Transl Clin Pharmacol. 2021 Jun;29(2):73-77
https://doi.org/10.12793/tcp.2021.29.e11
pISSN 2289-0882·eISSN 2383-5427

Translational and Clinical Pharmacology TCP

Commentary

Adequacy of safety data for regulatory approval of pediatric indication through extrapolation algorithm

Min Soo Park [1,2,3,*]

[1]Department of Clinical Pharmacology, Severance Hospital, Yonsei University College of Medicine, Seoul 03722, Korea
[2]Department of Pediatrics, Yonsei University College of Medicine, Seoul 03722, Korea
[3]Department of Pharmaceutical Medicine and Regulatory Science, Graduate Program, Yonsei University College of Medicine, Seoul 03722, Korea

Received: May 30, 2021
Revised: Jun 14, 2021
Accepted: Jun 15, 2021

***Correspondence to**
Min Soo Park
Department of Clinical Pharmacology, Severance Hospital, and Department of Pediatrics, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.
E-mail: minspark@yuhs.ac

ORCID iDs
Min Soo Park
https://orcid.org/0000-0002-4395-9938

Reviewer
This article was invited and reviewd by peer experts who are not TCP editors.

Conflict of Interest
- Authors: Nothing to declare
- Reviewers: Nothing to declare
- Editors: Nothing to declare

This commentary deals with the realistic difficulty arising from the haziness as to what safety data should mean, especially for regulatory authorities to feel confident that approval of new drug indications for pediatric populations could be endowed, and when you were guided that complete extrapolation of adult efficacy data would be possible with an additional pharmacokinetic (PK) study, but safety data cannot be extrapolated.

A randomized controlled trial (RCT) is considered as the gold standard for generating evidence for establishing clinical efficacy and safety of a new treatment or drug, especially in the regulatory process for the new drug approval or market authorization. In general, clinical efficacy can be shown through statistical proof based on the study design that encompasses adequate sample size with power. Depending on the estimated effect size over the control and variability, confirmatory trials can be of sample sizes of a few hundred to several thousand over several years. These trials are carried out with the primary focus on efficacy.

Safety data are collected along the way throughout all phases of drug development. Information on the safety is accumulated to detect any meaningful incidences that might influence the regulatory decision for the so-called “establishing safety”. The nature of drug exposure varies from single escalating doses in a handful of healthy volunteers as in first-in-human studies and human pharmacology studies to multiple doses given to a limited number of patient populations for a relatively short period of time as in dose-finding efficacy studies to elicit pharmacological responses or to detect differences in surrogate biomarker expressions. Perhaps the most relevant exposure in clinical trials that adverse effects might possibly be detected, as close to the nature of exposure in the real clinical settings, would come from the therapeutic confirmatory trials involving several thousand patients with underlying disease states, given a wide range of doses, exposed for a relatively long period, accompanied by various concomitant illnesses, and others. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E1 guideline recommends about 1,500 subjects to be exposed over 6 to 12 months for drugs intended for the long-term treatment (chronic or repeated intermittent use for longer than 6 months) of non-life-threatening diseases, but at the same time alluding to the possibility of accepting smaller numbers with supplementation through post-marketing surveillance (PMS) requirements [1].

But even in these trials, the sample size is based on the efficacy measures not on the safety aspect. Even if the actual number of patients targeted in a trial would far exceed the calculated minimum, statistically valid sample size for the confirmatory phase 3 trials, probably even the largest number of subjects would rarely exceed a few thousand. Data acquired through 2 adequate and well-controlled clinical investigations involving around a thousand patients would most likely be enough to establish effectiveness [2]. But for safety, the number or the duration of exposure would never be satisfactory, considering the fact that the safety evaluation during clinical drug development is not expected to characterize rare adverse events (AEs), for example, those occurring in less than 1 in 1,000 patients [1].

As per pediatric use information to be labeled, it is preferable to base it on adequate and well-controlled studies conducted in the pediatric population. However, given the difficulties associated with the testing of drugs in the pediatric population, it is not always required to conduct RCT in the pediatric population. The pediatric extrapolation strategy, as laid out in 1994 by Food and Drug Administration (FDA) in 21 Code of Federal Regulations Part 201 [3] and described in the "US FDA Guidance for Industry: General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products" (2014) [4], serves as a means to minimize unnecessary drug exposure in pediatric populations as well as to save time and resources for conducting clinical efficacy trials in the pediatric subpopulations that might be replaced with the extrapolated findings from adult data, whenever possible. Dunne et al. [5] reported 82.5% of the drug products utilized extrapolation of efficacy from adult data (complete for 14.5% and partial for 68%) for pediatric indications submitted to US FDA between 1998 and 2008. The similarity of disease progression and of response to intervention between children and adults makes it possible to fully extrapolate efficacy data from adequate and well-controlled studies in adults to the target pediatric population, if appropriate doses can be defined through additional PK studies in children. In other words, full-scale therapeutic confirmatory studies can be omitted. But the premise for this schema is that efficacy related data can be extrapolated whereas safety data from adult studies cannot; additional safety trials at the identified dose(s) are recommended, if not suggested. This is common for all 3 options laid out in the guidance.

Unfortunately, there is no clear instruction as to how much and what kind of safety data should be generated and submitted in this situation. When it is said that "safety data cannot be extrapolated", it implies that the drug exposures in adults in the clinical trials could elicit different safety responses in children, and one should be cautious in defining the adequacy of safety data. But at the same time, we should caution against demanding unrealistic and full-scale safety-only trials based on pure hypothetical uncertainty of how children differ from adults in terms of safety. The aforementioned US FDA Guidance suggests that the extent of the required pediatric safety studies may take into consideration prior experience with similar drugs in pediatric populations, the seriousness of the AEs in adults or in pediatric populations, when this information is available, and the feasibility of conducting studies in pediatric patients. European Medicines Agency recommends that safety information from a source population may be used to predict short-term risks related to the mode of action of the drug and related to dose. Nevertheless, the generation of new safety data is needed in the target population to address unexpected (age-specific) risks [6]. In ICH E11, it is emphasized that the most relevant safety data for pediatric studies ordinarily come from adult human exposure as well as animal studies including juvenile animal studies [7,8].

https://doi.org/10.12793/tcp.2021.29.e11

If there is a concern raised by animal data, should we go on to prove it through safety trials in children? If there is no concern shown up to adult therapeutic confirmatory trials, should we require a safety trial in children at all? If so, how large and how long should it be? How large it may be, can it differentiate between the true occurrence of AEs and the baseline noise or natural occurrence in real-life settings? Is it right to conduct trials in children to see what kinds of AEs develop and how severe?

For drug approval in general, safety data are collected from a series of studies from phase 1 through therapeutic confirmatory studies in phase 3, enough for the approval for adult uses. The statement that adult data cannot be extrapolated for safety does not mean that the safety information in adults is useless in children. With logical reasoning and thorough scrutiny, a lot can be learned from the adult data even for safety issues. Do preclinical/nonclinical study results, esp. data from juvenile animals, support the reasonable doubts? If anything is different between adults and children in terms of occurrence of adverse effects, it would most likely be the effects on the growth and development. Although there are adverse effects not related to the dose, such as idiosyncratic or immunologic reactions that are rare and unpredictable, most of the adverse effects are dose- or concentration-dependent and are extensions of pharmacological effects. They are often predictable and follow the same principle of PKs both in adults and children. If scientific reasoning and clinical data suggest reasonable doubts or signals of adverse effects in children, it is important to collect and analyze enough safety data to be assured before the drug can be approved and widely used in clinics. A review of the drugs that gained approval in pediatric indications through Best Pharmaceuticals for Children Act and Pediatric Research Equity Act in the US shows that safety information in children for most drugs comprise safety data collected in the PK or pharmacodynamic human pharmacology studies or in the course of early phase 2 as a part of therapeutic exploratory studies if a confirmatory efficacy study is not needed. Most safety data come from pediatric exposure in the magnitude of a few dozens to hundreds.

In cases where a complete extrapolation is possible with only an additional PK study in children, those children enrolled in the PK study would be the only children who would be exposed to the drug for the purpose of extrapolation of adult efficacy data. The safety data obtained through the PK study in a few dozen pediatric patients may not be enough for approval of a new pediatric indication. Additional safety data would be desperately needed, but at the same time it is extremely difficult to define how much and what kind of safety data should be generated and submitted. Demanding a formal clinical trial for safety data for approval of pediatric indication may be out of phase with the initial intention of utilizing extrapolation schema. This dilemma forces us to resort to other means that might not be conventional. Perhaps a conditional approval with a post-approval safety data submission in the form of PMS or others may be an option. Utilization of safety reports on the "off-label uses" may help. Safety issues reported for other drugs in the same class used in clinical settings may be of importance. It appears that the amount of exposure would be of less importance than the relevance of safety issues in children. Any signals or reasonable doubts of serious long-term adverse effects on growth and development warrant a more definitive safety evidence prior to approval.

Safety data can only come from the experience of exposure to the pediatric population since it is not to be extrapolated directly from adult data. Perhaps a deeper understanding of pharmacological mechanisms of toxicity in pediatric age groups may help justify the extrapolation of adult safety data to some extent. Exposure of children to drugs not approved

https://doi.org/10.12793/tcp.2021.29.e11

for use either in the form of a clinical trial or as an off-label use in medical care settings is a risk-taking experience. In most cases, drugs that undergo pediatric development are by nature most likely subject to off-label uses long before final approval of pediatric indications. The safety information regarding such uses, if it can be obtained in the form of evaluable databases, would be an invaluable asset to be used in the process of pediatric development. Utilization of any of the existing data such as safety issues associated with 'off-label uses' either in the form of registries, off-label use reports, or publication in academic journals would be of great help.

There is no set rule to clearly delineate how much and what kinds of safety data should be generated and submitted. However, the adequacy of the amount of safety data should always be balanced on the risk-benefit scale. Drugs for rare diseases are approved based on rather discrete criteria. Pediatric indications are somewhat similar to rare diseases in some cases but at a lesser degree. Based on the medical necessity or urgency, approval of pediatric indications can be fast-tracked with less assurance of safety, most likely as good as it gets in reality. Conditional approvals with post-approval safety data generation could be an option. When we start out to develop pediatric indications through extrapolation schema, it would be advisable to investigate the AE reports associated with 'off-label uses' or set out to collect safety data from those uses in the first place. It would be much more reasonable and realistic than conducting a separate safety trial involving hundreds of children, the size of which would not be enough to detect rather common AEs, with an inevitable delay of approval. With regard to informing safety of drugs used in a pediatric population, the use of real-world data is an option. At the 2016 American College of Clinical Pharmacology Annual Meeting Symposium stakeholders for pediatric drug development convened and discussed the use of big data and real-world data to inform trial design and for the feasibility of substitution for efficacy and safety data obtained in clinical trials [9]. A clinical data warehouse from the electronic medical record in neonatal intensive care units in North America, composed of real-world data on multiple aspects of care including safety profiles, has been used to examine drug use, feasibility for clinical trials, and drug safety. PK models have been used to simulate drug exposures, which then were linked to safety outcomes [10,11].

After all, we eventually arrive at a conclusion that it would be extremely difficult to generate a substantial volume of clinical trial-driven safety data adequate for regulatory approval of pediatric indications. Having agreed on the current status, we need to look into the feasibility of utilizing resources such as real-world data and off-label use registries rather than clinging onto the traditional RCTs for that purpose. It would require a major paradigm shift in the thinking of the regulatory bodies based on innovative regulatory science.

REFERENCES

1. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. The extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life-threatening conditions E1 [Internet]. https://database.ich.org/sites/default/files/E1_Guideline.pdf. Accessed March 3, 2021.
2. Food and Drug Administration (US). Guidance for industry: demonstrating substantial evidence of effectiveness for human drug and biological products: draft guidance. Silver Spring (MD): FDA; 2019.
3. Department of Health and Human Services (US). 21 CFR Part 201. 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 (US). Guidance for industry: general clinical pharmacology considerations for pediatric studies for drugs and biological products. Silver Spring (MD): FDA; 2014.
5. 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:e1242-e1249.
PUBMED | CROSSREF
6. European Medicines Agency. Reflection paper on the use of extrapolation in the development of medicines for paediatrics. Amsterdam: EMA; 2018.
7. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Clinical investigation of medicinal products in the pediatric population E11 (R1) [Internet]. https://database.ich.org/sites/default/files/E11_R1_Addendum.pdf. Accessed March 3, 2021.
8. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Final concept paper. Pediatric extrapolation [Internet]. https://database.ich.org/sites/default/files/E11A_EWG_Concept_Paper.pdf. Accessed March 3, 2021.
9. Mulugeta LY, Yao L, Mould D, Jacobs B, Florian J, Smith B, et al. Leveraging big data in pediatric development programs: proceedings from the 2016 American College of Clinical Pharmacology Annual Meeting Symposium. Clin Pharmacol Ther 2018;104:81-87.
PUBMED | CROSSREF
10. Hornik CP, Benjamin DK JrSmith PB, Pencina MJ, Tremoulet AH, Capparelli EV, et al. Electronic health records and pharmacokinetic modeling to assess the relationship between ampicillin exposure and seizure risk in neonates. J Pediatr 2016;178:125-129.e1.
PUBMED | CROSSREF
11. Salerno S, Hornik CP, Cohen-Wolkowiez M, Smith PB, Ku LC, Kelly MS, et al. Use of population pharmacokinetics and electronic health records to assess piperacillin-tazobactam safety in infants. Pediatr Infect Dis J 2017;36:855-859.
PUBMED | CROSSREF