Guideline on Using Real-World Study to Support the Development and Evaluation of Pediatric Drugs

(Final)

English Translation by: Rui Chen, Pingyan Chen, Lindsey Wang

Disclaimer: The English is for information only and not an official translation and under any dispute the Chinese will prevail.

Center for Drug Evaluation, NMPA

August 2020

Table of Contents

Guideline on Using Real-World Study to Support the Development and Evaluation of Pediatric Drugs

1. Introduction

In general, drug development requires scientifically designed and well-controlled studies in the target treatment population to evaluate the efficacy and safety of the drug. The development of pediatric drugs adheres to the same principle and requires appropriate study data to support the rational use in the targeted age group of pediatric patients. However, compared with adult studies, in practice, clinical trials involving pediatric subjects would face more difficulties and challenges when adhering to traditional trial designs and study methods. Pediatric clinical trials are often difficult to conduct or progress slowly, which results in insufficient evidence to evaluate the efficacy and safety of drugs used in children, subsequently affecting the accessibility and standardization of drug use in pediatric clinical practice. Therefore, determining how to use new study methods to obtain the evidence of rational use of drugs in children is an issue that has been deeply communicated and discussed among drug regulatory agencies, pharmaceutical industry and academia worldwide. As one of the new study methods, Real World Study/Research (RWS/RWR) has been gradually used in supporting the development and review of pediatric drugs, providing support for the registration of new drugs, extension of pediatric indications, and optimization of pediatric dosing regimens .

On August 18, 2017, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) issued the addendum to ICH E11: Clinical Investigation of Medicinal Products in the Pediatric Population E11 (R1). The addendum introduced the application of RWS to pediatric drug development. On January 7, 2020, NMPA issued the "Guidance on Using Real-World Evidence to

Support Drug Development and Regulatory Evaluation (Final)", which clearly pointed out that the use of real-world evidence is a strategy for pediatric drug development.

In view of the above, considering China's practical needs for pediatric drug development and the timely communication of new study methods to drug regulatory authorities, in conjunction with the implementation of the ICH E11 (R1) guideline in China, this guideline has been formulated to assist drug development and clinical investigators in better understanding the application of the "Guidance on Using Real-World Evidence to Supporting Drug Development and Regulatory Evaluation (Final)" in pediatric drug development.

This guideline focuses on introducing common situations and concerns in RWS that support pediatric drug development in China at present. For basic concepts, principles, study design, and statistical methods related to RWS, please refer to the "Guidance on Using Real-World Evidence to Supporting Drug Development and Regulatory Evaluation (Final)." This guideline applies to all types of pediatric drugs, including chemical drugs, traditional Chinese medicines, and biological products.

This guideline only represents the current views and understanding of drug regulatory authorities and is intended for reference by drug development and clinical investigators, not mandatory or legally binding. The content of this guideline will be continuously improved with the progress of scientific research and the accumulation of practical experience. When applying this guideline, please also refer to the ICH E11 (R1) guideline, the "Guidance on Using Real-World Evidence to Supporting Drug Development and Regulatory Evaluation (Final)," and other relevant domestic or foreign technical guidelines.

2. The Difference and Rational Integration of RWS and Traditional RCT

Randomized Controlled Trial (RCT) is a type of clinical trial that uses randomization and appropriate control design. It is widely used in drug clinical trials as the "gold standard" for evaluating drug efficacy.

RWS collects real-world data related to patients in real-world environments and obtains clinical evidence of the value and potential benefits or risks of medical products through analysis, which is known as real-world evidence.

It is reasonable and feasible to conduct RWS or traditional RCT in children. The choice of either or both, and the timing of their respective applications, depend on a deep understanding and overall control of specific disease characteristics, target population characteristics, drug properties, trial conditions, and etc. The principle should be to ensure that the evaluation requirements for drug efficacy and safety are met, to conserve children's study resources as much as possible, and to balance data quality with study efficiency. Based on current knowledge, reasonable integration of RWS and traditional RCT will be an appropriate strategy for the development of pediatric drugs, where the two are mutually complementary and supportive.

For example, although RCT that strictly control experimental conditions have higher study efficiency, in certain therapeutic areas, RCT involving children are facing practical problems such as difficulty in recruitment and high dropout rate, resulting in decreased study efficiency or inability to provide sufficient study information. Adopting a properly designed RWS or incorporating RWS elements into RCT, is an optional way to improve study efficiency or expand study evidence. It should be noted that RWS cannot completely replace RCT in the absence of a reasonable basis.

3. Common Situation of RWS Used in Pediatric Drug Development in China

RWS is not just simple data collection but obtaining reliable data in real medical environments to answer specific drug-related questions. Currently, in the development of pediatric drug in China, real-world studies are more commonly applied in the following situations:

3.1 Post-market clinical safety and efficacy studies of drugs with new active ingredients approved for pediatric use in China.

Obtaining clinical safety and efficacy information after a drug is approved for marketing is an important part of drug life-cycle management and a routine study task for new active ingredient drugs. For drugs with new active ingredients approved for pediatric use, especially for drugs used in long-term treatment of chronic diseases, it is an important regulatory requirement to conduct post-market clinical safety and efficacy studies.

The purpose of post-marketing clinical safety and efficacy studies is mainly to observe the long-term efficacy of drugs and their impact on the growth and development of children, as well as to collect other rare or long-term adverse reactions. Other questions related to the efficacy or safety noted in pre-marketing clinical studies will also be addressed in post-marketing studies.

An appropriate RWS design should be selected based on the pharmacological characteristics of the drug, patient characteristics, and clinical usage is essential. Pragmatic Clinical Trials (PCTs) can be used, particularly when obtaining evidence related to efficacy, observing a specific age group or specific organs, or collecting data on specific adverse reactions. In the design of a control group for a PCT, if

randomization is not performed, attention should be paid to the matching of baseline characteristics, disease progression, and dosing regimens between groups. For the collection of rare or long-term adverse reactions, observational studies can also be considered due to the extended observation period.

3.2 Drugs that have been approved for use in adults and children overseas, and in adults in China, can be applied for use in Chinese children through the strategy of data extrapolation.

There are mainly two situations involved as below: for imported originators (or locally produced originators), which have been approved for use in both adults and children overseas and in adults in China, an application is made to extend the indication to pediatric use in China; for domestic generic drugs (or imported generic drugs), which have been approved for the same adult indications as the originators, an application is made to add the use of the originators for Chinese children approved overseas.

Extrapolation conclusion should be obtained according to the method recommended in the "Technical Guideline for Extrapolation of Adult Data to Pediatric Populations". For cases that meet the criteria for exempting clinical trials in children, it is usually required to conduct post-marketing RWS . This is to validate the rationality of pediatric doses in China based on the extrapolation, collect safety data on drug use, and provide a basis for possible dose optimization for Chinese children, particularly for indications covering low age children or other special patient populations, or special issues related to formulation, dosage form, administration, medical behavior, etc. Different RWS designs can be considered based on the degree of uncertainty of the extrapolation conclusion.

3.3 Off-label use data support the expansion of indications for pediatric use of commonly used clinical drugs marketed in China.

Currently, there is a limited number of pediatric drugs in China, and most pediatric diseases are treated using drugs indicated for both adults and children. However, the expansion of drug indications from adults to children is often lagging, leading to some clinically common drugs that have been marketed in China for many years being used off-label in pediatric patients.

If there is a large amount of relatively standardized clinical prescription data that meets the requirements of data quality and statistical analysis, or if there are drugs with conditions to collect prospective clinical prescription data, the RWS method can be applied to support the expansion of indications to pediatric use.

On the premise of ensuring that the collected data meets the quality and statistical analysis requirements of real-world data, retrospective studies can be considered. At the beginning of the study, the target population is determined, and based on historical data (generated before the start of the study), the efficacy and safety of the drug under evaluation are analyzed. At the same time, a comparative analysis of the efficacy and safety of the drug under evaluation and clinical standard treatment (if there is no clinical standard treatment, then a recognized clinical common treatment method is selected) is provided as much as possible. If the existing clinical prescription data cannot meet the data quality and statistical analysis requirements of RWS, prospective RWS needs to be considered.

3.4 Rare disease.

Real-world data can serve as historical or external controls for single-arm studies in the development of drugs for rare diseases or pediatric critical illnesses, premature infants,

or neonatal diseases that lack effective treatment options due to scientific, ethical, or implementation reasons, where traditional RCT may not be feasible.

3.5 Other situations.

RWS can also be applied to expand (such as extending to younger children) or refine the target population, optimize dosages or frequency of administration (such as refining doses based on weight or body surface area), improve or modify drug administration or processes (such as administering with different types of juice or jam), pharmacoeconomic or quality of life research, etc. These situations typically involve drugs that have already been approved for pediatric use in China, for which the therapeutic effects of drugs should be further improved and information on rational medication in children be expanded according to the actual pediatric clinical needs in China and based on the known evidence of drug safety and efficacy study. It is recommended to choose an appropriate RWS design according to the study purpose.

4. Cases of RWS Used in Pediatric Drugs Development for Children in China

4.1 Case 1

Ibuprofen injection is a non-steroidal anti-inflammatory and analgesic drug, in the form of an injection for intravenous infusion, and was developed as a generic version of the original drug that was marketed overseas. This drug was first approved for use in Chinese adults. After being marketed for a period, it is applied for adding the approved pediatric indication of originator by waiver application of clinical studies in Chinese pediatrics. After being marketed for a period, it is applied for adding the approved pediatric indication of originator by waiver application of clinical trials in Chinese pediatrics. According to the "Technical Guidelines for Extrapolation of Adult Drug

Data for Use in Clinical Trials and Related Information in Pediatric Populations", the drug provided relatively complete evidence and was ultimately approved for use in children through the exemption of clinical studies before being marketed.

This product is a generic drug, and the dosage for Chinese pediatric population was estimated through pediatric extrapolation modeling, based on the data for pediatric clinical studies from the original drug. Although clear data source, reliable quality and scientific analysis are presented, and evidence supporting pediatric use in China is provided, it is still necessary to verify the rationality of the doses for Chinese pediatric patients after the marketing due to the lack of direct study data concerning Chinese pediatric patients. After consulting with pediatric clinical experts, it was found that in clinical practice in China, the main population receiving intravenous anti-inflammatory and analgesic drugs are emergency low-age pediatric patients who are unable to cooperate with oral administration, and this population is both the most important beneficiary and the highest-risk group for this drug. Therefore, the product approval requires the RWS on low-age children after the market launch, to complete the validation of dosage rationality in the age group that receives the greatest benefit and has the highest risk (low-age children). The study results will be used to strengthen the extrapolation conclusions and evaluate whether it is necessary to adjust the current product insert.

4.2 Case 2

The inhaled fluticasone propionate aerosol is a glucocorticoid developed by GlaxoSmithKline and has been imported into China for over ten years for the treatment of asthma in pediatric and adult patients. The product applied for an extension of the approved age range in China, from "≥4 years old" to "≥1 year old " based on clinical evidence from foreign clinical studies in children ≥1 year old. According to the

"Technical Guideline for Extrapolation of Adult Drug Data for Use in Pediatric Clinical Trials and Related Information Usage", the product has a clear pharmacological mechanism, reliable foreign clinical study evidence in children, and a domestic clinical application basis in pediatric population. The clinical efficacy in pediatric population is clear and after benefit-risk evaluation, the waiver for conducting clinical studies in Chinese pediatric patients was approved, and the product was approved to extend its approved age range in China to children ≥1 year old. At the same time, the approval requires post-marketing safety studies of drug use in Chinese pediatric patients with asthma aged 1-4 years old. Which means, under the precondition of no concerns about efficacy and overall safety, further evidence of safety for lower age groups in China was required.

As required in the approval letter, the product has completed a RWS aimed at monitoring the safety of the drug used in 1-4 year old patients. Clinical data of pediatric patients was collected and analyzed at designated sites. The drug was administered strictly according to the recommended dosage and administration methods for 1-4 year old patients as stated in the product package insert. In addition to designing general safety observational variables, targeted safety observational variables were also designed for the drug's risk information in the product package insert. The study results were used to supplement safety evidence and evaluate whether it is necessary to adjust the current product package insert.

5. Problems That Need Attention

As a form of clinical studies, RWS also need to follow the general principles of clinical studies, as well as the special considerations of pediatric clinical study. With good design, high-quality data, and reliable statistical methods, RWS can support drug registration and regulatory decisions.

Compared with adults, basic research work and clinical studies on children are relatively limited. When applying RWS, special attention should be paid to the knowledge and information of developmental physiology, pathophysiology, pharmacology, and therapeutics related to children.

The feasibility of using RWS in pediatric drug development faces challenges, including whether pediatric clinical information resources and network construction can meet the requirements of data collection and analysis, and whether study sites are qualified for information collection. Such issues may affect the quality of evidence and thus should be considered in pediatric drug development plans.

The use of RWS to support pediatric drug development is still under gradual construction and improvement. Drug developers and clinical researchers are encouraged to maintain effective communication with drug regulatory agencies regarding the application of RWS in pediatric drug development, in order to establish a broader consensus.

6. References

[1] Corrigan-Curay Jacqueline,Sacks Leonard,Woodcock Janet. Real-World Evidence and Real-World Data for Evaluating Drug Safety and Effectiveness.[J]. JAMA,2018,320(9).

[2] Crisafulli Salvatore,Sultana Janet,Ingrasciotta Ylenia,Addis Antonio,Cananzi Pasquale,Cavagna Lorenzo,Conter Valentino,D'Angelo Gabriella,Ferrajolo Carmen,Mantovani Lorenzo,Pastorello Maurizio,Scondotto Salvatore,Trifirò Gianluca. Role of Healthcare Databases and Registries for Surveillance of Orphan Drugs in the Real-world Setting: the Italian Case Study.[J]. Expert Opinion on

Drug Safety,2019,18(6).

[3] EMA. Draft Scientific Guidance on Post-authorization Efficacy Studies[EB/OL].(2015-11-30)https://www.ema.europa.eu/en/news/supporting-better-use-medicines.

[4] FDA. Framework For FDA's Real-world Evidence Program[EB/OL]. https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RealWorldEvidence/UCM627769.pdf.

[5] FDA. Use of Real World Evidence to Support Regulatory Decision Making for Medical Devices. [S]. 2017.

[6] Geva Alon,Abman Steven H,Manzi Shannon F,Ivy Dunbar D,Mullen Mary P,Griffin John,Lin Chen,Savova Guergana K,Mandl Kenneth D. Adverse drug event rates in pediatric pulmonary hypertension: a comparison of real-world data sources.[J]. Journal of the American Medical Informatics Association : JAMIA,2020,27(2).

[7] Lasky Tamar,Carleton Bruce,Horton Daniel B,Kelly Lauren E,Bennett Dimitri,Czaja Angela S,Gifkins Dina,Osokogu Osemeke U,McMahon Ann W. Real-World Evidence to Assess Medication Safety or Effectiveness in Children: Systematic Review.[J]. Drugs - real world outcomes,2020.

[8] NMPA. Technical Guideline for Extrapolation of Adult Drug Data for Use in Clinical Trials and Related Information in Pediatric Populations (In Chinese: 成人用药数据外推至儿科人群的技术指导原则), 2017.05

[9] NMPA. Guidance on Using Real-World Evidence to Supporting Drug Development and Regulatory Evaluation (Final) (In Chinese:真实世界证据支持

药物研发与审评的指导原则(试行)), 2020.01

[10] Lulu Jia, Yunrui Yu, Yiwei Liu, et al. Establishing the pediatric clinical medicine comprehensive evaluation system: exploration of the method and path [J]. Journal of International Pharmaceutical Research, 2016, 43(04):585-590.

[11] Yuan Shi, Yanru Chen, Long Chen. Application of real world study in neonatal medicine [J]. Chinese Journal of Contemporary Pediatrics, 2018, 20(03):169-173.