Extrapolation of Adult Data and Other Data in Pediatric Drug-Development Programs

WHAT'S KNOWN ON THIS SUBJECT: Extrapolation of efficacy, an approach first proposed in 1994, can increase the efficiency of pediatric drug development. Little has been published on its practical application and whether it can achieve the objectives of increased efficiency and increased pediatric drug labeling.

WHAT THIS STUDY ADDS: Extrapolation can be used successfully to decrease the number of pediatric patients and studies required for pediatric drug development. Approaches have changed over time with growing knowledge and experience regarding the assumptions underlying extrapolation for particular therapeutic classes and indications.

abstract

OBJECTIVES: In 1994, the US Food and Drug Administration (FDA) proposed an approach, based on extrapolation of efficacy findings from adults to the pediatric population, to maximize the use of adult data and other data when designing pediatric drug-development programs. We examined the experience of the FDA in using extrapolation to evaluate how and when it was used and any changes in scientific assumptions over time.

METHODS: We reviewed 370 pediatric studies submitted to the FDA between 1998 and 2008 in response to 159 written requests (166 products) issued under the Pediatric Exclusivity Provision. We identified cases in which efficacy was extrapolated from adult data or other data, we categorized the type of pediatric data required to support extrapolation, and we determined whether the data resulted in new pediatric labeling.

RESULTS: Extrapolation of efficacy from adult data occurred for 82.5% of the drug products (137 of 166). Extrapolation was defined as complete for 14.5% of the products (24 of 166) and partial for 68% of them (113 of 166). Approaches to extrapolation changed over time for 19% of the therapeutic indications studied (13 of 67). When extrapolation was used, 61% of the drug products (84 of 137) obtained a new pediatric indication or extension into a new age group; this number decreased to 34% (10 of 29) when there was no extrapolation.

CONCLUSIONS: Extrapolating efficacy from adult data or other data to the pediatric population can streamline pediatric drug development and help to increase the number of approvals for pediatric use. *Pediatrics* 2011;128:e1242–e1249

AUTHORS: Julia Dunne, MD, FRCP,[a] William J. Rodriguez, MD, PhD,[a] M. Dianne Murphy, MD,[a] B. Nhi Beasley, PharmD,[b] Gilbert J. Burckart, PharmD,[c] Jane D. Filie, MD,[d] Linda L. Lewis, MD,[e] Hari C. Sachs, MD,[f] Philip H. Sheridan, MD,[g] Peter Starke, MD,[h] and Lynne P. Yao, MD[i]

[a]Office of Pediatric Therapeutics, Office of the Commissioner, Divisions of [b]Cardiorenal Products, [d]Anesthesia, Analgesia, and Rheumatology Products, [e]Antiviral Products, [f]Pediatric and Maternal Health Staff, [g]Neurology Products, [h]Pulmonary and Allergy Products, and [i]Gastroenterology Products, and [c]Office of Clinical Pharmacology, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland

KEY WORDS
extrapolation, efficacy, pediatric drug-development programs

ABBREVIATIONS
CHF—congestive heart failure
FDA—Food and Drug Administration
WR—written request

The views presented in this article do not necessarily reflect those of the Food and Drug Administration.

www.pediatrics.org/cgi/doi/10.1542/peds.2010-3487

doi:10.1542/peds.2010-3487

Accepted for publication Jul 29, 2011

Address correspondence to Julia Dunne, MD, FRCP, Food and Drug Administration, Office of Pediatrics, 13B-45, 5600 Fishers Lane, Rockville, MD 20857. E-mail: julia.dunne@fda.hhs.gov

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: *The authors have indicated they have no financial relationships relevant to this article to disclose.*

This article examines the experience of the US Food and Drug Administration (FDA) in extrapolating efficacy in pediatric drug-development programs, focusing on how and when extrapolation was used, its impact on labeling, and changes in approaches over time. Historically, medicines were not developed for pediatric use, which necessitated decades of off-label use for most pediatric prescribing.[1,2] Reasons for this included a lack of commercial incentives for the pharmaceutical industry, parents' unwillingness to enroll their children in clinical trials, a lack of trained pediatric investigators, the special vulnerabilities of the pediatric population, and the unique ethical and methodologic challenges of conducting pediatric research. Other challenges include the relatively small pediatric patient population, compared with adult populations, and the special protections provided to children in clinical trials. These and other limitations mean that fewer patients are available to enroll in pediatric clinical trials, compared with adult trials. This drives the need to minimize the number of subjects enrolled in pediatric clinical trials and the need to maximize the usefulness of the data obtained, while still ensuring that the trials are feasible, robust, and interpretable.

In 1994, as a first step toward ensuring the most efficient use of all relevant data in the planning of pediatric drug-development programs specifically, the FDA finalized a set of rules for the extrapolation of efficacy to the pediatric population from adequate, well-controlled studies with adults.[3] Such extrapolation depends on a series of evidence-based assumptions. Two fundamental assumptions are that there are similar disease progressions and similar responses to intervention in the adult and pediatric populations. A third assumption is that the 2 populations have similar exposure-response relationships. The FDA examines several factors before making assumptions of similarity, including disease pathogenesis, criteria for disease definition, clinical classification, measures of disease progression, and pathophysiologic, histopathologic, and pathobiological characteristics. Support for these assumptions may be derived, for example, from sponsor data, published literature findings, expert panel, workshop, or consensus documents, or previous experience with other products in the same class; the FDA decides whether the available evidence is sufficient for authorization of a drug for pediatric use.

When applicable, the use of extrapolation should reduce the number and complexity of pediatric trials necessary to achieve pediatric labeling, although supportive pediatric data are still required. For systemically active drugs, these data ordinarily include pharmacokinetic data for the relevant pediatric age groups, for determination of appropriate doses, and safety information. The FDA uses the age group categorization provided in International Conference on Harmonization guideline E11, that is, preterm newborn infants, term newborn infants (0–27 days), infants and toddlers (28 days to 23 months), children (2 to 11 years), and adolescents (12 to 16–18 years, depending on region). Other supportive pediatric data may include pharmacodynamic studies, studies supporting safety and/or efficacy, and relevant premarketing or postmarketing studies or experience. Efficacy may be extrapolated between pediatric age groups if there are no significant age-related differences. Safety profiles may differ between populations, which precludes extrapolation of safety information.

The 1997 Food and Drug Modernization Act[4] and its subsequent reauthorization[5,6] provided an incentive program through which an innovator drug company can receive an additional 6-month period of marketing exclusivity if it responds to an FDA-issued written request (WR) for pediatric studies of its drug. Since the enactment of the Food and Drug Modernization Act, the FDA has requested almost 1000 pediatric trials[7] and has gained a unique perspective on pediatric study design.

METHODS

We focused on pediatric studies submitted between February 1998 and February 2009 in response to FDA-issued WRs. A multidisciplinary FDA working group including representatives from the therapeutic review divisions and the offices of pediatric therapeutics, clinical pharmacology, and pediatric and maternal health staff reviewed and tabulated the contents of the WRs, the submitted studies, and the final labeling according to drug and therapeutic indication.

We assessed the use of efficacy extrapolation by the FDA by using the FDA pediatric study decision tree[8] (Fig 1), which provides an assumption-based framework for determining the pediatric studies necessary for labeling on the basis of the ability to extrapolate efficacy from adult data or other data. We reviewed each WR for pediatric data and classified it according to the use of extrapolation (ie, no extrapolation, partial extrapolation, or complete extrapolation). If the assumptions required for extrapolation do not apply (option A in Fig 1), then extrapolation cannot be used and, after pharmacokinetic studies are conducted to establish the correct dose, efficacy must be demonstrated independently in the pediatric population with the FDA standard for proof of efficacy, that is, 2 adequate, well-controlled trials. Drugs for use in pediatric oncology are an exception. Pediatric tumors are rare and biologically distinct from tumors

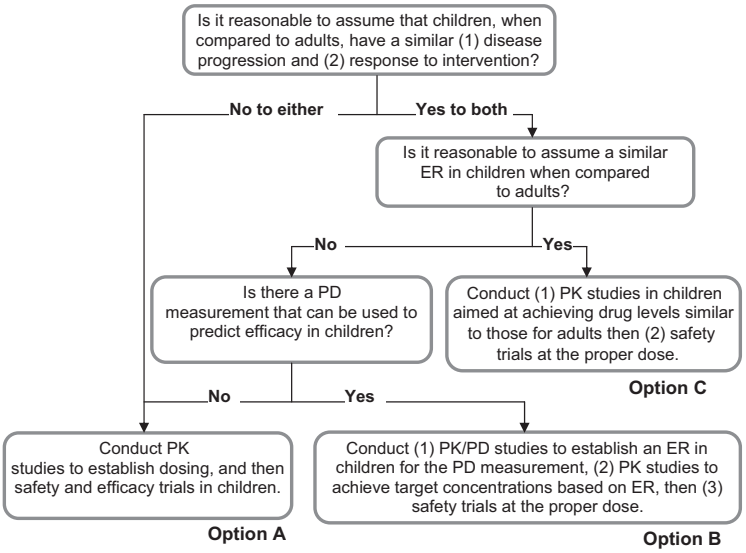

FIGURE 1

Pediatric study decision tree. This algorithm can be applied to systemically active drugs administered through the oral, intravenous, subcutaneous, or other routes. When applicable, the pediatric dose and dosage regimen can be estimated from adult and pediatric pharmacokinetic data. The algorithm does not apply to locally active drugs, such as drugs administered topically, intranasally, or through oral inhalation. For such drugs, pharmacokinetic data are relevant for the estimation of systemic exposure in relation to safety but are not helpful for the estimation of appropriate effective pediatric doses, because the relevant biospace is local to the skin, nasal passages, or lung and not the blood. Consequently, for locally active products, the correct dose must be estimated clinically and then tested for each age group. ER indicates exposure response; PD, pharmacodynamic; PK, pharmacokinetic.

in adults. Effective therapies also are rare; therefore, activity usually is assessed noncomparatively, by measuring disease-specific surrogate measures or clinically relevant end points with a limited number of patients.

Complete extrapolation of efficacy (option C in Fig 1) relies on robust data supporting the assumptions that there are similar disease progressions, responses to intervention, and exposure-response relationships in adult and pediatric populations. The effective dose is identified by matching systemic exposures between adult and pediatric populations. Complete extrapolation is supported by pediatric pharmacokinetic and safety data or, in certain cases, pediatric safety data only.

Partial extrapolation of efficacy is used when there is uncertainty about ≥ 1 of the assumptions underlying complete extrapolation. The pediatric evidence required to support partial extrapolation ranges from a single adequate, well-controlled trial to confirm efficacy to a pharmacokinetic/pharmacodynamic (exposure-response) study to confirm response in the pediatric population. The latter can be used to confirm the similarity of the exposure-response relationship when there is evidence to support the assumptions that disease progressions and responses to intervention are similar in the adult and pediatric populations and there is a pharmacodynamic measurement that can predict efficacy in the pediatric population (option B in Fig 1).

When we identified extrapolation of efficacy, we recorded the type of extrapolation used, the FDA's assumptions justifying extrapolation, the supportive evidence requested from pediatric studies, and whether the aim was to confirm efficacy, to confirm responses, or to confirm doses. In all cases, the safety assessment was separate and was not a primary focus of the review. We also identified which pediatric age groups were studied, any extrapolation between age groups or from other data, whether the approaches resulted in a new or extended pediatric indication, and whether the approach changed for a particular therapeutic indication and/or drug class over time.

RESULTS

The review included 159 FDA-issued WRs and 370 pediatric studies. This represents 166 drug products; a WR is issued for a particular active moiety, and >1 drug product may be involved. Depending on the robustness of the data supporting the assumptions required for extrapolation of efficacy and the resulting degree of certainty in the assumptions, the evidence required to label a product for use for the relevant pediatric age groups ranged from pediatric pharmacokinetic and safety data or safety data only (complete extrapolation) to a complete program including pediatric pharmacokinetic data and 2 adequate, placebo-controlled, pediatric safety and efficacy trials (no extrapolation). A summary of the approaches used and the underlying assumptions, the frequency of their use, the studies requested and their purpose, and the labeling outcomes is provided in Table 1. Lists of all products reviewed, pediatric studies requested, and labeling decisions are available in Supplemental Table 4, Supplemental Table 5, Supplemental Table 6, Supplemental Table 7, Supplemental Table 8, Supplemental Table 9, and Supplemental Table 10.

There was no extrapolation of efficacy for 17% of the products (29 of 166) in the review (Table 1). Those products covered 15 therapeutic indications, including major depressive disorder, asthma, and solid tumors (Supplemen-

TABLE 1 Summary of Approaches to Use of Extrapolation of Efficacy From Adult Population to Pediatric Population

Extrapolation of Efficacy From Adult Data	Assumptions Made to Extrapolate Efficacy	Purposes of Pediatric Studies	Supportive Evidence Requested From Pediatric Studies	Products for Which WRs Issued, *n*/*N* (%)	New or Expanded Pediatric Indication Achieved, *n*/*N* (%)
No extrapolation	Disease/condition and/or response to intervention are not similar.	Demonstration of efficacy and assessment of safety.	Two adequate, well-controlled, efficacy and safety trials plus pharmacokinetic data.	19/166 (11)	7/19 (37)
		For oncology products only, demonstration of response and assessment of safety.	For oncology products only, sequential approach starting with phase 1/2. Do not proceed if no evidence of response.	10/166 (6)	3/10 (30)
Partial extrapolation	Disease/condition and/or response to intervention are similar but there is some uncertainty about the strength of assumptions.	Confirmation of efficacy and assessment of safety.	Single, adequate, well-controlled, efficacy and safety trial plus pharmacokinetic data.	67/166 (40)	35/67 (52)
	Disease/condition and/or response to intervention are similar but there is less uncertainty about the strength of assumptions (or patient numbers are such that it would not be feasible to conduct a controlled or adequately powered study).	Confirmation of response and assessment of safety.	Single, controlled or uncontrolled, efficacy and safety trial (qualitative data) plus pharmacokinetic data.	20/166 (12)	15/20 (75)
			Single exposure-response trial (not powered for efficacy determination) plus pharmacokinetic and safety data, pharmacokinetic/pharmacodynamic and uncontrolled efficacy data plus safety data, or pharmacokinetic/pharmacodynamic data plus safety data.	26/166 (16)	19/26 (73)
Complete extrapolation	Disease/condition and/or response to intervention are similar and there is a high degree of certainty about the strength of assumptions.	Exposure data to confirm age- appropriate dose and assessment of safety.	Pharmacokinetic and safety data.	10/166 (6)	9/10 (90)
	Disease/condition and/or response to intervention are similar and there is a high degree of certainty about the strength of assumptions. Dose assumed to be the same (eg, topical application).	Assessment of safety.	Safety data only.	14/166 (8)	6/14 (43)

tal Table 4). In most cases, efficacy was not extrapolated because the disease or condition was not considered to be sufficiently similar in the adult and pediatric populations or the disease or condition rarely occurred in adults. In a few cases, the product was not authorized for use for the adult indication and efficacy could not be extrapolated. The relatively low rate of pediatric labeling achieved with this approach (34% [10 of 29 products]) resulted in part from deficiencies in the design and execution of the efficacy trials, which reflected the prevailing lack of knowledge regarding optimal end points and trial design for some pediatric conditions. In some cases, however, trial failure may reflect real differences between the adult and pediatric populations with respect to the particular disease and responses to intervention (eg, many of the antitumor products).

Complete extrapolation, supported by pediatric pharmacokinetic and safety data, was used for only 6% of the products (10 of 166) (Table 1) and for 8 therapeutic indications, including allergic rhinitis, asthma, analgesia, and partial seizures (Supplemental Table 8). The approach achieved new pediatric labeling for 90% of products (9 of 10), but it was rarely used to extrapolate from the adult population to the pediatric population. It was used, however, to extrapolate from one pediatric indication to another closely related one (eg, from seasonal allergic rhinitis to chronic idiopathic urticaria). It also was used to support the approval of new formulations of drugs that already had been approved for the pediatric population and to extend a pedi-

TABLE 2 Extrapolation of Efficacy From Sources Other Than Controlled Adult Data for Same Indication

Source From Which Efficacy Extrapolated	Example of Extrapolation
Other pediatric age groups (different levels of evidence in different age groups)	Methylphenidate: from children to adolescents (1 controlled study requested); remifentanil: from data for age ≥1 y down to age 0–1 y on basis of supportive pharmacokinetic and efficacy data from safety study.
Other formulations of same active ingredient	From other ibuprofen formulations to ibuprofen suspension; from montelukast oral tablets and chewable tablets to montelukast oral granules for suspension.
Related pediatric indications	Loratidine: for seasonal allergic rhinitis and perennial allergic rhinitis, 1 trial for each enabled approval for both indications; same applied for ondansetron for postoperative nausea and vomiting and chemotherapy-induced nausea and vomiting.
Adult indication for (similar) pediatric indication	Celecoxib: from rheumatoid arthritis to juvenile idiopathic arthritis.

atric indication from an older pediatric age group to a younger pediatric age group (eg, montelukast oral tablets and chewable tablets) (Table 2). In a few cases (8% [14 of 166 products]), efficacy was extrapolated with the support of safety data only (ie, without pharmacokinetic data). This approach was used for 7 indications, in cases in which the available body of knowledge provided reassurance that pharmacokinetic data were unnecessary (Supplemental Table 9). The approach was used for a new formulation of ibuprofen, to extend the pediatric indications for desflurane to include nonintubated patients, and to extend the pediatric age range for a number of topically administered drugs. Fifty-seven percent of products (8 of 14) in this group failed to achieve labeling because the safety data raised concerns regarding safe use (eg, increased incidence of respiratory adverse events with desflurane among nonintubated patients). This emphasizes the importance of not extrapolating safety data to the pediatric population. In those cases, the pediatric safety data were included in the product label.

Partial extrapolation of efficacy was used for most of the drug products (61% [103 of 166]) (Table 1). A single adequate, well-controlled trial supported by pharmacokinetic data was requested for 67 drug products covering 35 therapeutic indications, including schizophrenia, migraine, chronic hepatitis B virus infection, and hypertension (Supplemental Table 5). Less frequently, the FDA required pediatric studies that were supportive of efficacy rather than confirmatory (ie, the studies were not powered for confirmation of efficacy). This approach was used for 18 drug products covering 13 therapeutic indications, including ulcerative colitis and various bacterial infections (Supplemental Table 6). Exposure-response studies were requested to confirm responses in cases in which efficacy could be predicted with a pharmacodynamic measurement. This approach was used for 26 products covering 11 therapeutic indications, including gastroesophageal reflux disease, HIV infection, sedation, and anesthesia (Supplemental Table 7).

We also identified extrapolation of efficacy from sources other than adult data (Table 2). Most commonly, the extrapolation was from efficacy data for one pediatric age group to another pediatric age group. This approach was used for indications such as asthma, rhinitis, and anesthesia.

We were unable to quantify the effect of extrapolation in reducing either the total number of pediatric studies requested or the total number of patients involved in pediatric trials. However, 2 adequate, well-controlled, pediatric trials (the FDA standard for proof of efficacy) were conducted for only 11% of the drug products (19 of 166) in the review (Table 1). When extrapolation was used, a single adequate, well-controlled trial, a single uncontrolled and/or unpowered efficacy trial, an exposure-response trial, and/or a pharmacokinetic study were requested to support the extrapolation of efficacy data from adults. For those products, the use of extrapolation resulted overall in a considerable reduction in the number of studies and patients needed for pediatric drug development.

New labeling for pediatric use was obtained for 61% of the products (84 of 137) for which extrapolation was used. In contrast, new pediatric labeling was achieved for only 34% of the products (10 of 29) for which there was no extrapolation of efficacy data (Table 1). The reasons why products failed to obtain labeling when extrapolation was used included failed or uninterpretable studies, insufficient data, high variability in pharmacokinetic studies, inability to achieve therapeutic concentrations in a relevant body compartment, or an unexpected safety signal. Failure to obtain pediatric labeling when there was no extrapolation of efficacy was usually because the trials were uninterpretable or failed to demonstrate efficacy or a response. Failure to demonstrate an effect may indicate lack of efficacy in the pediatric population. Other reasons include failure to establish the correct pediatric dose before starting exposure-response or efficacy studies, failure to power controlled efficacy studies adequately, use of an inappropriate (eg, adult) efficacy end point, and inadequate design (eg, omission of a placebo arm in dose-response studies).

TABLE 3 Changes in Approach to Extrapolation ($N = 13$)

Indication	Nature of Change
Analgesia	Initially FDA required independent proof of efficacy in pediatric population. After FDA workshop of experts in pediatric analgesia, FDA now accepts that, for opioids, nonsteroidal antiinflammatory drugs, acetaminophen, and local anesthetics, it is scientifically appropriate to extrapolate efficacy from adults to pediatric populations down to age 2–4 y. For analgesics with unknown mechanisms of action or novel analgesics for which pediatric relevance of the mechanism of action is unknown, adequate, well-controlled, efficacy studies and safety data are still necessary, after pharmacokinetic data are obtained to support dose selection.
Arrhythmia	FDA originally asked for a single, controlled, dose-response study, on the basis of continuity, and would have extrapolated between arrhythmias. Now less certainty about continuity between adult and pediatric populations and FDA would require 2 studies.
Detrusor instability secondary to neurologic impairment	FDA now grants waivers for patients ≤5 y of age. It used to request open-label studies with surrogate urodynamic end points. Since 2007, FDA has requested adequately controlled (including placebo), double-blind studies with clinical end points. FDA may not issue any more WRs for α-blockers for this indication, because 2 large, double-blind, placebo-controlled trials with clinically meaningful surrogate end points for tamsulosin and alfuzosin both yielded negative results.
GERD	FDA considers that the course of GERD in adults is not sufficiently similar to the course of pathologic gastroesophageal reflux in pediatric patients <1 y of age to permit extrapolation of adult efficacy data to this pediatric age group. Approaches in this age group may change because no trials to date have demonstrated efficacy for the 1–11-mo-old population. FDA originally requested a separate efficacy study with neonates but now requires a pharmacokinetic/pharmacodynamic/safety study.
Heterozygous familial hypercholesterolemia	For first statin, FDA required 2 adequate, well-controlled trials. For subsequent statins, FDA required a single trial. Since review of several positive single studies, FDA has accepted open-label, uncontrolled, efficacy studies showing similar LDL-lowering effects in adult and pediatric populations.
Hypertension	Extrapolation was used to label enalapril for use down to age of 1 mo on the basis of consistent pharmacokinetic data across pediatric (2 mo to 16 y) and adult age groups and positive controlled, dose-response study results for patients 6–16 y of age. However, FDA changed this approach after receiving data on antihypertensive drugs that showed no efficacy in pediatric age groups despite similar pharmacokinetic characteristics for pediatric and adult populations. Antihypertensive drugs now receive pediatric labeling only for age groups for which efficacy is confirmed.
JIA	First WRs focused on pharmacokinetic and safety data and extrapolated efficacy from the adult population in a traditional manner. Now FDA requests independent confirmation of efficacy in the pediatric population, except in certain cases where the drug is in a class with established efficacy in the pediatric population. Also, different considerations apply for symptom-modifying treatments, compared with disease-modifying therapies. In general, a single, adequate, well-controlled, pediatric trial is requested on the basis of the similarity between JIA and adult rheumatoid arthritis. For symptom-modifying treatments, FDA encourages inclusion of children with all 7 subtypes of JIA,[15] because children with all subtypes will be treated. In contrast, for disease-modifying drugs, efficacy is extrapolated from adult rheumatoid arthritis to the polyarticular subtype of JIA, because this subtype most resembles rheumatoid arthritis. Separate studies would be requested for the other subtypes.
Mania in association with bipolar disorder	For relapse prevention, efficacy is extrapolated from the adult indication for relapse prevention, supported by positive trial results for induction of remission in adolescents. FDA initially requested a separate, placebo-controlled study for relapse prevention, but sponsors reported difficulties in recruitment.
Migraine	Extrapolation was based on continuity between adult and pediatric populations. Designs of requested single controlled studies evolved over time as pediatric studies repeatedly failed to show efficacy, partly because of high placebo response rates for adolescents. A different pediatric end point is now used because of shorter duration of migraine headaches in adolescents, with an enrichment design to ensure recruitment of patients with longer-duration headaches. Initially efficacy was not extrapolated to age <12 y because of rarity and diagnostic uncertainty. Now studies are requested down to 6 y.
Osteogenesis imperfecta	Currently, no more WRs to be issued because available evidence indicates lack of efficacy.
Prophylaxis of organ rejection for patients receiving renal or hepatic transplants	Initial work with sirolimus (single controlled study against best local care) showed nonsuperiority. When everolimus studies were completed, FDA decided that neither sirolimus nor everolimus represented significant meaningful benefits, and waivers were granted for patients 0–16 y of age.
Rhinitis (topical nasal sprays)	Initially extrapolated completely from adults and older age groups to children <6 y of age because of perceived lack of feasibility. Studies with children ≤6 y of age are now considered feasible, and safety data (including pharmacokinetic data for systemic safety), a placebo-controlled, safety and efficacy study, and evaluation of age-appropriate doses are now requested.
Schizophrenia	For relapse prevention, extrapolation from adult indication for relapse prevention, supported by positive trial results for induction of remission in adolescents. FDA initially requested separate placebo-controlled study for relapse prevention, but sponsors reported difficulties in recruitment.

GERD indicates gastroesophageal reflux disorder; JIA, juvenile idiopathic arthritis; LDL, low-density lipoprotein.

There was no difference in failure rates between placebo- and active comparator-controlled trials.

Of the 67 different therapeutic indications studied, the FDA changed its approach to extrapolation for 13 (19%) as knowledge and experience increased (Table 3). The change allowed greater extrapolation in some cases, whereas the opposite was true in other cases.

DISCUSSION

Since 1997, the FDA has used extrapolation extensively when issuing WRs for pediatric studies. The process has evolved over time as the FDA and the

scientific community in general have increased their knowledge and experience of pediatric drug development. We have learned important lessons about extrapolation and the design of pediatric study protocols. There is no simple formula to determine whether there is adequate evidence to support the decision to extrapolate efficacy to the pediatric population. The decision should be based on a body of evidence that takes into account the scientific knowledge of all aspects of the disease and its natural history in the adult and pediatric populations, the interactions between developmental changes and the disease and responses to therapy, experience with other drugs in the same class and for the same indication, and the validity of the pediatric efficacy end points. When there is certainty regarding the scientific basis for extrapolation, there is greater likelihood of successful new pediatric labeling. In addition, the relatively high failure rate of controlled efficacy studies emphasizes the importance of incorporating verified scientific approaches and pediatric expertise in the development of successful pediatric study protocols.

The carvedilol trial illustrates a number of potential pitfalls in pediatric study design.[9,10] It was the first large, randomized controlled trial of a medication for children and adolescents with chronic heart failure (CHF), and it had a double-blind, 2-dose, placebo-controlled design. The study did not detect a treatment effect of carvedilol on the primary composite end point, possibly because children and adolescents with CHF receive no benefit from carvedilol because of differences in the causes of CHF in children and adolescents (dilated cardiomyopathy and congenital heart disease), compared with adults (ischemic heart disease). However, several factors in the study design and enrolled population also might have influenced the final result. The appropriate age-related dose was not established before the study. The higher dose was chosen through linear, weight-based extrapolation from adult doses. The lower dose was chosen arbitrarily as one-half of the higher dose. Trough carvedilol plasma levels measured during the study were lower in children and adolescents than in adults, given a similar dosage per unit weight. Subsequent work suggested that carvedilol pharmacokinetics depend on age as well as weight, and the doses used in that study might have been too low.[11,12] The composite study end point was not validated for heart failure studies with children and adolescents and might be inappropriate for developing children. The power calculation was based on adult data and greatly underestimated the 19% improvement in the placebo group observed during the study. In addition, there was no provision to examine a possible dose-response effect; the prespecified primary analysis compared the combined carvedilol group (low and high doses) with the placebo group. Also, the results suggested that carvedilol might have different effects in children and adolescents, depending on the underlying pathophysiologic condition. Additional work would be needed to prove this. Although the study is uninterpretable, these findings should inform future trials with children and adolescents with CHF.

The series of trials conducted with antihypertensive medications provided similar lessons. Our review contained WRs for 13 antihypertensive agents, 5 of which achieved labeling for pediatric use. An analysis of pediatric antihypertensive agent trial failures, which focused on 6 trials that all used the same trial design, concluded that careful attention to pediatric pharmacologic characteristics, to optimize the choice of doses for evaluation in efficacy trials and the selection of age-appropriate pediatric end points (eg, diastolic blood pressure), was important to avoid trial failure.[13] All 8 of the failed trials in our review, 3 of which were considered in the published analysis, illustrated the same issues of suboptimal dose selection and use of suboptimal end points. Trial failure also could be related to the use of a placebo-controlled withdrawal design, rather than a placebo-controlled, parallel-group design. The use of a withdrawal design arose from ethical concerns about using placebo for an extended period and the risks of untreated hypertension for children with hypertension secondary to renal or vascular causes. However, withdrawal studies depend on subjects becoming hypertensive again shortly after the administration of study medication is stopped. This might not have been the case, particularly after the use of longer-acting antihypertensive agents. In addition, because most of the enrolled subjects had hypertension secondary to obesity, an ethical case could be made for a simple placebo-controlled, parallel-group design combined with therapeutic lifestyle changes.[14]

Since recent changes in US legislation, pediatric drug development is becoming more integrated in the overall drug-development program and, increasingly, the FDA issues comprehensive WRs that encompass a complete pediatric development program. Since October 2007, an FDA internal multidisciplinary pediatric review committee has reviewed all WRs with the aim of achieving a consistent coherent approach across therapeutic areas.

CONCLUSIONS

Extrapolation of efficacy from the adult population to the pediatric population has helped to maximize the use of existing information to increase the efficiency

of pediatric drug-development programs while maintaining the goal of increasing the number of safe effective medicines approved for pediatric use on the basis of scientifically robust data. In the past decade, the FDA has tested its assumptions about extrapolation and has modified its approaches as knowledge and experience have increased. The approaches are still being refined. Experience gained with failed trials underscores the need to verify critical assumptions about doses, responses, and end points during the development and conduct of pediatric trials.

ACKNOWLEDGMENTS

In addition to the authors, the following FDA employees were members of the working group and participated in the review: Jogarao V. Gobburu and Elena V. Mishina (Center for Drug Evaluation and Research, Office of Clinical Pharmacology); Arzu Selen (Office of New Drug Quality Assessment); Ana Szarfman (Office of Biostatistics); Denise Cook, Lucious Lim, Joette Meyer, Christine Nguyen, Thomas Smith, Kristen Snyder, and Mary Roberts (Office of New Drugs); and Robert M. Nelson (Office of the Commissioner, Office of Pediatric Therapeutics). We thank Barbara J. Gould (Office of New Drugs) for administrative support.

REFERENCES

1. Shirkey HC. Therapeutic orphans. *J Pediatr*. 1968;72(1):119–120
2. Wilson JT. An update on the therapeutic orphan. *Pediatrics*. 1999;104(3):585–590
3. Food and Drug Administration. Specific requirements on content and format of labeling for human prescription drugs: revision of "pediatric use" subsection in the labeling: final rule. *Fed Regist*. 1994;59
4. Food and Drug Administration. Food and Drug Administration Modernization Act of 1997. Available at: www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDAMA/FullTextofFDAMAlaw/default.htm. Accessed March 7, 2011
5. Food and Drug Administration. Best Pharmaceuticals for Children Act. Available at: www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/ucm148011.htm. Accessed March 7, 2011
6. Food and Drug Administration. Food and Drug Administration Amendments Act of 2007. Available at: www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049870.pdf. Accessed March 7, 2011
7. Food and Drug Administration. Breakdown of requested studies report. Available at: www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm050001.htm. Accessed March 7, 2011
8. Food and Drug Administration. *Guidance for Industry: Exposure-Response Relationships: Study Design, Data Analysis, and Regulatory Applications*. Washington, DC: Food and Drug Administration; 2003. Available at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072109.pdf. Accessed March 7, 2011
9. Shaddy RE, Curtin EL, Sower B, et al. The Pediatric Randomized Carvedilol Trial in Children With Heart Failure: rationale and design. *Am Heart J*. 2002;144(3):383–389
10. Shaddy RE, Boucek MM, Hsu DT et al. Carvedilol for children and adolescents with heart failure: a randomized controlled trial. *JAMA*. 2007;298(10):1171–1179
11. Albers S, Meibohm B, Mir TS, Läer S. Population pharmacokinetics and dose simulation of carvedilol in paediatric patients with congestive heart failure. *Br J Clin Pharmacol*. 2008;65(4):511–522
12. Nishiyama M, Park IS, Yoshikawa T, et al. Efficacy and safety of carvedilol for heart failure in children and patients with congenital heart disease. *Heart Vessels*. 2009;24(3):187–192
13. Benjamin DK Jr, Smith PB, Jadhav P, et al. Pediatric antihypertensive trial failures: analysis of endpoints and dose range. *Hypertension*. 2008;51(4):834–840
14. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*. 2004;114(suppl 2):555–576
15. Weiss JE, Ilowite NT. Juvenile idiopathic arthritis. *Rheum Dis Clin North Am*. 2007;33(3):441–470, vi

Extrapolation of Adult Data and Other Data in Pediatric Drug-Development Programs

Julia Dunne, William J. Rodriguez, M. Dianne Murphy, B. Nhi Beasley, Gilbert J. Burckart, Jane D. Filie, Linda L. Lewis, Hari C. Sachs, Philip H. Sheridan, Peter Starke and Lynne P. Yao

Pediatrics 2011;128;e1242; originally published online October 24, 2011; DOI: 10.1542/peds.2010-3487

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Extrapolation of Adult Data and Other Data in Pediatric Drug-Development Programs

Julia Dunne, William J. Rodriguez, M. Dianne Murphy, B. Nhi Beasley, Gilbert J. Burckart, Jane D. Filie, Linda L. Lewis, Hari C. Sachs, Philip H. Sheridan, Peter Starke and Lynne P. Yao

Pediatrics 2011;128;e1242; originally published online October 24, 2011;
DOI: 10.1542/peds.2010-3487