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ARTICLE

Pediatric dosing for locally acting drugs in submissions to the U.S. Food and Drug Administration between 2002 and 2020

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Abstract

Deriving pediatric doses for locally acting drugs (LADs) presents a unique challenge because limited systemic exposure hinders commonly used approaches such as pharmacokinetic matching to adults. This study systematically evaluated drug development practices used for pediatric dose selection of LADs approved by the U.S. Food and Drug Administration from 2002 to 2020. The three study objectives were: (1) to determine the dose selection approach for the labeled pediatric dose, (2) to examine the studied pediatric dose(s), and (3) to evaluate the characteristics of the pediatric clinical programs used to support the labeled pediatric dose. A total of 187 pediatric submissions were characterized for the labeled and studied pediatric doses of LADs. The pediatric dose was predominantly labeled as a flat dose (91%) and at a single-dose level (67%) similar to adults. The majority (68.4%) of the submissions had the same labeled dose for pediatrics and adults. Independent pharmacodynamic/efficacy studies in pediatric patients commonly (64.2%) provided supportive evidence for the labeled pediatric dose. Inhalation, nasal, and injectable submissions had the highest number of clinical trials, lowest usage of an extrapolation of efficacy approach, and utilized diverse approaches in selecting the studied pediatric doses. This article highlights approaches for LAD dosing in pediatric patients and can be used to inform drug development of these products in the pediatric population.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

For systemically absorbed drugs, dosing from adult drug development programs can be leveraged to inform pediatric dose selection; however, locally acting drugs (LADs) pose a challenge of not being systemically absorbed and limit the utilization of approaches such as exposure matching.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study assessed LAD dosing practices through the following aims: (1) determine the dose selection approach for the labeled pediatric dose, (2) examine the studied pediatric dose(s), and (3) evaluate the characteristics of the pediatric clinical programs used to support the labeled pediatric dose.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This study demonstrated that the majority of the labeled pediatric dose was at a single-dose level and utilized a flat dosing approach. The labeled pediatric dose was commonly same as adult dose, and pediatric pharmacodynamic/efficacy studies supported the labeled pediatric dose selection. Inhalation, nasal, and injectable programs had the most complex pediatric drug development programs.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Review of these programs provides the clinical pharmacology and drug development communities with approaches for LAD dosing in pediatric patients.

INTRODUCTION

Drug development in pediatric patients is an evolving science. Developmental, anatomical, and physiological changes that occur in pediatric patients increase the complexity of pediatric efficacy evaluation, safety evaluation, and dose selection. Many drugs are initially developed in adults, and adult data are used to inform dosing for pediatric studies. Several strategies have been used to inform pediatric dose selection, including allometric scaling, exposure matching, and model-informed drug development (MIDD) approaches such as physiologically based pharmacokinetic modeling.[1–3]

In a systematic review of pediatric dosing methods between 2012 and 2020, more than half of pediatric programs utilized MIDD, and the top three strategies for selecting an initial study dose were empirical experience with the product, allometric scaling, and exposure matching. Titration to target response, pharmacokinetic/pharmacodynamic (PK/PD) studies, and exposure matching were identified as the most common strategies for the pivotal dose selection.[1]

Deriving pediatric doses for locally acting drugs (LADs) presents a unique challenge since limited systemic exposure prevents the utility of common dose selection methods that leverage PK data such as exposure matching to adults. A lack of confidence in dose selection could also limit the use of extrapolation of efficacy and result in a larger and more complex pediatric drug development programs.[4] Even in cases where the disease manifestation in adults and children is deemed to be similar, uncertainty as to what dose results in a similar therapeutic effect between adults and children can limit the application of pediatric extrapolation approaches for LADs.

Therefore, practices for developing and approving LAD dosing in pediatrics were evaluated in this project with the following three objectives: (1) determine the dose selection approach for the labeled pediatric dose, (2) examine the dose selection approach for the studied pediatric dose(s), and (3) evaluate the extent of the pediatric clinical programs used to support the labeled pediatric dose.

METHODS

Identification of LADs with pediatric labeling

A subset of drugs with pediatric labeling approved by the U.S. Food and Drug Administration's (FDA's) Center for Drug Evaluation Research (CDER) was selected from the FDA's public pediatric labeling site (Figure 1).[5] LADs were defined as those not intended to be absorbed into the bloodstream and whose mechanism of action occurred at the site of drug administration). Drug products were identified as LADs based on a review of the labeling language in the following sections of the prescribing information (PI): Indications and Usage, Dosage and Administration, Pediatric Use, Clinical Pharmacology, and Clinical Studies. A 19-year study timeframe from 2002 to 2020 was chosen to obtain a sufficiently large database of LAD regulatory submissions to facilitate a reasonable evaluation. In addition, 2002 was the enactment date of the Best Pharmaceuticals for Children Act (BPCA) and is the year in which pediatric reviews were posted on a public website.[6]

Each pediatric labeling update for the selected LADs in the pediatric labeling database was captured as a submission. When the different indications and/or age groups

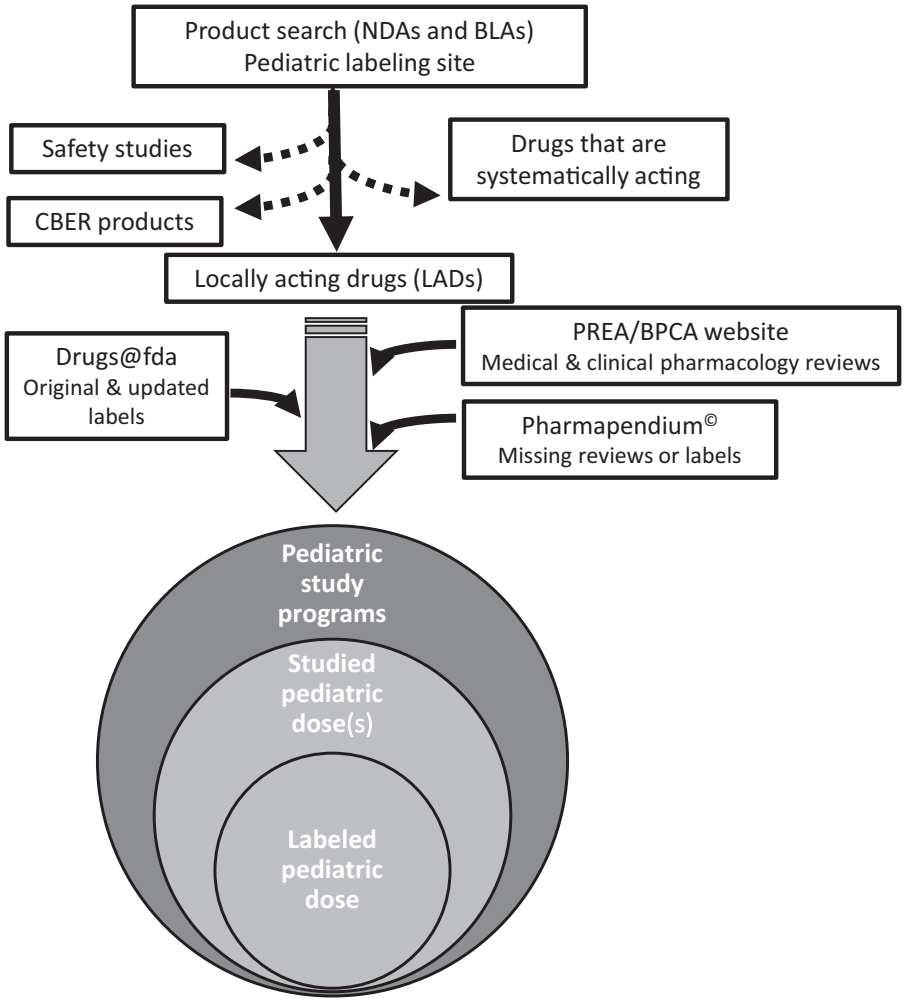

FIGURE 1 Schematic of project workflow. BLA, biologics license application; BPCA, Best Pharmaceuticals for Children Act; CBER, Center for Biologics Evaluation and Research; LAD, locally acting drug; NDA, new drug application; PREA, Pediatric Research Equity Act.

had different dosing regimens within one labeling update, they were captured as separate submissions to aid with categorization. Excluded from the list were submissions resulting from safety post-marketing studies of drugs already indicated for the pediatric population (Figure 1). Submissions that did not receive approval for the studied pediatric indication(s) or age group were analyzed separately from those approved to get an understanding of their pediatric clinical programs and the studied doses.

Data extraction

Information regarding dose and characteristics of the pediatric study programs were collected from publicly available FDA websites such as Drugs@FDA, pediatric labeling changes spreadsheet, and the Pediatric Research Equity Act (PREA)/BPCA pediatric website, as well as Pharmapendium.[6–10] For 5% of the submissions, the labels or regulatory reviews were missing from the publicly available FDA sources. This information was instead obtained from internal FDA sources and are only reported at a summary level without disclosure of the names of the drug products in this article. Information extracted from the data sources included therapeutic indications, labeled pediatric and adult doses, studied pediatric doses, and other characteristics of the pediatric study programs such as the number and type of pediatric clinical studies, number of studied doses, and utilization of extrapolation of efficacy approach. Subsequently, the collected data were categorized and analyzed as presented in Table S1, Figure 1, and Table 1.

Data categorization and analysis

Labeled pediatric dose

The labeled pediatric dose was categorized based on whether the dose level was labeled at a single-dose level

TABLE 1 Definitions used for categorizing labeled and studied pediatric doses for locally acting drugs (LADs).

Pediatric dose level	
Single-dose level	Dose that is given at a single-dose level
Multiple-dose levels	Dose that is presented as a range of doses/concentrations/volumes and includes a range of doses and titration to target
Other	Dose level that does not fit into any of the above categories
Pediatric dose strategy	
Flat dose	Dose strategy without correction for body weight
Body size-based dose	Dose strategy that includes weight-based dose, weight-band dose, and body surface area (BSA) dose
Other	Dose strategy that does not fit into any of the above categories
Labeled pediatric dose	
Same as adult dose (SAAD)	If the dose language between adults and pediatric dose is the same and the same concentration and dosage strength are used in pediatrics and adults
Not same as adult dose	If the dose language between adults and pediatrics is different
Supportive evidence for labeled pediatric dose	
Pharmacodynamic (PD)/efficacy studies	Dose supported by independent pediatric PD/efficacy studies with a measurable clinical outcome
Based on literature review	Dose that relies on data and information from the literature
Safety study(ies)	Dose that is supported by safety clinical studies
Other	Dose support that does not fit into any of the above categories
Support for studied pediatric dose	
Same as adult dose	Dose selected is same as adult dose with no further explanation in review documents
Based on efficacy in adults or older pediatric patients	Dose selected is based on previously shown efficacy in adults or older pediatric population
Based on a previously studied product in pediatric patients	Dose selection supported by a previously studied drug product in the pediatric population
Based on studies in another indication in pediatric patients	Dose studied is based on a different approved indication in the pediatric population
Other	Dose support that does not fit into any of the above categories

or was presented as multiple-dose levels, and if the pediatric dose strategy was labeled based on body size or without correction for body size (flat dosing; see definitions in Table 1). In both scenarios, if the dosing did not fit either category, it was labeled as "other."

Next, the labeled pediatric dose was compared to the labeled adult dose and assigned "same as adult dose" (SAAD) when dosing was identical between the adult and all the pediatric populations. The labeled pediatric dose was assigned "not SAAD" when dosing between adult and one or more of the pediatric populations was different.

To assess the supporting evidence for the labeled pediatric dose, the types of studies and data available in the pediatric clinical programs were evaluated. The categories were defined as "PD/efficacy studies" when the sponsor performed independent PD/efficacy pediatric studies, "literature-based assessment" when the only data provided came from the literature, "safety studies" when the pediatric data only included safety studies, or "other" when the program did not fit into the aforementioned categories (see definitions in Table 1).

Studied pediatric dose(s)

The doses evaluated within the pediatric studies and the supportive evidence available to support those studied pediatric dose(s) were assessed. The supportive evidence was categorized as follows: "based on studies in another indication in pediatric patients" when the dose studied was based on a different approved indication of the same product in the pediatric population, "based on a previously studied product in pediatric patients" when the dose selection was supported by a different previously studied and approved drug product in the pediatric population, or "based on efficacy in adults or older pediatric patients" when dose selection was only supported by previous safety and efficacy in adults or older pediatric population. In addition, when the supportive evidence for the studied pediatric dose could not be found and if the comparison between the labeled pediatric and adult doses was SAAD, the studied pediatric dose was categorized as "same as adult dose." The category "other" was used when the studied dose did not

fit into any of the aforementioned categories (see definitions in Table 1).

In addition, information on the number of doses and/or dosing regimens studied was collected. The dosing regimens studied were categorized as "same as pediatric labeled dose" if the studied pediatric dose was the same as the labeled pediatric dose, and "studied pediatric doses lower or higher (or both) than the labeled dose" was assigned if the sponsor studied lower and/or higher than the labeled pediatric dose in addition to the labeled pediatric dose.

Pediatric clinical programs

Other characteristics of the pediatric clinical programs such as the number and type of pediatric clinical trials and the utilization of extrapolation of efficacy approach were captured. Utilization of extrapolation of efficacy for pediatric approval was captured based on the description in the FDA reviews.

RESULTS

Characteristics of LADs

A total of 137 drug products approved for pediatrics between January 2002 and December 2020 that met the definition of LADs were identified. For these products, a total of 187 pediatric submissions were identified. The most common routes of administration were dermal (34%), ophthalmic (23%), inhalation (14%), and oral (11%) (including tablets, capsules, and oral suspensions; Figure 2). Other routes of administration included nasal, injectable (including intramuscular, intradermal, intraoral, intratympanic, and intravitreal), otic, and vaginal and intrauterine.

A total of 25 submissions (15 products) were identified that did not receive FDA approval for the proposed pediatric indication due to the following reasons: 12% (3/25) due to lack of pediatric enrollment, 12% (3/25) due to inadequate efficacy and safety, 16% (4/25) due to inadequate safety, and the remaining 60% (15/25) due to insufficient efficacy. They were represented by 33% (5/15) dermal, 27% (4/15) inhalation, 13% (2/15) ophthalmic, 6.7% (1/15) oral, 6.7% (1/15) nasal, 6.7% (1/15) injectable, and 6.7% (1/15) suppository products.

Assessment of labeled pediatric dose(s) for LADs

The pediatric dose was labeled at a single-dose level in 67% (125/187) of submissions, at multiple-dose levels in 28% (52/187) of submissions, and in the other category in 5% (10/187) of submissions (Figure 3a). Multiple-dose levels included 40% (21/52) labeled with titration to target dosing and 60% (31/52) allowing use of a range of doses. The dose level category was similar between adults and pediatrics in 82% (147/179) of the submissions. The dose level comparison to adults was not feasible for eight submissions that were for pediatric-specific diseases/conditions.

Of the 187 pediatric submissions, the labeled pediatric dose was a flat dose in 91% (169/187) of submissions, body size-based dosing (including body surface area, weight-band, and weight-based dose) in 4% (8/187) of submissions, and 5% (10/187) used other strategies (e.g., diagnostic agents where the dose is chosen by the

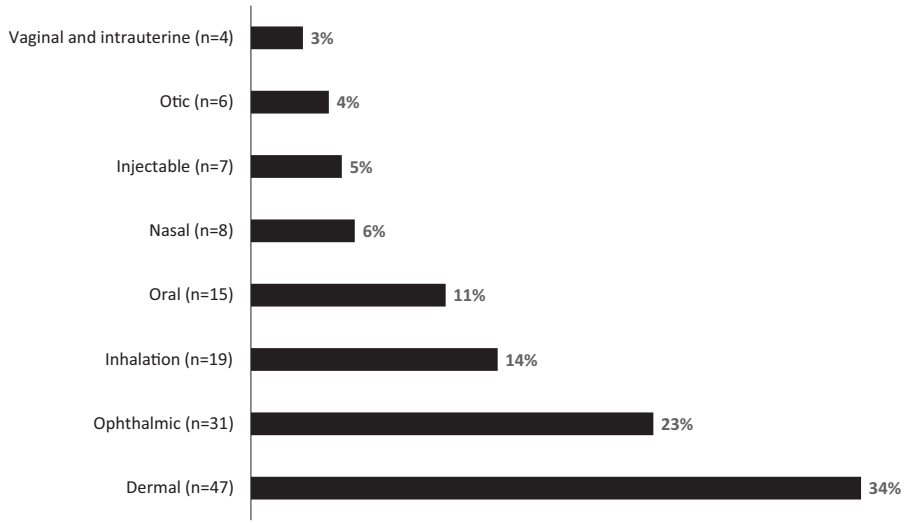

FIGURE 2 Products by route of administration ($n = 137$).

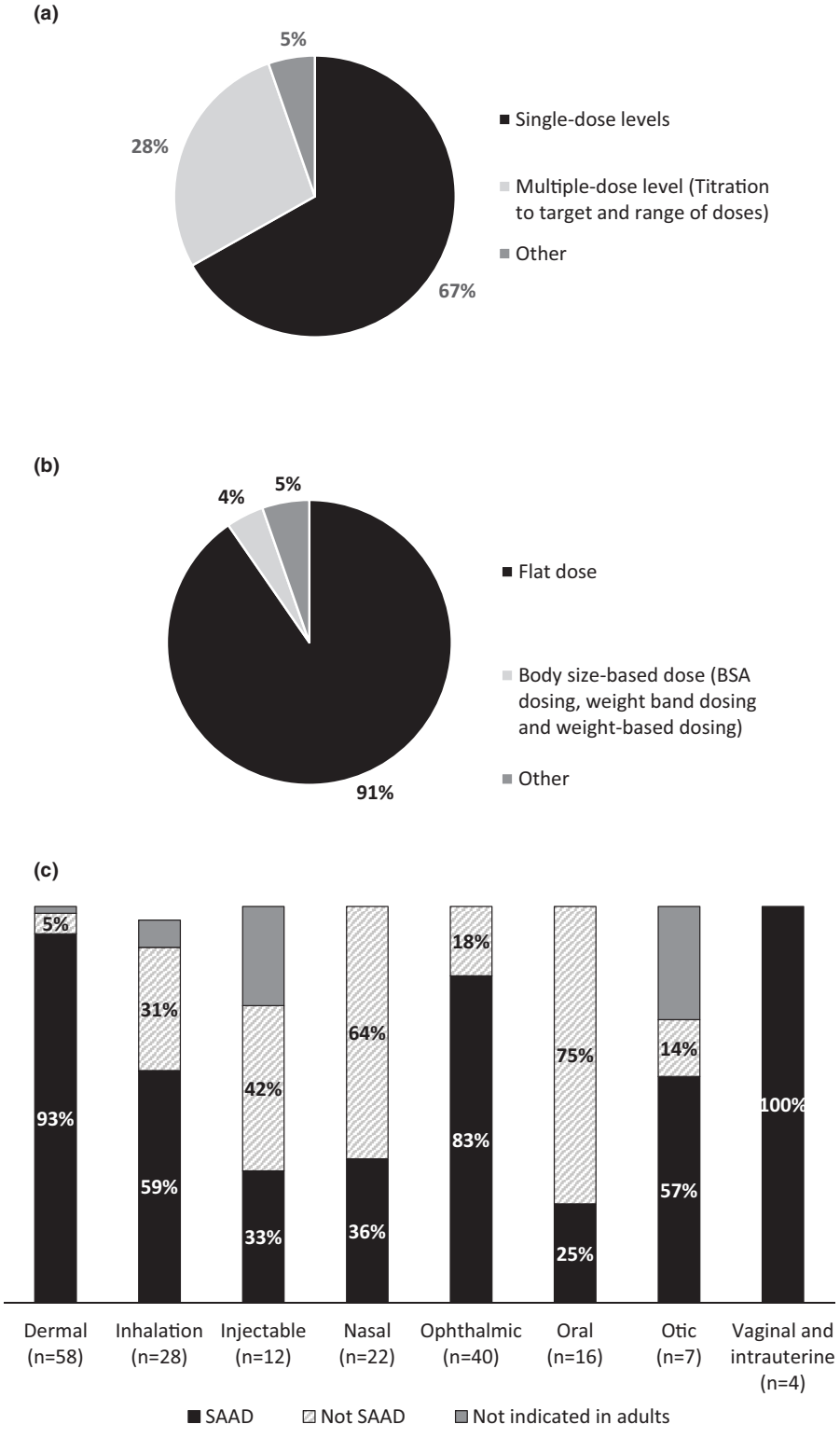

FIGURE 3 (a-c) Assessment of labeled pediatric dose for 187 submissions. (a) Dose level. (b) Dose strategy. (c) Labeled pediatric dose categorization. BSA, body surface area; SAAD, same as adult dose.

physician)[11–13] (Figure 3b). The dose strategy was similar between adults and pediatrics in 90% (161/179) of the submissions. The dose strategy could not be compared to adults for eight submissions that were for pediatric specific diseases/conditions.

Overall, the dose/dosing regimen labeled for pediatric was the same as adults (SAAD) in 68.4% (128/187) of submissions. SAAD was most commonly seen for vaginal and intrauterine (100%, 4/4), dermal (93%, 54/58), ophthalmic (83%, 33/40), and inhalation (61%,

17/28) (Figure 3c). Regardless of whether the dose was SAAD, the supportive evidence for the labeled pediatric dose was categorized as 64% (120/187) of submissions supported by independent pediatric PD/efficacy studies, 21% (39/187) supported by safety studies only, 10% (18/187) were based on literature review, and the remainder of the submissions utilized other approaches to support the labeled pediatric dose. Fifty percent or more of the submissions across all routes of administration except ophthalmic and vaginal and intrauterine had independent PD/efficacy studies in pediatrics (Figure 4). The supportive evidence for the labeled pediatric dose was pediatric safety studies for 40% (23/58) of dermal submissions, 23% (9/40) of ophthalmic submissions, 18% (4/22) of nasal submissions, 8% (1/12) of injectable submissions, 6% (1/16) of oral submissions, and 4% (1/28) of inhalation submissions (Figure 4). The supportive evidence for the labeled pediatric dose was based on literature review for 28% (11/40) of ophthalmic submissions, 25% (3/12) of injectable submissions, and 25% (4/16) of oral submissions. All (4/4) of the vaginal and intrauterine submissions were approved based on other means such as extrapolation of efficacy from adults or older pediatric age groups without any pediatric studies performed (Figure 4).

Evaluation of the studied pediatric doses for LADs

Evaluation of the studied pediatric doses involved capturing the doses, the relationship between the studied dose(s) to the labeled pediatric dose, and assessing the underlying evidence to support the dose selection. Twenty-eight submissions with pediatric approvals based on extrapolation of efficacy from adult findings, literature reviews, or adult bioequivalence studies that did not have any pediatric clinical programs were excluded from this analysis. The studied pediatric dose was SAAD in 48.4% (77/159) of submissions. Studied doses were supported by data on a previously studied product in pediatrics (21.4%, 34/159), data in adults or older pediatric patients for the same product (18.2%, 29/159), data for the same product in a different indication in pediatrics (3.8%, 6/159), and the remainder were supported by other means (8.2%, 13/159). An example of the other category is the pediatric studied dose that was selected based on clinician experience such as in the case of lidocaine hydrochloride indicated for providing local analgesia prior to venipuncture or onabotulinumtoxin A for treatment of upper limb spasticity. In addition, the studied pediatric dose for sevelamer carbonate tablets, a non-absorbed phosphate binder indicated for the control

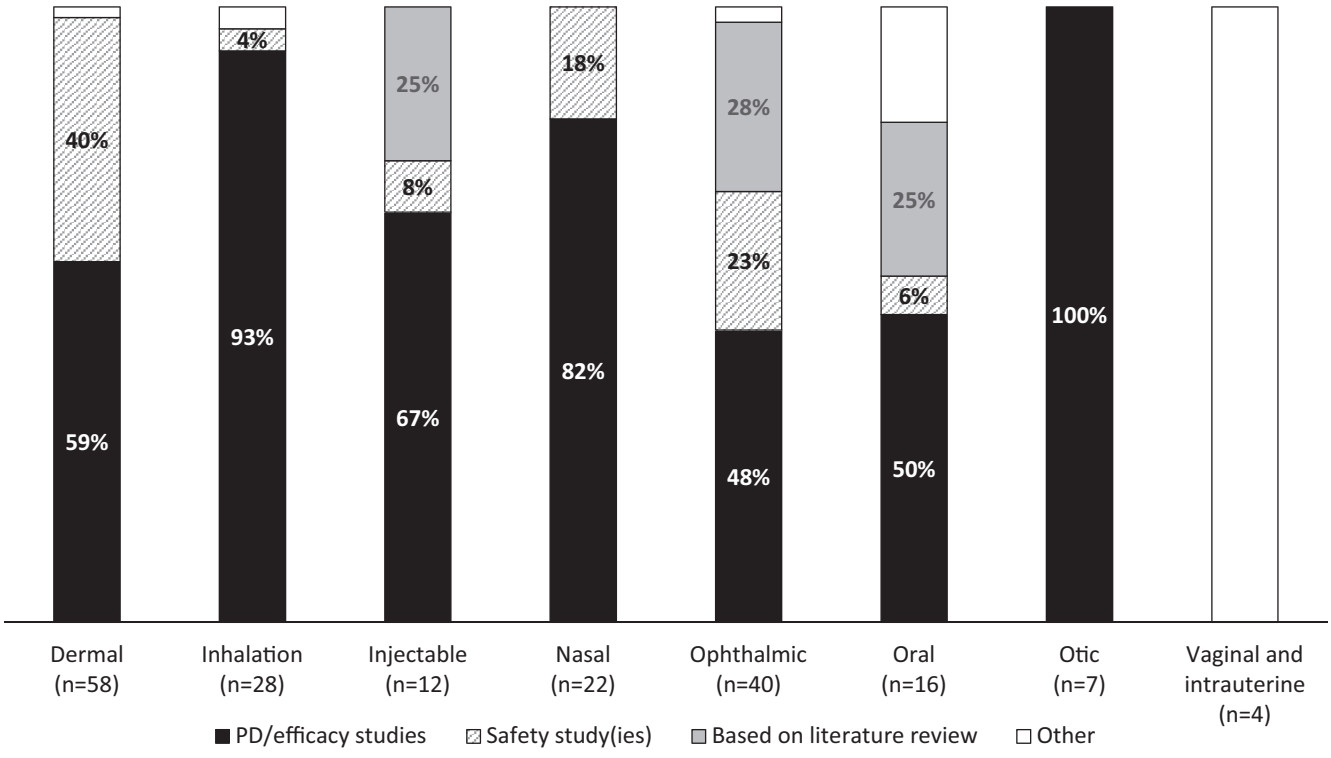

FIGURE 4 Categorization of pediatric clinical development programs to support the labeled pediatric dose ($n = 187$). PD, pharmacodynamic.

of serum phosphorus with chronic kidney disease, was based on a percentage of adult dose.[14] The dose studied in pediatric studies was SAAD in 75% (43/57) of dermal and 71% (20/28) of ophthalmic submissions (Figure 5a). Inhalation, nasal, and injectable submissions had the most diverse approaches for selecting doses for pediatric studies and utilized different supporting evidence approaches across their submissions (Figure 5a).

For the 25 submissions that did not receive pediatric indications, the studied pediatric dose was most commonly supported by data from adults or older pediatric patients (52%, 13/25) and SAAD (20%, 5/25; data not shown).

Thirty-nine percent of submissions (62/159) studied more than one dose and/or dosing regimen in the pediatric studies. Submissions for injectable (100%, 9/9), inhalation (85%, 23/27), oral (67%, 6/9), and nasal (50%, 11/22) included studies evaluating more than one dose and/or dosing regimen (Figure 5b).

Across submissions, 33% (52/159) studied doses lower or higher in addition to the labeled pediatric dose(s) and 67% (107/159) studied only the labeled pediatric dose(s). Eighty-six percent of ophthalmic, 82% of dermal, 71% of otic, 67% of oral, and 59% of nasal submissions studied only the labeled pediatric dose (Figure 5c). In contrast, 67% of submissions for both injectable and inhalation products studied doses lower or higher in addition to the labeled pediatric dose (Figure 5c).

Characteristics of the pediatric clinical programs for LADs

The size of the pediatric drug development programs ranged from one to up to 11 pediatric clinical trials. For dermal products, 60% (34/57) of the submissions had one or two pediatric clinical trials. In contrast, 57% (16/28) of inhalation submissions had four or more pediatric clinical trials per submission (data not shown).

The utilization of extrapolation of efficacy from adults or older pediatric groups to younger pediatric groups was evaluated based on the availability of explicit information in the FDA regulatory reviews. An extrapolation of efficacy approach is used when there is sufficient evidence about the similarity of disease and response to the intervention.[15] Extrapolation of efficacy approach was utilized in 39% (64/164) of submissions. Among the 28 submissions with no pediatric clinical trials that were excluded from the previous analysis, five submissions utilized the extrapolation of efficacy approach, and they were included in this analysis (the other 23 submissions were based on literature reviews or bioequivalence assessments). The five submissions included four contraceptive submissions (levonorgestrel-releasing intrauterine systems and segesterone acetate and ethinyl estradiol vaginal system) and a submission for an inhalation product (albuterol sulfate).[16–20]

Overall, the extrapolation of efficacy approach was utilized in 100% of vaginal and intrauterine submissions, 67% of oral submissions, 49% of dermal submissions, and 46% of ophthalmic submissions. Nasal, inhalation, otic, and injectable submissions less commonly utilized the extrapolation of efficacy approach with only 27%, 18%, 14%, and 11% of their submissions, respectively, indicating the use of extrapolation of efficacy approach (Figure 6). An example of the extrapolation of efficacy approach is dapsone for the topical treatment of acne vulgaris in pediatric patients aged 9 to <12 years old in which the sponsor conducted only a safety study. The efficacy was extrapolated from the older pediatric age group (12 years and older) to this younger pediatric population (9 to <12 years old).[21]

DISCUSSION

Considerations surrounding pediatric dosing remain an integral part of pediatric drug development. Pediatric trials are often initiated after the efficacy and safety for the drug has been determined in adults.[22,23] This approach allows for a reference range of systemic exposures from adults to be leveraged to inform a target range of systemic exposure in children.[22] However, this approach is generally not applicable for LADs because there is little or no systemic absorption. Even when LADs have some systemic exposure, the plasma concentration profiles of these products are generally not reliable surrogate end points for their pharmacological activities.[24] In fact, according to the FDA's guidance on allergic rhinitis product development, efficacy trials in pediatric patients are recommended for intranasal formulations regardless of whether the drug under development has been approved in adults, due to the plasma concentration of such drugs not being consistently detectable or a reliable measure of efficacy.[25]

Differences in anatomy and physiology between adults and pediatrics and the characteristics of the relevant drug delivery device (e.g., size and shape) can affect the efficacy and safety of LADs and have implications related to dose.[26] Pediatric doses are commonly prescribed using body size-based dosing, but they can also be given as flat doses. Flat dosing has been reported to offer certain advantages over body size-based dosing such as higher patient compliance, reduced risk of dose calculation errors by clinicians, easier preparation and administration, as well as cost-effectiveness.[26] In our study, 91% of the submissions were labeled as flat doses in the pediatric population consistent with adult dosing. In addition, 68% of submissions were labeled for pediatrics at the same as

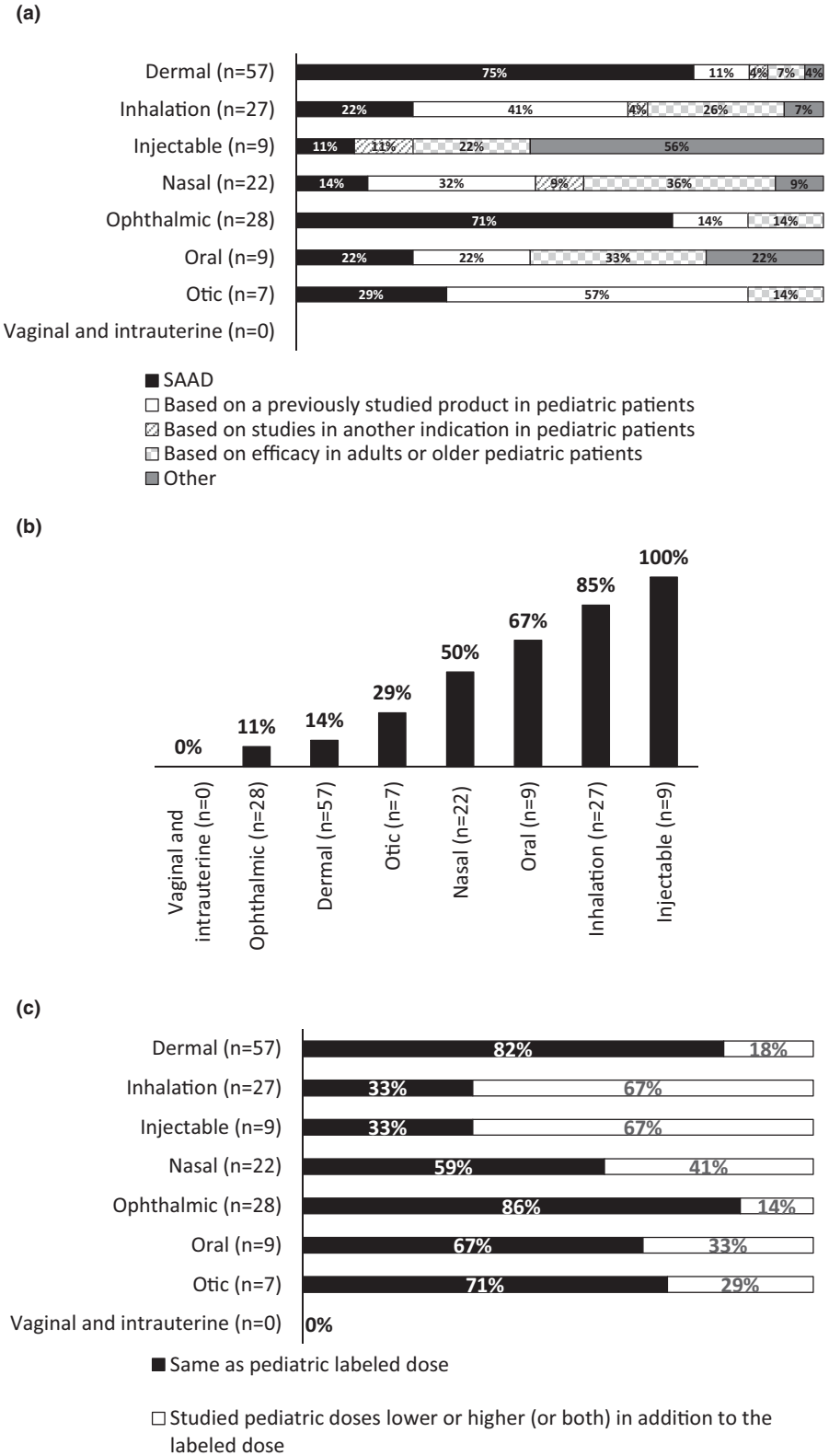

FIGURE 5 (a) Supportive evidence for the studied pediatric dose ($n = 156$). Studies approved based on literature reviews and bioequivalence studies that did not have any pediatric clinical programs were excluded from this analysis. (b) Percentage of pediatric programs that studied more than one dose and/or dosing regimen. (c) Categorization of doses studied in pediatric study plans with same as pediatric labeled dose (shaded in black) and doses lower or higher (or both) in addition to the labeled dose (shaded in white). SAAD, same as adult dose.

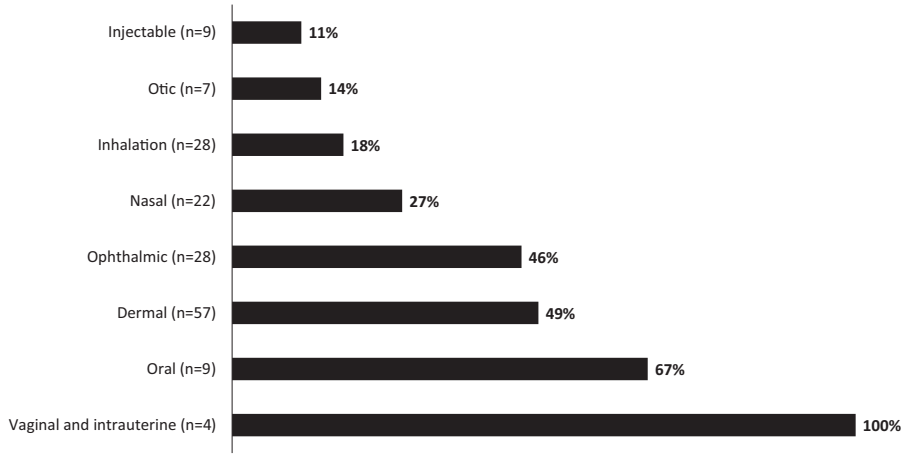

FIGURE 6 Extrapolation of efficacy approach from adults or older pediatric population to younger pediatric population ($n = 164$). Five of 28 submissions without pediatric clinical programs were included in this analysis because they utilized the extrapolation of efficacy approach. The remainder of 23 submissions, approved based on literature reviews and bioequivalence studies that did not have any pediatric clinical programs, were excluded from this analysis.

adult dose. Long-term effects of using fixed adult doses for prolonged therapy in pediatric patients have not been adequately studied. However, injectables, nasal, and oral LAD products were more likely to be labeled in pediatrics at doses different from those labeled for adults. Additionally, inhalation, injectable, nasal, and oral products commonly studied more than one dose and/or dosing regimen in the pediatric studies.

While regulatory guidelines require sponsors to consider age-appropriate formulations,[27,28] there are currently no requirements for the development of age-appropriate delivery devices despite the need to ensure that an adequate amount of drug is delivered, for instance via the intranasal route. For this reason, the FDA recommends that all key clinical trials such as dose-ranging studies and confirmatory efficacy and safety trials be conducted with the to-be-marketed product for intranasal products.[25]

LADs not only present challenges to new drug applications (NDAs) but to generic drug development as well. In the product development phase, optimization and product scale-up become difficult because of limited methods of comparing pre- and post-product change. Sponsors are also less reluctant to make major manufacturing improvements if additional clinical studies are warranted to validate the changes.[24] For generic LAD products, a bioequivalence study with the clinical end point is often used instead of commonly used PK end points used for most generics.[24,29]

These complexities may translate to drug development programs for pediatrics. Green et al., who did not consider LADs in their report, reported the most common pivotal dosing strategies in pediatric programs were titration to target response in 33% of programs, PK/PD studies (30%), and exposure matching (20%).[1] In our study, PD/efficacy studies commonly supported the labeled pediatric dose across most routes of administration. Independent PD/efficacy studies in pediatric patients were conducted for 64% of LAD submissions ranging from 48% of ophthalmic submissions to 93% of inhalation submissions. Injectable products and drug–device combination products such as inhalation and nasal submissions reported the highest number of clinical trials and assessed more than one dose and/or dosing regimen in their pediatric studies. In the case of the inhalation and nasal products, the maturational difference in the respiratory tract (diameter, length, and geometry of the passages) likely played a role in this diversity of approach. As for injectables, difference in the skin and subcutaneous thickness and fat content between pediatric and adult subjects likely contributed to the observed differences.

An upward shift in the usage of extrapolation of efficacy approach in pediatric studies has occurred over time; between 2015 and 2020, 71% of the of drugs utilized extrapolation of efficacy (complete + partial) compared to 63% of the drugs listed in the 2009–2014 assessment of pediatric approvals.[15] In our study, extrapolation of efficacy was utilized for 39% of submissions. Injectable, nasal, and inhalation submissions had the lowest reported usage of extrapolation of efficacy approach. Of the submissions that used extrapolation of efficacy, the labeled pediatric dose for 75% (48/64 submissions) was SAAD.

It has been reported by a number of authors that one in every five pediatric trials fails because of inappropriate trial design, inadequate participant enrollment, and poor dose selection.[1,22,23] Our database of pediatric LADs identified 25 submissions (15 products) that were not approved

by the FDA due to lack of pediatric enrollment or inadequate efficacy and/or safety data.

This study has several limitations that should be acknowledged. First, our list of approved LADs with pediatric submissions between 2002 and 2020 was developed using publicly available information and may not have been a comprehensive list. Approved LADs in the timeframe were identified based on evaluation of their mechanism of action and the routes of administration by two independent researchers, but some submissions may have been missed. In addition, the data source could have missed some pediatric submissions. Second, there was a limitation in categorization as submissions could have multiple indications with multiple pediatric age groups with different studied and labeled dosing regimens in some cases. However, consistent methodology and the use of adjudication by the second researcher was used for categorization.

In summary, this study highlights similarity in dosing approaches for LADs between adults and pediatric patients despite challenges such as limitation in utilization of approaches such as exposure matching. Contrary to our expectation of limited application of extrapolation of efficacy approaches for LADs, the study showed that more than one in three submissions used such approach. However, pediatric programs for LADs commonly included PD/efficacy studies. Additionally, this study showed that drug–device combination products such as inhalation and nasal products in addition to injectable products had the most complex pediatric development programs.

This systematic evaluation of dosing for LADs can inform development of a structured dosing approach in the pediatric population and provide insight into future best practices. The work has helped identify potential LAD product types with the most complex development programs that could be targeted to further streamline pediatric drug development programs.

AUTHOR CONTRIBUTIONS

All authors wrote the manuscript and designed the research. G.A.A. performed the research and analyzed the data.

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CONFLICT OF INTEREST STATEMENT

The authors declared no competing interests for this work.

DISCLAIMER

The opinions expressed in this article are those of the authors and should not be interpreted as the position of the U.S. Food and Drug Administration.

REFERENCES

1. Green FG, Park K, Burckart GJ. Methods used for pediatric dose selection in drug development programs submitted to the US FDA 2012-2020. *J Clin Pharmacol*. 2021;61(Suppl. 1)):S28-S35. doi:10.1002/jcph.1853
2. Grimstein M, Yang Y, Zhang X, et al. Physiologically based pharmacokinetic modeling in regulatory science: an update from the U.S. Food and Drug Administration's Office of Clinical Pharmacology. *J Pharm Sci*. 2019;108(1):21-25. doi:10.1016/j.xphs.2018.10.033
3. Wang J, van den Anker JN, Burckart GJ. Progress in drug development-pediatric dose selection: workshop summary. *J Clin Pharmacol*. 2021;61(Suppl. 1)):S13-S21. doi:10.1002/jcph.1828
4. Dunne J, Rodriguez WJ, Murphy MD, et al. Extrapolation of adult data and other data in pediatric drug-development programs. *Pediatrics*. 2011;128(5):e1242–e1249. doi:10.1542/peds.2010-3487
5. U.S. Food and Drug Administration. New Pediatric Labeling Information Database. Accessed October 26, 2020. https://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase
6. U.S. Food and Drug Administration. Reviews of pediatric studies conducted under BPCA and PREA from 2012-present. Accessed October 26, 2020. https://www.fda.gov/drugs/development-resources/reviews-pediatric-studies-conducted-under-bpca-and-prea-2012-present
7. U.S. Food and Drug Administration. Reviews of pediatric studies conducted under BPCA and PREA from 2007-2012. Accessed October 26, 2020. https://www.fda.gov/drugs/development-resources/reviews-pediatric-studies-conducted-under-bpca-and-prea-2007-2012
8. U.S. Food and Drug Administration. Reviews of pediatric studies conducted under BPCA and PREA from 2002-2007. Accessed October 26, 2020. https://wayback.archive-it.org/7993/20170111081709/http:/www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm161894.htm
9. Elsevier. PharmaPendium. Accessed December 17, 2020. https://www.pharmapendium.com/login/email
10. U.S. Food and Drug Administration. Drugs@FDA. Accessed October 26, 2020. https://www.accessdata.fda.gov/scripts/cder/daf/
11. U.S. Food and Drug Administration. FDA label for sodium picosulfate, magnesium oxide, and anhydrous citric acid oral solution. Accessed November 16, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/209589s006lbledt.pdf

12. U.S. Food and Drug Administration. FDA label for balanced salt ophthalmic solution with hypromellose, dextrose and glutathione. Accessed November 16, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/022193lbl.pdf
13. U.S. Food and Drug Administration. FDA label for phentolamine mesylate injection. Accessed November 16, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022159s011lbl.pdf
14. U.S. Food and Drug Administration. FDA clinical review for sevelamer carbonate tablets. Accessed November 16, 2020. https://www.fda.gov/media/102586/download
15. Samuels S, Park K, Bhatt-Mehta V, et al. Pediatric efficacy extrapolation in drug development submitted to the US Food and Drug Administration 2015-2020. *J Clin Pharmacol*. 2022;63:307-313. doi:10.1002/jcph.2160
16. U.S. Food and Drug Administration. FDA clinical review for levonorgestrel-releasing intrauterine system (Liletta). Accessed November 16, 2020. https://www.fda.gov/media/92554/download
17. U.S. Food and Drug Administration. FDA review for levonorgestrel-releasing intrauterine system (Mirena). Accessed November 16, 2020. https://www.fda.gov/media/80202/download
18. U.S. Food and Drug Administration. FDA clinical review for levonorgestrel-releasing intrauterine system (Skyla). Accessed November 16, 2020. https://www.fda.gov/media/85815/download
19. U.S. Food and Drug Administration. FDA multi-disciplinary review for segesterone acetate and ethinyl estradiol vaginal system. Accessed November 16, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/209627Orig1s000MultidisciplineR.pdf
20. U.S. Food and Drug Administration. FDA clinical review for albulterol sulfate powder inhaler. Accessed November 16, 2020. https://www.fda.gov/media/98400/download
21. U.S. Food and Drug Administration. FDA clinical review for dapsone gel. Accessed November 16, 2020. https://www.fda.gov/media/131968/download
22. Abdel-Rahman SM, Reed MD, Wells TG, Kearns GL. Considerations in the rational design and conduct of phase I/II pediatric clinical trials: avoiding the problems and pitfalls. *Clin Pharmacol Ther*. 2007;81(4):483-494. doi:10.1038/sj.clpt.6100134
23. Zhang Y, Wang Y, Khurana M, et al. Exposure-response assessment in pediatric drug development studies submitted to the US Food and Drug Administration. *Clin Pharmacol Ther*. 2020;108(1):90-98. doi:10.1002/cpt.1809
24. Lionberger RA. FDA critical path initiatives: opportunities for generic drug development. *AAPS J* 2008;10(1):103–109. doi:10.1208/s12248-008-9010-2
25. US Food and Drug Administration. Guidance for Industry: Allergic Rhinitis: Developing Drug Products for Treatment. Accessed January 30, 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/allergic-rhinitis-developing-drug-products-treatment-guidance-industry
26. Batchelor HK, Marriott JF. Formulations for children: problems and solutions. *Br J Clin Pharmacol*. 2015;79(3):405-418. doi:10.1111/bcp.12268
27. U.S. Food and Drug Administration. Guidance for Industry: E11 Clinical Investigation of Medicinal Products in the Pediatric Population. Accessed November 16, 2020. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e11-clinical-investigation-medicinal-products-pediatric-population
28. U.S. Food and Drug Administration. Guidance for Industry: general clinical pharmacology considerations for pediatric studies of drugs, including biological products. Accessed January 30, 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/general-clinical-pharmacology-considerations-pediatric-studies-drugs-including-biological-products
29. Zhao L, Kim MJ, Zhang L, Lionberger R. Generating model integrated evidence for generic drug development and assessment. *Clin Pharmacol Ther*. 2019;105(2):338-349. doi:10.1002/cpt.1282

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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