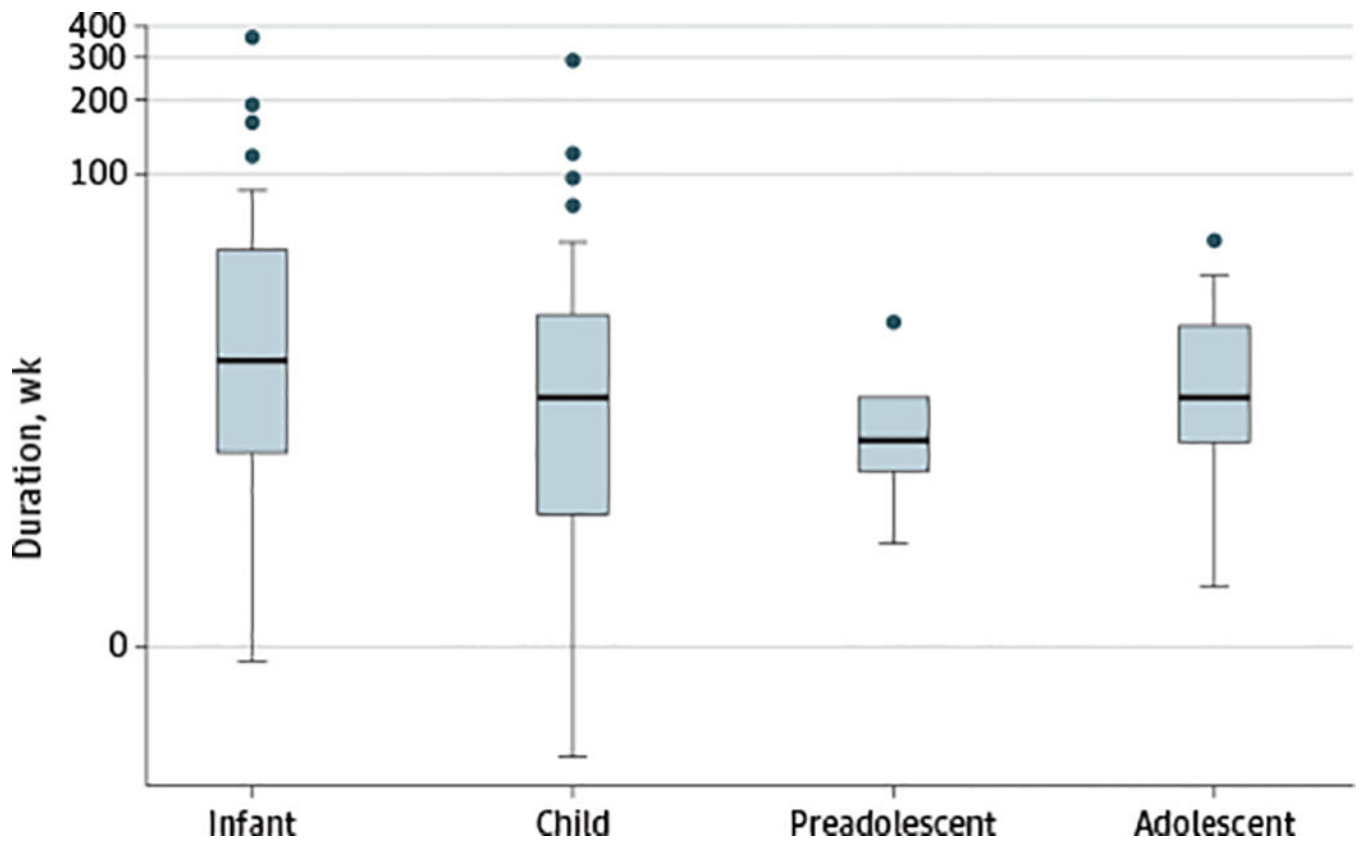
**Figure 1.**  
CONSORT Diagram





**Figure 2. Maximum Trial Duration by Therapeutic Category**

The black lines represent the median duration per therapeutic category. Upper and lower bounds of the box represent the 75th (quartile 3 [Q3]) and 25th (quartile 1 [Q1]) percentiles, respectively. The whiskers represent the following values:  $Q3 + 1.5(Q3 - Q1)$  and  $Q1 - 1.5(Q3 - Q1)$ . Outliers within each therapeutic category are denoted by circles.



**Figure 3. Maximum Trial Duration by Age Category**

The black lines represent the median duration per age group. Upper and lower bounds of the box represent the 75th (quartile 3 [Q3]) and 25th (quartile 1 [Q1]) percentiles, respectively. The whiskers represent the following values:  $Q3 + 1.5(Q3 - Q1)$  and  $Q1 - 1.5(Q3 - Q1)$ . Outliers within age group category are denoted by circles.

**Table 1.**

## Drugs Used for Long-term Therapy and Supporting Trials by Therapeutic Category

Category	Drugs, No. (%)		Trials, No. (%) (N = 306)
	Overall (N = 86)	With Extension Trials (n = 30)	
Neurology	25 (29)	14 (47)	109 (35.6)
Pulmonary	16 (19)	3 (10)	91 (29.7)
Infectious diseases	14 (16)	3 (10)	35 (11.4)
Gastrointestinal	10 (12)	0	26 (8.5)
Biologic	6(7)	4(13)	20 (6.5)
Cardiology	5 (6)	5(17)	8 (2.6)
Hematology	5 (6)	0	6 (2.0)
Endocrine	4(5)	1(3)	6 (2.0)
Miscellaneous	1 (1)	0	5 (1.6)
Dermatology	0	0	0

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**Table 2.**

Percentage of Drugs by Maximum Trial Duration for Long-term Therapeutics

Maximum Trial Duration, Median, wk	Drugs, No. (%)		
	Total (N = 86)	Long-term Intermittent (n = 19)	Long-term Continuous (n = 67)
<52	52 (61)	13 (68)	39 (58)
52 to <104	21 (24)	5(26)	16 (24)
104 to<156	3(4)	0	3(5)
156 to <208	2(2)	0	2 (3)
208 to <260	2 (2)	0	2 (3)
260	6 (7)	1(5)	5 (8)

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