



Extrapolation as a Default Strategy in Pediatric Drug Development

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Abstract

Pediatric drug development lags adult development by about 8 years (Mulugeta et al. in *Pediatr Clin* 64(6):1185–1196, 2017). In such context, many incentives, regulations, and innovative techniques have been proposed to address the disparity for pediatric patients. One such strategy is extrapolation of efficacy from a reference population. Extrapolation is currently justified by providing evidence in support of the effective use of drugs in children when the course of the disease and the expected treatment response would be sufficiently similar in the pediatric and reference population. This paper's position is that, despite uncertainties, pediatric drug development programs should initially assume some degree of extrapolation. The degree to which extrapolation can be used lies along a continuum representing the uncertainties to be addressed through generation of new pediatric evidence. In addressing these uncertainties, the extrapolation strategy should reflect the level of tolerable uncertainty concerning the decision to expose a child to the risks of a new drug. This judgment about the level of tolerable uncertainty should vary with the context (e.g., disease severity, existing therapeutic options) and can be embedded into pediatric drug development archetypes to ascertain the extent of studies needed and whether simultaneous development for adults and adolescents be considered.

Keywords Pediatric drug development · Pediatric regulations · Extrapolation · Treatment landscape archetypes

Regulatory Landscape and Ethical Principles of Pediatric Research

The careful balance between incentives and obligations has stimulated pediatric research and transformed the way medicines are developed and labeled. In the United States (US) alone, the US Food and Drug Administration (FDA) has issued more than 450 Written Requests for new pediatric

studies as of October 2019 [1]. In addition, the FDA has made labeling changes in 854 drugs, including 199 from studies performed under Best Pharmaceuticals for Children Act (BPCA) alone, 131 under BPCA and Pediatric Research Equity Act (PREA), 475 under PREA only, and 49 under the Pediatric Rule (a precursor to PREA) since 2007. Most of these labeling changes are based on new pediatric studies [2, 3]. The European Medicines Agency (EMA) and its Pediatric Committee reported that the number of agreed Pediatric Investigation Plans (PIPs) has surpassed 1200 out of more than 2000 submitted applications or modifications of the initial applications [4]. Furthermore, more than 260 new medicines for use by pediatric patients have been authorized, with most of them linked to the Pediatric Regulation's requirements [5]. Evidence for a more robust pediatric medicines development also comes from ClinicalTrials.gov where more than 600 industry sponsored pediatric clinical trials are underway. Of the 626 clinical trials which

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are recruiting or not yet recruiting, majority are being conducted in more than one country.¹

The multi-regional nature of most pediatric development programs highlights the need to harmonize scientific and regulatory principles of pediatric clinical trial conduct. However, a dilemma exists in finding a balance between the obligation to conduct clinical trials in children to evaluate safe and effective treatment options for pediatric indications and the need to protect children against the unknown risks and harms from trial participation and the use of unapproved medicines [6, 7]. There is broad international agreement on the ethical principles governing the conduct of clinical trials in children. Children should only be enrolled in a clinical trial if the scientific and/or public health objectives cannot be met through enrolling subjects who can provide informed consent (cf. *scientific necessity*²; see also International Council for Harmonization (ICH) E11 (R1) [8] and EMA Reflection Paper on Extrapolation) [9]. Furthermore, children should not be placed at a disadvantage after being enrolled in a clinical trial, either through exposure to excessive risks or by failing to get necessary healthcare. The challenge that remains is how these principles should inform the necessary scope of study under regulatory requirements for pediatric drug development.³

In the US, drugs being developed for children are subject to the same evidentiary standards for efficacy and safety as drugs developed in adults (see 21CFR 314.50 and PHS Act, 505(d)); that is, effectiveness is determined based on adequate and well-controlled investigations. This is echoed by the EMA where marketing authorization (MA) is granted based on the provision of adequate evidence on clinical

efficacy and safety. An important means to balance between obtaining data to inform treatment options and protecting children participating in trials is to avoid enrolling children in studies that are duplicative [10]. In this regard, the US and EU regulations suggest a strategy of designing pediatric programs to provide complementary information. This strategy is based on assessing the relevance of existing information in the adult population to the pediatric population, in terms of the disease, drug pharmacology, and clinical response to treatment. This strategy, further, identifies the gaps or level of uncertainty that need to be addressed to extend a conclusion of adequate evidence of efficacy and safety from the adult to the pediatric population [11]. Such a strategy is called “*pediatric extrapolation*” and is adopted broadly by ICH member parties⁴ to maximize the use of pre-existing information and to reduce the amount of, or general need for, additional information to reach conclusions of effective and safe use of drugs in children.

This paper discusses extrapolation as a default scientific strategy for investigational pediatric product development (Sect. 2). Three treatment landscape archetypes will be introduced to help frame the discussion of extrapolation pertaining to similarity in disease progression and response to treatment. A discussion on disease similarity is provided in Sect. 3. There are many examples where diseases may vary between the reference and pediatric populations, but the treatments or standards of care may be similar in a way that could support extrapolation. Section 4 discusses similarity in treatment response. This section also discusses the potential role for further data generation and considerations on how to stagger or defer further evidence generation, in the context of prospective benefit and risks. Section 5 provides a brief discussion on extrapolation methods and innovative trial designs and analytics. Section 6 provides further recommendations.

Extrapolation as Core Scientific Strategy for a Streamlined Clinical Development

When a regulatory decision is made to require pediatric studies for the linked adult indication, it implicitly assumes that the disease is “sufficiently similar.” The ethical requirements for pediatric drug development also indicate that a degree of extrapolation is appropriate. More specifically, meeting the ethical requirement for a

¹ ClinicalTrials.gov search using status=recruiting or not yet recruiting, age=child, study type=interventional, study phase=phase 3–4, funder type=industry. Accessed December 22, 2019.

² Belmont Report entitled Ethical Principles and Guidelines for the Protection of Human Subjects of Research is codified in HHS regulations as 45 CFR part 46 which includes four subparts. Subpart D pertains to Special Protections for Children as Research Subjects. In the EU, children as vulnerable subjects are covered in Directive 2001/20/EC (Clinical Trials Directive). Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations, and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. OJ L 121, 1.5.2001, p. 34.

³ Both the FDA and EMA define children as the age prior to obtaining the legal age of majority. Physiological development and maturity of organs, pathophysiology and natural history of the disease or condition, available treatment options, and the pharmacology of the investigational product are factors to be considered in determining the subgroups in pediatric studies, e.g., adolescents (12 to less than 21 yrs old), children (2 to less than 12 yrs old), infants (29 days to less than 2 yrs old), and neonates (first 28 days of life). These pediatric studies will be interchangeably referred to as pediatric drug development.

⁴ Member parties that have implemented the guideline include ANVISA (Brazil), EC (Europe), FDA (US), HSA (Singapore), Health Canada (Canada), MFDS (Republic of Korea), MHLW/PMDA (Japan), NMPA (China), Swissmedic (Switzerland), and TFDA (Chinese Taipei).

sufficient prospect of direct benefit to justify the risks using adult data assumes that the observed clinical benefit is likely to be observed in children. These observations support the conclusion that using extrapolation in this setting should be a default strategy unless proven unwarranted (see also [12]). Any program that does not explore the use of extrapolation should justify why it is not being utilized.

By incorporating extrapolation, a pediatric drug development program can be streamlined, facilitating concurrent approval (i.e., with adults) in specific pediatric subpopulations (e.g., adolescents) to enable their timely access to these drugs. This approach will prevent or reduce off-label pediatric use of the drug [13]. Usually this streamlined development is done based on certain factors, including the mechanism of action of the drug, the indication being pursued and implications for pediatric cohorts, the current treatment landscape within which the drug is being developed (e.g., existing therapies or no existing therapies) to name a few. To help frame these considerations, there are three potential treatment landscapes (or “archetypes”) for an investigational drug. These include as follows:

- A. *First in class or first in indication in adults* In this archetype, there are no approved drugs in adults. However, there may be Phase 2 studies in adults establishing proof of direct benefit for the drugs in the class. There are no studies for the class of drugs in children. For example, anifrolumab for systemic lupus erythematosus.
- B. *Established class where adult trials have confirmed safety and efficacy achieving registration* In this archetype, there are approved drugs in the same class in adults. There are no approved drugs in the class for children. For example, ofatumumab in relapsing/remitting multiple sclerosis, glecaprevir/pibrentasvir for chronic HCV infection, or cinacalcet for secondary hyperparathyroidism (HPT) in patients with chronic kidney disease (CKD) receiving dialysis.
- C. *Established class where adult and pediatric trials have been conducted, achieving registration* In this archetype, there are approved drugs in the same class for adults and children. For example, everolimus for acute rejection in renal transplant.

Alternatively, classes of drugs where adequate and well-controlled studies including both adult and pediatric populations were successful also justify the framework for extrapolation. Identifying the applicable archetype for an investigational drug will shape what types of assessments are necessary to determine similarity between reference and target population and the knowledge gaps.

Similarity of Disease Manifestation and Progression

The assessment of disease similarity includes an evaluation of several factors, such as the epidemiology and natural history of the disease, its underlying etiology, pathophysiology, and tissue findings (histopathology); clinical presentation or manifestation of the disease (signs and symptoms); criteria for disease diagnosis, classification, onset, and disease severity; and comorbidities. Of note, age dichotomization (e.g., pediatric/adult) alone is an arbitrary characterization from a disease perspective and is often based on ethical, sociocultural, and operational (e.g., care location) considerations. Information on the factors above may evolve dynamically and correlate with the above archetypes, i.e., the more established the class becomes (e.g., archetype C), the more information on the similarity or dissimilarity of the pediatric and adult disease is available.

In some instances, portability of response measures, e.g., similar endpoints, may be used to characterize disease progressions providing supportive evidence of similarity. In infections, for example, the disease etiology and the clinical response endpoint definitions in adults and children are generally the same making it possible for many pivotal trials in infectious diseases to include children (e.g., TB [14, 15]). In asthma, on the other hand, while the same drugs are used to treat adults and children, the underlying disease has some differences; for example, presence of atopy is strongly associated with asthma in children where atopy is variably associated in adult phenotypes [16]. However, reversible airway obstruction on spirometry can be reliably measured both in older children (ages 7–18 years) and adults suggesting that differences in disease etiology do not preclude extrapolation when the same endpoint can be applied. The decision to include adolescents (and perhaps younger children) in pivotal clinical trials with adults builds on the same logic as extrapolation (i.e., the disease and response to treatment are similar and assessments of safety in children can be measured).

Within these archetypes, understanding disease progression in adults may help characterize the natural progression of disease in children through disease progression modeling (see Griggs [17] for muscular dystrophy, de Winter [18] for diabetes, or in the case of HCV infection in children below 3 years of age). Longitudinal data, often using continuous biomarkers and disease severity, can be used to model the disease dynamics over time. As therapeutic interventions may alter disease progression as measured, for example, by a pharmacodynamic effect, combining PK-PD models with disease progression models may help to understand the influence of drug

treatment on disease processes and may also help identify gaps in knowledge of the disease and response to treatment between use in adults and pediatric patients (see also [19]).

There currently is no universal answer to the question “When is it reasonable to assume similarity of disease and disease progression?” The answer depends in part on the indication, clinical consensus of meaningful difference, and the definition of the criteria for delineating when “similar is similar enough.” There are cases when the variability within the drug–disease interaction is wide but evidence from clinical experience over time, particularly in the case of Archetype C, suggests that the response of the drug may be similar. For example, FDA now accepts that, for opioids, non-steroidal anti-inflammatory drugs, acetaminophen, and local anesthetics, it is scientifically appropriate to extrapolate efficacy from adults to pediatric populations down to age 2–4 years [20, 21]. Importantly, there are other situations where clinical differences are observed that do not affect treatment response, e.g., irritable bowel disease [22], hypertension [23], or venous thrombosis [24]. In these cases, disease dissimilarity would not stop a clinician from treating a child with a compound demonstrated to be effective in adults. Hence, evidence of dissimilarity of disease progression may not preclude extrapolation. Additionally, disease dissimilarity does not mean that a drug has a dissimilar risk when used in children compared to adults. Nevertheless, understanding the differences in diseases may be helpful to appraise whether such differences will result in a substantively different treatment response when the same drug is used in children. Table 1, for example, shows three indications in different development archetypes, where there probably are some minor differences in disease progression, but similar drugs are used in adult and children. Finally, the drug developer should also keep in mind that where differences in disease progression are present, establishing the appropriateness of the reference efficacy data for use in an extrapolation approach is essential to inform the benefit–risk.

Similarity of Drug Response

Establishing similarity in response to treatment within a given disease requires an assessment of the mechanism of action of the drug or drug class, knowledge of dose–response, and a systematic assessment and synthesis of available clinical trial data and any other relevant evidence from clinical practice (e.g., from other pediatric age groups, related pediatric indications, and adult indications). Similarity of clinical response may also come from other indications (e.g., similar mechanistic target) being studied, or from other products used to treat the same indication. Table 2 shows examples of investigational drugs representative of each of the three archetypes. In each of these diseases, evidence

to support the extrapolation approach is assessed using the treatment response in adults and adolescents for the class in question and the treatment response for other classes. The investigational drug in Archetype B and C may be able to benefit from information from other drugs in the same class or other classes. For an investigational drug within a well-established class, relevant data are available from other in-class drugs to establish a reasonable expectation for similarity in response. For Archetype A, uncertainty may remain as to whether similarity in response is expected.

It is possible that data may suggest a dissimilar response, a risk for dissimilar response, or even a lack of efficacy (see also [25]). If the difference identified can be explained in relation to a specific biomarker, then it may be helpful to describe the degree to which this biomarker explains differences in efficacy, safety, and benefit–risk. Possible approaches include quantitative synthesis or meta-analysis of existing treatment data, disease response models, PK–PD dose–response models, or systems pharmacology approaches. Whatever method is used, developers will also want to consider if the differences could result in a clinically meaningful loss of efficacy or an unfavorable benefit–risk.

If efficacy for drugs in the class have not been established in either adults or children (e.g., Archetype A), there may be uncertainty whether efficacy in adults will predict efficacy in children. In this situation, a Phase 2 or Phase 3 study demonstrating efficacy in adults provides evidence of clinical benefit. However, the line of reasoning that efficacy can be translated to children has not been established definitively in these cases. Such a line of reasoning may be informed by other classes of drugs where both adult and pediatric development have been completed, but uncertainty may remain in the absence of data in the new class of drugs. When similarity of disease and response to treatment has been established in one class of drug for the same indication, this could support the conclusion that the drug target present in adults with that disease remains the same in the pediatric disease. For example, results from the belimumab Pluto study demonstrated that extrapolation is possible with a first-in-class pediatric approval, based on an extrapolation strategy building on general clinical manifestations and response (see [26]).

Where data are limited, e.g., Archetype A, it may be helpful to include non-clinical data and insights generated from modeling and simulations. If there is a correlation between exposures and clinical response in that same population or a pharmacodynamic endpoint correlates with a clinical endpoint, then models can show that at the given exposures in children a comparable response can be expected. Furthermore, organ maturation, translating to the maturation of metabolic processes, helps to inform the PK–PD characteristics of a drug within each age subgroup. In these cases, PK data from adult studies and from pediatric studies in other

Table 1 Examples of indications where treatments are similar in adults and children in three different development archetypes

	Type A: First in Class Indication: Lupus [2]	Type B: Established Class in Adults Indication: Relapsing–Remitting Multiple Sclerosis [1]	Type C: Established Class in Adults and Children Indication: Acute rejection in Renal Transplant [3]
Investigational Drug MOA	Type α/β receptor No drugs with the same MOA are approved for adults in this indication	B cell–depleting anti-CD20 Ocrelizumab, which targets CD20 marker on B lymphocytes, is approved for this indication in adults	mTOR Sirolimus + rapamycin, an mTOR inhibitor + macrolide, is approved for this indication in adults
Approved drugs	Immunosuppressants: azathioprine, cyclophosphamide, belimumab Antimalarials: Hydroxychloroquine Corticosteroids: Prednisolone	First-line immunomodulatory therapy: interferon beta-1a, interferon beta-1b, and glatiramer acetate Second-line immunomodulatory therapy: natalizumab, mitoxantrone, fingolimod, teriflumide, azathioprine, rituximab, dimethyl fumarate, daclizumab, alemtuzumab, and ocrelizumab	Calcineurin Inhibitors: Cyclosporine Tacrolimus Mycophenolic Acids: Mycophenolate Mofetil Antiproliferative: Azathioprine mTOR: Sirolimus Everolimus Corticosteroids: Prednisone Belatacept
Unapproved drugs in treatment guidelines	Immunosuppressants: methotrexate, mycophenolate mofetil Corticosteroids: Prednisone NSAIDs: aspirin, ibuprofen, naprosyn, or indomethacin No drugs with the same MOA are approved for children in this indication	Azathioprine Minocycline Mycophenolate Mofetil (MMF) Rituximab Simvastatin No drugs with the same MOA are approved for children in this indication	Calcineurin Inhibitors: Voclosporin
Children			Sirolimus + rapamycin, an mTOR inhibitor + macrolide, is approved for this indication in children aged 13 and older
Approved drugs	Immunosuppressants: azathioprine, cyclophosphamide, belimumab Antimalarials: Hydroxychloroquine Corticosteroids: Prednisolone	First-line immunomodulatory therapy: interferon beta-1a, interferon beta-1b, and glatiramer acetate (12 years of age and older) Second-line immunomodulatory therapy: fingolimod	Corticosteroids: Prednisone (Extrapolated; the efficacy and safety of prednisone in the pediatric population are based on the well-established course of effect of corticosteroids which is similar in pediatric and adult populations) Calcineurin inhibitors: Cyclosporine (13 and older) Tacrolimus Mycophenolic Acids: Mycophenolate Mofetil (3 months and older) *Treatment regimen is generally a combination of three of the above drugs Antiproliferative: Azathioprine
Unapproved drugs in treatment guidelines	Immunosuppressants: methotrexate, mycophenolate mofetil Corticosteroids: Prednisone NSAIDs: aspirin, ibuprofen, naprosyn, or indomethacin		

See Ref. [35–37]

indications can be used to support the assumptions of the model. A discussion on the reliability of the model predictions also should be included.

Of note, there will be additional information (e.g., natural history or epidemiological data relevant to similarity or differences in disease, PK, PD, and clinical response) that will emerge during the development program. As such, the extrapolation plan should continuously be refined as new data emerge. Pediatric extrapolation is an iterative process.

Regardless of the archetype that applies to an investigational product, some degree of extrapolation of information will inevitably be included. For this reason, similarity of the drug response needs to be evaluated to support extrapolation, with the understanding that additional data may need to be generated to do so. To support this, clinical trials in the program need to be designed in a way that allows for validation of the similarity of the clinical response at a comparable exposure, i.e., leverage information when it is warranted and refrain from such leveraging when not justifiable. A simple way of doing this is to ensure the similarity in the design of the adult and pediatric trials. While this may not always be feasible, one can argue that a trial result in children showing consistent direction of treatment effect as in adults, despite some numerical differences, may be indicative of similarity of the disease.

Extrapolation and Finding Knowledge Gaps or Uncertainties

A properly designed extrapolation plan will not only detail the components to be evaluated to establish similarity of disease progression and drug response, but also identify the knowledge gaps and uncertainties that need to be addressed by additional data. The extrapolation plan would include the clinical investigation(s) needed to fill that knowledge gap and validate the initial assumption about extrapolation. The three components used to establish similarity are the same components where knowledge gaps may exist, i.e., (1) dose, (2) efficacy, and (3) safety and tolerability (see also [27]). Extrapolation of the safety and tolerability of a drug to the pediatric population may be challenging. The extrapolation of dose will be dependent on PK, PD, and dose–response data being generated. When scientifically and clinically necessary, such knowledge gaps may be addressed by conducting a dedicated safety and PK trial in the pediatric population.

For efficacy, critical factors in assessing knowledge gaps include how much efficacy information is available from the reference population, how much that information informs efficacy in the pediatric population, and how much data are still needed to support the extrapolation of efficacy. Information synthesized in the reference population is similar to

a meta-analytic estimate of the treatment effect along with its precision. The degree of similarity of the disease and drug response will determine the degree to which information from the adult population is applicable to the pediatric population. The more data are available for the drug class is, e.g., Archetype C, the more established this degree of similarity. If it has been established that the disease in the adult and pediatric population is not similar, there will be uncertainty in the efficacy of the drug beyond what is acceptable for extrapolation purposes. Hence, the information that can be borrowed from the reference population will generally be less than what is needed to conclude efficacy and will need to be supplemented by additional data. To fill this knowledge gap, the plan may be to conduct either PK/PD, dose–response, an uncontrolled clinical trial, or a randomized and controlled clinical trial. Note that all these trials provide information about efficacy but with different levels of information or trial rigor. The necessary rigor of the trial is determined by the amount of information already obtained, the benefit–risk balance, consideration of unmet need, and feasibility of a trial in that disease and age groups. In Archetype A, for example, if there is high unmet need, one may tolerate a higher probability of a false-positive conclusion (depending of course on the therapeutic index and risks of the investigational treatment). If so, all one may need is an uncontrolled PK/PD trial as opposed to a randomized clinical trial.

One example where the determination of unmet need can be an important consideration is the question of when to study a first-in-class agent where efficacy and safety have not yet been established clearly in adults (Archetype A). Extending enrollment of an existing adult trial to adolescents to accelerate labeling for the pediatric indication may deserve thoughtful consideration when evidence of clinical benefit has been established from adult Phase 2 trials. In indications where there is an unmet medical need and in particular for drugs with favorable benefit–risk profile, accelerating pediatric drug development could be achieved by the inclusion of adolescents in adult Phase 2 and/or 3 clinical trials. In addition, the lack of available alternative treatments in the context of disease severity may justify exposure to the risks of the investigational drug based on the prospect of potential clinical benefit and a favorable benefit–risk profile for trial participation (see 21 CFR 50.52). Alternatively, if there are safety concerns for the drug, a cautious approach may be prudent even in high unmet need settings. However, this must be weighed against the cost of delaying the investigation of the drug in children until further adult efficacy and safety data are available; the broader pediatric population may be exposed to off-label use following the approval of the adult indication.

For deferred development, as shown in Table 3, there are cases when development cannot commence until an

Table 2 Example of an investigational drug in each archetype and how development programs leverage information on response in adults and adolescents for the class within which an investigational drug belongs and the treatment response of other classes of drugs

	Type A: First in Class Indication: Lupus	Type B: Established Class in Adults Indication: Relapsing–Remitting Multiple Sclerosis	Type C: Established Class in Adults and Children Indication: Acute rejection in Renal Transplant
Investigational new Drug MOA Treatment in Adult Indication	Type α/β receptor No drugs with the same MOA are approved for adults in this indication	B cell–depleting anti-CD20 Ocrelizumab, which targets CD20 marker on B lymphocytes, is approved for this indication in adults	mTOR Sirolimus + rapamycin, an mTOR inhibitor + macrolide, is approved for this indication in adults
Treatment response for the investigational drug	Phase 2 response: At week 52, patients treated with anifrolumab achieved greater responses in SRI(4) (40.2% versus 62.6% [$P < 0.001$] and 53.8% [$P = 0.043$] with placebo [2])	RMS patients on ofatumumab had a reduction in annualized relapse rate (ARR) by 50.5% (0.11 vs. 0.22) and 58.5% (0.10 vs. 0.25) compared to teriflumomide (both studies $p < 0.001$) in ASCLEPIOS I and II studies, respectively [2]; Ofatumumab showed a relative risk reduction of 34.4% in 3-month confirmed disability progression (CDP) ($p = 0.002$) and 32.5% in 6-month CDP ($p = 0.012$) versus teriflumomide in pre-specified pooled analyses [1]	Everolimus: The primary efficacy endpoint of study A2309 was a composite consisting of the first occurrence of treated BPAR (local assessment), death, graft loss, or loss to follow-up measured at 12 months following kidney transplantation. Based on the ITT population, 25.3%, 21.9%, and 24.2% of the patients experienced efficacy failure within 12 months, in the everolimus 1.5 mg, 3.0 mg, and Myfortic groups, respectively [3]
Treatment response of another drug in the same class	No approved treatment in adults in this class	In Study 1 ocrelizumab phase 3 annualized relapse rate (ARR) 0.156 vs 0.292 interferon beta-1a. In Study 2 ARR is 0.155 ocrelizumab vs 0.290 interferon beta-1a. Proportion of patients that are relapse free is 83% ocrelizumab vs 71% for Study 1 and 82% ocrelizumab vs 72% interferon beta-1a in Study 2. Pooled risk reduction for disability progression is 40% ($p = 0.0001$) [4]	Sirolimus: The rate of efficacy failure at 6 months was lower in the two sirolimus groups (2 mg 18.7%, $p = 0.002$; 5 mg 16.8%, $p < 0.001$) than in the azathioprine group (32.3%). The frequency of biopsy-confirmed acute rejection episodes was also lower (2 mg 16.9%, $p = 0.002$; 5 mg 12.0%, $p < 0.001$; azathioprine 29.8%). At 12 months, survival was similar in all groups for grafts (97.2%, 96.0%, and 98.1%) and patients (94.7%, 92.7%, and 93.8%) The percentages of 1-year patient survival, graft survival, and biopsy-confirmed acute rejection rates were not significantly different between the sirolimus-treated patients (96.7%, 96.7%, and 6.4%, respectively) and the cyclosporine-treated patients (100%, 95.4%, and 16.6%, respectively) [5]

Table 2 (continued)

	Type A: First in Class Indication: Lupus	Type B: Established Class in Adults Indication: Relapsing–Remitting Multiple Sclerosis	Type C: Established Class in Adults and Children Indication: Acute rejection in Renal Transplant
Treatment response of a drug in another class	Belimumab SRI rates were observed to be significantly higher in the belimumab 1 and 10 mg/kg group than with placebo at the end of week 52 (51% and 58% vs. 44%) [6]	Fingolimod annualized relapse rate is 0.18 vs 0.40 in placebo; percentage of patients without relapse 70% fingolimod vs 46% on placebo; hazard ratio of disability progression is 0.70 (0.52, 0.96) Fingolimod annualized relapse rate 0.16 vs 0.33 in interferon 1ab; percentage of patients without relapse 83% fingolimod vs 70% on interferon 1ab; hazard ratio of disability progression 0.71 (0.42, 1.21) [7]	Tacrolimus: Efficacy failure, defined as biopsy-proven acute rejection (BPAR), graft loss, death, and/or loss to follow-up, at Month 12 in the PROGRAF group is 20.4% compared to CsA/MMF/CS (36.2%), CsA/MMF/CS/Daclizumab (31.6%), and Sirolimus/MMF/CS/Daclizumab (46.4%) [8]
Treatment in Adolescents Indication	No drugs with the same MOA are approved for children in this indication	No drugs with the same MOA are approved for children in this indication	Sirolimus + rapamycin, an mTOR inhibitor + macrolide, is approved for this indication in children aged 13 and older
Treatment response for the investigation drug and treatment response of another drug in the same class			Sirolimus: Efficacy failure at Month 12 in the intention-to-treat (ITT) population (n = 102) was numerically more frequent in subjects randomly assigned to receive the combination of sirolimus and a C Inh than in the subjects allocated to standard therapy (29/65, 44.6% versus 12/37, 32.4%, respectively). When comparing only subject 18 years old or younger (24/53, 45.3% versus 11/25, 44.0%, respectively) efficacy failure rates were similar [9] Initial work with sirolimus (single controlled study against best local care) showed non-superiority. 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;
Treatment response in other class	Belimumab at week 52, SRI rates were 52.8% for those in the belimumab 10 mg/kg group compared to 43.6% for those in the placebo group [10]	Fingolimod annualized relapse rate 0.122 vs 0.675 in interferon 1ab; percentage of patients without relapse 86% fingolimod vs 45.8% on interferon 1ab; hazard ratio of disability progression 0.71 (0.42, 1.21)	Tacrolimus: Use in pediatric kidney transplant patients is based on adequate and well-controlled studies of Astagraf XL in adult kidney transplant patients and supported by pharmacokinetic and safety data in pediatric transplant patients 4 years of age and older who are able to swallow capsules intact and Prograf (tacrolimus) capsules in adult and pediatric transplant patients

See Ref. [38–47]

Table 3 Similarity of Response and Potential for Simultaneous Development in Adults and Adolescents

	Efficacy and Safety of class established in adults only ^a	Efficacy and Safety of class established in children	Unique safety signal in adults for the drug	Simultaneous development ^b
Investigational drug belongs to Well-established Class	Yes	Yes	No	Yes
	Yes	No	No	Yes
	Yes	Yes	Yes	Possibly
	Yes	No	Yes	Defer
Investigational drug is aiming for First in class/First in indication	Yes	No	Yes	Defer
	Yes	No	No	Yes
	No	No	Yes	Defer

^aFor first in class this will be proof of direct benefit from Phase 2b adult study

^bFor deferred development or possible simultaneous development, an additional check on whether there is positive benefit–risk may need to be evaluated

acceptable benefit–risk profile is established in the adult indication which could mean after approval of the adult indication. This decision may depend on whether the safety profile will be elucidated in further adult trials or only after approval as part of post-marketing safety surveillance. If the adult development proceeds despite such a safety signal, it may be appropriate for the adolescent program to proceed as well.

Extrapolation Plan and Use of Innovative Clinical Trial Designs

Innovative clinical trial designs are integral to implementation of extrapolation plans. For example, if the rationale for extrapolation has not yet been established (e.g., Archetype A) and is dependent on the benefit–risk evaluation for the pediatric population, the clinical development for an investigational drug in adults and children may be done either in parallel or staggered as seen in Table 3. If the effect size observed in adult proof of concept trials is substantial, i.e., undermining the assumption of equipoise in a placebo-controlled pediatric trial, it may be difficult to enroll the trial with a placebo arm. In this scenario an exposure–response study and/or an uncontrolled trial could be used to avoid the need for a placebo. Open label trials may also be used depending on the effect size observed in the adult trial(s). The acceptable type 1 error or tolerable uncertainty may also be higher. Furthermore, many of these designs may be supplemented using external control data if similarity in populations can be guaranteed (see for example [28, 29]).

In established classes, i.e., Archetypes B and C, simultaneous development of the drug in adults and children may be the norm unless safety concerns specific to the pediatric population or subpopulations have been identified. In these archetypes, the ability to leverage data through Bayesian statistics or other meta-analytic tools needs to be explored to

speed development and ensure feasibility of development, for example, when competing drugs are in the market (see [30–32]). Alternative strategies utilizing multi-sponsor master protocols can leverage a common control and/or gain efficiency through leveraging of data from similar compounds. There are additional advantages of a platform trial that may not include a common control. It may be possible to leverage exposure–response studies with or without another uncontrolled trial, particularly in the case where the use of extrapolation has been clearly established.

Discussion

It is a clear ethical obligation to ensure that children are not enrolled in unnecessary clinical studies. This obligation compels us to explore the use of extrapolation, when scientifically and clinically appropriate, to the fullest extent possible when designing pediatric clinical development programs. Extrapolation is an inductive inference that extends known experience and/or data (“reference”) into an area not known or previously experienced (“target”) to arrive at a (credible, but inherently uncertain or probabilistic) knowledge of the unknown area. Efficacy is a causal inference that is extrapolated from the “reference” (e.g., adult) population to the “target” (e.g., pediatric) population based on a descriptive inference of sufficient similarity between the two populations. Similarity of the progression of the disease and the drug response between these two populations are the two key “descriptive” attributes on which extrapolating efficacy was proposed a priori by FDA in 1992 and in the ICH E11(R1) guideline and the EMA reflection paper [9–33]. Extrapolation should be a default strategy for the extension of adult labeling, where appropriate, to the pediatric population.

Knowledge of the similarity of disease and similarity of response will be on a continuum of uncertainty; decisions about extrapolation built on a dichotomy of these concepts

may not be appropriate. The archetypes presented here are to facilitate a nuanced discussion of extrapolation but can also be used as a guide to structured extrapolation implementation. Despite uncertainty, pediatric drug development programs should initially assume that some form of extrapolation is possible and the program plan revised as evidence for or against the use of extrapolation emerges. In the current regulatory environment, detailed agreements are required early in investigational drug development (i.e., upon completion of adult human PK characterization (EU), end of phase 2 (US)) which does not provide enough flexibility for timely or efficient modification of pediatric plans using adult data prior to finalization of the agreement. In view of this issue, implementation of extrapolation requires greater regulatory flexibility than is currently afforded in order to accommodate the iterative nature of product development.

Whether a drug is effective or offers a prospect of clinical benefit involves a causal inference. From a policy perspective, these judgments differ in the degree of tolerable uncertainty (i.e., the acceptable risk of being wrong). Efficacy (from an FDA regulatory perspective) requires either two clinical trials, one clinical trial with overwhelming evidence or one clinical trial with additional supporting evidence (21 CFR 514.4) [34]. Establishing pediatric efficacy may not require this same level of certainty where adult efficacy has been demonstrated. The tolerable uncertainty concerning the decision to approve a new drug (i.e., efficacy) is framed by the risk of being wrong across an entire population. The tolerable uncertainty concerning the decision to expose a child to the risks of a new drug in a research protocol (i.e., prospect of direct benefit) is framed by the risks and potential benefits to that individual child. Arguably, the lack of safe and effective treatment options for a smaller pediatric population with severe life-threatening disease argues for a level of tolerable uncertainty closer to that of individual clinical decisions. When a drug is known to be effective in adults, we should be willing to incorporate this information into our pediatric program planning, if there is reasonable evidence of similarity of disease progression and drug response between the adult and pediatric populations.

There is one goal in pediatric drug development: to provide safe and effective medicines that are appropriately labeled for use in children. In view of this, pediatric drug development should keep pace with the speed of innovation in developing medicines. It is in our children's and society's best interest to ensure that evidence is generated thoughtfully and efficiently to inform the appropriate use of therapies across pediatric populations. The use of innovative methodologies such as pediatric extrapolation will help us deliver on this promise. Analytic tools that can be used to "borrow" adult data, along with adaptive study designs to manage uncertainty, are helpful methods for enhancing efficiency in extrapolation. Both drug developers and regulatory

agencies should assess the role of innovative approaches in every pediatric plan they receive or issue. Incentives are needed to encourage more efficient and innovative programs to robustly inform the appropriate use of therapies across pediatric populations. Examples of successful plans, innovative approaches, and fruitful regulatory interactions can be persuasive steps to encourage further innovation that will serve our children well.

References

1. US FDA. *Written Requests Issued*. <https://www.fda.gov/drugs/development-resources/written-requests-issued>. Accessed 25 Nov 2020.
2. US FDA. *New Pediatric Labeling Information Database*. <https://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase>. Accessed 25 Nov 2020.
3. Mulugeta YL, Zajicek A, Barrett J, Sachs HC, McCune S, Sinha V, Yao L. Development of drug therapies for newborns and children: the scientific and regulatory imperatives. *Pediatr Clin*. 2017;64(6):1185–96.
4. EMA. Medicines https://www.ema.europa.eu/en/medicines/ema_group_types/ema_pip/field_ema_pip_decision_type%253Aname_field/P%3A%20decision%20agreeing%20on%20a%20investigation%20plan%2C%20with%20or%20without%20partial%20waiver%28s%29%20and%20or%20deferral%28s%29 Accessed 30 Sept 2020.
5. Tomasi P. Paediatric clinical trials: need for capacity building. *J Clin Stud*. 2013;5(3):10–6.
6. Roth-Cline M, Nelson R. The ethical principle of scientific necessity in pediatric research. *Am J Bioeth*. 2014;14(12):14–5.
7. Nelson RM. The use of pediatric extrapolation to avoid unnecessary pediatric clinical trials. *Am J Bioeth*. 2020;20(4):114–6.
8. International Conference on Harmonization. *Addendum to ICH E11: Clinical Investigation of Medicinal Products in the Pediatric Population*. https://database.ich.org/sites/default/files/E11_R1_Addendum.pdf. Accessed 25 Nov 2020.
9. EMA. European Medicines Agency (EMA). *Reflection Paper on the Use of Extrapolation in the Development of Medicines for Paediatrics*; 2018. https://www.ema.europa.eu/en/documents/scientific-guideline/adopted-reflection-paper-use-extrapolation-development-medicines-paediatrics-revision-1_en.pdf. Accessed 25 Nov 2020.
10. Roth-Cline M, Gerson J, Bright P, Lee CS, Nelson RM. Ethical considerations in conducting pediatric research. In: *Pediatric Clinical Pharmacology*. Berlin: Springer; 2011. p. 219–244
11. US Food and Drug Administration. *Draft Guidance for Industry: General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products*. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425885.pdf>. Accessed 1 Jan 2020.
12. Ollivier C, Mulugeta YL, Ruggieri L, Saint-Raymond A, Yao L. Paediatric extrapolation: a necessary paradigm shift. *Br J Clin Pharmacol*. 2019 Apr;85(4):675–9.
13. Committee on Drugs, & MMM. Off-label use of drugs in children. *Pediatrics*. 2014;133(3):563–7.
14. Infectious Disease Society of America. *Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children*. <https://www.idsociety.org/practice-guideline/diagnosis-of-tb-in-adults-and-children/>. Accessed 25 Nov 2020.

15. Kaye KS, Petty LA, Shorr AF, Zilberberg MD. Current epidemiology, etiology, and burden of acute skin infections in the United States. *Clin Infect Dis*. 2019;68(Supplement_3):S193–9.
16. Dharmage SC, Perret J, Custovic A. Epidemiology of asthma in children and adults. *Front Pediatr*. 2019;7:246.
17. Griggs RC, Moxley RT, Mendell JR, Fenichel GM, Brooke MH, Pestronk A, et al. Prednisone in duchenne dystrophy: a randomized, controlled trial defining the time course and dose response. *Arch Neurol*. 1991;48:383–8.
18. De Winter W, DeJongh J, Post T, Ploeger B, Urquhart R, Moules I, et al. A mechanism-based disease progression model for comparison of long-term effects of pioglitazone, metformin and gliclazide on disease processes underlying type 2 diabetes mellitus. *J Pharmacokinetic Pharmacodyn*. 2006;33(3):313–43.
19. Conklin LS, Hoffman EP, van den Anker J. Developmental pharmacodynamics and modeling in pediatric drug development. *J Clin Pharmacol*. 2019;59(Suppl 1):S87–94.
20. Dunne J, Rodriguez WJ, Murphy MD, Beasley BN, Burckart GJ, Filie JD, et al. Extrapolation of adult data and other data in pediatric drug-development programs. *Pediatrics*. 2011;128(5):e1242–9.
21. Sun H, Temeck JW, Chambers W, Perkins G, Bonnel R, Murphy D. Extrapolation of efficacy in pediatric drug development and evidence-based medicine: progress and lessons learned. *Ther Innov Regul Sci*. 2017;2017:1–7.
22. Hyams J, Damaraju L, Blank M, Johanns J, Guzzo C, Winter HS, et al. Induction and maintenance therapy with infliximab for children with moderate to severe ulcerative colitis. *Clin Gastroenterol Hepatol*. 2012;10(4):391–9.
23. Vorhies EE, Ivy DD. Drug treatment of pulmonary hypertension in children. *Pediatr Drugs*. 2014;16(1):43–65.
24. Male C, Lensing AW, Palumbo JS, Kumar R, Nurmeev I, Hege K, et al. Rivaroxaban compared with standard anticoagulants for the treatment of acute venous thromboembolism in children: a randomised, controlled, phase 3 trial. *Lancet Haematol*. 2020;7(1):e18–27.
25. Zhang Y, Wang Y, Khurana M, Sachs HC, Zhu H, Burckart GJ, Alexander J, Yao LP, Wang J. Exposure-response assessment in pediatric drug development studies submitted to the US Food and Drug Administration. *Clin Pharmacol Ther*. 2020 Jul;108(1):90–8.
26. Ruperto N, Abud-Mendoza C, Viola DO, Calvo I, Levy DM, Gallegos JC, et al. FRI0181 the PLUTO study: intravenous belimumab in children with systemic lupus erythematosus. 2019.
27. Ollivier C, Thomson A, Manolis E, Blake K, Karlsson KE, Knibbe CAJ, Pons G, Hemmings R. Commentary on the EMA reflection paper on the use of extrapolation in the development of medicines for paediatrics. *Br J Clin Pharmacol*. 2019;85(4):659–68 ((**complementary to EMA reflection on extrapolation**)).
28. NDA25513 Cross Discipline Teal Lead Review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125513Orig1s000CrossR.pdf. Accessed 25 Nov 2020.
29. NDA25141 Medical Review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/125141s0000_Myozyne_MedR.pdf. Accessed 25 Nov 2020.
30. Gamalo-Siebers M, Hampson L, Kordy K, Weber S, Nelson RM, Portman R. Incorporating innovative techniques toward extrapolation and efficient pediatric drug development. *Ther Innov Regul Sci*. 2019;53(5):567–78.
31. Schoenfeld DA, Zheng H, Finkelstein DM. Bayesian design using adult data to augment pediatric trials. *Clin Trials*. 2009;6(4):297–304.
32. Gamalo-Siebers M, Savic J, Basu C, Zhao X, Gopalakrishnan M, Gao A, et al. Statistical modeling for Bayesian extrapolation of adult clinical trial information in pediatric drug evaluation. *Pharm Stat*. 2017;16(4):232–49.
33. Weber K, Hemmings R, Koch A. How to use prior knowledge and still give new data a chance? *Pharm Stat*. 2018;17(4):329–41.
34. US Food and Drug Administration. Code of Federal Regulations Title 21; 2017.
35. T1-1. Fanouriakis A, Kostopoulou M, Alunno A, Aringer M, Bajema I, Boletis JN, et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis*. 2019;78(6):736–45.
36. T1-2. Level B, Level A. *Practice Guideline: Disease-modifying Therapies for Adults with Multiple Sclerosis*. 2018. https://cdn-links.lww.com/permalink/wnl/a/wnl_2018_04_19_raegrant_neurology2017835181r1_sdc3.pdf. Accessed 25 Nov 2020.
37. T1-3. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transpl*. 2009;9:S1–155.
38. T2-1. Furie R, Khamashta M, Merrill JT, et al. Anifrolumab, an anti-interferon- α receptor monoclonal antibody, in moderate-to-severe systemic lupus erythematosus. *Arthr Rheum*. 2017;69:376–86.
39. T2-2. Ofatumumab USPI. 2009. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125326s060lbl.pdf. Accessed 25 Nov 2020.
40. T2-3. FDA Statistical Review. 2020. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/021560s000statr.pdf. Accessed 25 Nov 2020.
41. T2-4. Ocrelizumab USPI. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761053lbl.pdf. Accessed 25 Nov 2020.
42. T2-5. Sirolimus USPI. 1999. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021110s058lbl.pdf. Accessed 25 Nov 2020.
43. T2-6. Navarra SV, Guzmán RM, Gallacher AE, Hall S, Levy RA, Jimenez RE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. *The Lancet* 2011;377(9767):721–31.
44. T2-7. Fingolimod USPI. 2010. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/022527s26lbl.pdf. Accessed 25 Nov 2020.
45. T2-8. Tacrolimus USPI. 2009. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/050708s027,050709s021lbl.pdf. Accessed 25 Nov 2020.
46. T2-9. FDA Medical Officer Executive Summary. <https://wayback.archive-it.org/7993/20170112052802/http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM163206.pdf>. Accessed 25 Nov 2020.
47. T2-10. Ruperto N, Abud-Mendoza C, Viola DO, Calvo I, Levy DM, Gallegos JC, et al. FRI0181 the PLUTO study: intravenous belimumab in children with systemic lupus erythematosus. 2019.

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