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Regulatory considerations for paediatric drug evaluation in China

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ABSTRACT

The regulatory guidelines for the research and development of paediatric drugs are still evolving in China. The formulation of the guidelines started from learning and borrowing existing experience, and gradually changed to the exploration and improvement of local guidelines, which was not only in line with international standards but also had breakthroughs, innovations and Chinese characteristics. In this paper, the current setting of paediatric drug research and development in China and corresponding technical guidelines have been introduced from regulatory perspectives, and the accessibility of further improvement in regulatory strategies has also been discussed.

WHAT IS ALREADY KNOWN ON THIS TOPIC?

⇒ The regulatory guidelines for the research and development of paediatric drugs are still evolving in China. The China's drug regulatory agency has established several guidelines using existing standards as the reference.

WHAT THIS STUDY ADDS?

⇒ This study introduced the current setting of paediatric drug research and development in China and corresponding technical guidelines from regulatory perspectives. In addition, this study also discussed the accessibility of further improvement in regulatory strategies.

In China, based on the data of China's National Maternal and Child Health Surveillance System, the top five causes of death among children under 5 years old in 2017 are preterm birth or low birth weight, pneumonia, birth asphyxia, congenital heart disease and accidental asphyxia, accounting for 55.7% of all deaths.[1] In terms of malignant tumours, which are also a major cause of death among children, the top five tumours among the discharged patients with tumours accounted for 57.21% of leukaemia, 16.21% of unknown and other tumours, 8.15% of lymphoma, 5.63% of brain tumour and 3.31% of bone tumour based on the data of the National Center for Pediatric Cancer Surveillance.[2] However, there is a huge shortage of paediatric drugs in China.

In the past decade, China's drug regulatory agency has established guidelines for the research and development (R&D) and regulation of paediatric drugs using existing standards as the reference. Four regulatory documents have been issued, including Guidelines 2014, 2016, 2017 and 2020 (table 1).[3–6] As can be seen from the content of these technical guidelines, regulatory considerations for clinical studies on paediatric drugs in China are slowly changing.

The guidelines released in 2014 and 2016 were largely based on ICH E11 and did not consider regional drug R&D. The 2017 guidelines referred to the framework of the *General Clinical Pharmacy Considerations for Paediatric Studies for Drugs and Biological Products* established by the Food and Drug Administration (FDA),[7] and provided suggestions for adapting existing clinical research evidence from overseas adults and children to support the simplification or waiver of clinical studies on Chinese children. The most recent guidelines issued in 2020 are completely based on the paediatric drug R&D in China, and are the world's first regulatory guidelines that specified the application of real-world studies in paediatric drug R&D.

In May 2020, China officially began to implement the ICH E11 supplementary document *Clinical Investigation of Medical Products in the Paediatric Population E11 (R1)*; meanwhile, China's drug regulatory agency has been working on local guidelines for clinical studies on paediatric drugs in China. The aim is to refine the technical requirements related to the key steps or challenges of these clinical studies within the framework of ICH E11(R1) to ensure that clinical studies meet international standards, and also address specific issues related to local implementation that are not covered in ICH E11(R1). Thus, China's drug regulatory policies are still in the development stage.

Table 1 Four regulatory documents issued in China from 2014 to 2020

	Guidelines	Key points
Guideline 2014	Guideline on Pharmacokinetic Studies in Paediatric Population	Pharmacokinetic characteristics of paediatric population Pharmacokinetic study design and methodology Ethical considerations
Guideline 2016	Guideline on Clinical Trials in the Paediatric Population	Data and safety monitoring Age stratification of subjects Time point of starting drug clinical trials in paediatric population Design of drug clinical trials in paediatric population Selection of paediatric dosage forms Clinical trials of paediatric rare disease Ethical considerations
Guideline 2017	Guideline on Extrapolation from Adults to Paediatric Patients	Concept of extrapolation Process of extrapolation Modelling and simulation Basic principles and requirements
Guideline 2020	Guideline on the Use of Real-World Research to Support Development and Regulatory Evaluation for Paediatric Drugs	Differences and reasonable integration between real-world research and traditional randomised controlled clinical trials Common situations in which real-world research is used in children's drug development in China Cases

In this paper, the current setting of paediatric drug R&D in China and corresponding technical guidelines have been introduced from regulatory perspectives, and the accessibility of further improvement in regulatory strategies has also been discussed.

USING REAL-WORLD DATA TO TURN INTO EVIDENCE TO SUPPORT EXTENSION IN DRUG INDICATION FOR PAEDIATRICS

In the preceding decades, once a new drug is approved for marketing based on the data of adult patients, it is then used off-label in children with the same indication. Several drugs have been approved for paediatric patients in other countries but not in China, and they are used off-label domestically. It is extremely important and urgent to regulate off-label drug use in children in order to ensure the efficacy and safety of drugs.[8] Greater international collaboration and expert consensus in recent years have updated the clinical usage of paediatric drugs. For drugs that have not been approved for children in China but have been approved for adults and children abroad, the paediatric dosage basis is often derived from overseas-approved medication information, and refers to clinical guidelines or expert consensus. Dose optimisation is generally carried out according to the response of Chinese children to drugs in the real-world clinical practice, and the expert consensus is updated accordingly.

For the off-label drugs, once the dosage regimen is evidence based and reflects the current clinical needs, the regulatory agencies should aim to approve the use of the aforementioned off-label drugs by collaborating with academics and drug developers. In the *Guideline on the Use of Real-World Research to Support Development and Regulatory Evaluation for Paediatric Drugs*, it suggests that the real-world research can be used to support the extension of indications to children if a large amount of standardised clinical prescription data that meet the requirements for data quality and statistical analysis are available, or can be obtained through prospective collection. In the guideline, the specific uses of real-world data are as follows: (1) real-world data can be approved for post-marketing clinical safety and efficacy of new active ingredient medicines for Chinese children; (2) for drugs approved for use in adults and children overseas and for adults in China, the data extrapolation strategy can be used to apply for use in Chinese children; (3) for commonly used clinical drugs marketed in China, off-label drug data can be used to support the extension of indications to children; (4) for the rare disease drugs, real-world data can be used as historical or external controls for single-arm studies; (5) others, real-world data can also be used for dosage optimisation of drugs, etc.

INTEGRATION STRATEGIES FOR BRIDGING AND EXTRAPOLATION SUPPORTED BY THE ICH E5, E11(R1) AND E11A GUIDELINES

Multiregional clinical trials are an effective way of improving the efficiency of drug R&D, especially for children. China rarely participates in international multiregional drug trials involving children[9] due to a lack of agreement with the pharmacological companies, as well as the domestic drug regulatory policies that limit enrolment of children. Therefore, several drugs that have been tested in international multiregional clinical trials on paediatric subjects cannot be approved for use in China due to a lack of data on Chinese children. In case a drug has been approved internationally for use in both adults and children, the approval of adult application in China will not be affected in the absence of research data on Chinese children. This may however increase off-label use of that drug among children. Therefore, it is imperative that the China's drug regulatory agency should encourage pharmacological companies to extrapolate the international clinical data through modelling and simulation and statistical analysis to infer the reasonable dosage for Chinese children, on the basis of proven racial sensitivity in existing clinical studies.

The integration of ICH E5, E11(R1) and E11A guidelines not only considers the potential impact of racial

differences on clinical safety and efficacy but also encourages maximum utilisation of existing data of domestic and overseas adult studies and overseas children studies, realises the cross-racial extrapolation of evidence of clinical safety and efficacy, and reduces unnecessary studies in children. Although the purpose and methods may differ, the integration strategy of bridging and extrapolation has the same core point as the paediatric extrapolation introduced in ICH E11(R1) and E11A, which is to reduce unnecessary clinical studies in children. Of course, this strategy should not be construed as 'simplifying' or 'lowering requirements'. This strategy is a double-edged sword. On the positive side, it saves resources and expedites the accessibility of paediatric drugs in China. On the negative side, if improperly used, it may expose children to unexpected medication risks. Therefore, technical guideline of *Guideline on the Use of Real-World Research to Support Development and Regulatory Evaluation for Paediatric Drugs* has been issued that emphasises evaluation of the reliability of existing data, prediction of results using statistical methods and clear evaluation requirements for approved drugs, including determining what post-marketing clinical studies are required based on the uncertainty in the predicted results, so as to consolidate the benefit–risk assessment for paediatric applications.

DIFFERENTIATED REGISTRATION REQUIREMENTS FOR GENERIC DRUG R&D IN PAEDIATRIC PATIENTS

In the Chinese market, it is very common that the original drug is not imported but the generic drug is already on the market. Generic drugs account for a significant proportion in China[10] since the regulatory requirements enable these drugs to enter the market after completing the efficacy confirmatory clinical trials for Chinese patients. However, the clinical trials for generic drugs are limited to adult subjects regardless of whether the indications of the original drug include paediatric patients. Furthermore, the generic pharmaceutical companies only apply for adult indications. Even when the pharmaceutical companies simultaneously apply for approval for both adult and paediatric use, they do not provide the paediatric information believing that adult data are sufficient to support approval for paediatric indications. Although many drugs are approved for use in both children and adults, there are differences in indications (eg, diseases), dosage, frequency and mode of administration, which require clinical validation in children. Therefore, in the absence of reasonable evidence, it is not advisable to omit the investigation plan for paediatric patients or completely rely on that of adult patients.

At present, the China's drug regulatory agency attaches considerable importance to the R&D of generic drugs for children in order to expand the category of paediatric drugs in China. First, the drug regulatory agencies stipulate that in case of significant differences in clinical diagnosis, clinical symptoms, outcomes or dosage, frequency and mode of administration between adult and paediatric patients, independent confirmatory clinical trials involving Chinese paediatric patients are recommended to be conducted to provide direct evidence for paediatric applications. If there are multiple indications for children, it is recommended selecting indications with wide dose range, large age span, high-risk sensitivity and extensive clinical benefits. Second, if there is sufficient clinical evidence for the original drug in paediatric patients, and drugs with similar mechanisms or with different dosage forms of the same active ingredient have been approved for use in Chinese children, no additional studies are needed for paediatric patients once the confirmatory clinical trials have been successfully completed for adult patients (post-marketing studies may be required). Finally, the requirement for studies in children should be determined according to the urgency of actual clinical needs in China, the characteristics of indications and the patients, and the pharmacological mechanism of the drugs.

EVALUATION OF CHILD-SPECIFIC DRUGS BASED ON CLINICAL NEEDS AND APPLICATIONS

Child-specific drugs refer to drugs with no instructions for adults, but only for children in the drug label, including clear indications, usage and dosage, appropriate specifications and dosage forms, and safety information for children. Compared with the common drugs for adults and children, child-specific drugs have the advantages of improving the acceptance and comfort of paediatric patients, and reducing the risks of inaccurate measurement as well as drug waste. In recent years, more and more pharmaceutical companies are importing or simulating drug specifications or dosage forms specifically for the paediatric population. Since these drugs are usually derived from existing mediation for both adults and children, their registration requirements are often different from the innovative, improved or generic drugs. It is necessary to fully consider the domestic clinical needs and the basis for the paediatric application of existing drugs to determine the possibility of paediatric clinical trial waiver.

For example, for drugs with clear clinical needs and long-term paediatric use, such as the routinely used hospital preparations, the main purpose of evaluation should be to control the pharmaceutical quality standards and clarify the clinical dosage regimen. Then, the drugs can be considered for paediatric clinical trial waiver and approval for marketing to achieve standardisation of drug quality and meet clinical needs. For child-specific drugs that derive from the approved common drugs in China, and whose dosage regimen is calculated by appropriate measurement method for children, the regulatory agencies can consider the paediatric clinical trial waiver and approval for marketing on the basis of a reasonable and feasible dosage regimen, in order to improve the convenience of clinical medication and reduce the additional risks caused by inappropriate measurement

methods. For paediatric critical care drugs that lack effective treatment methods, the clinical evidence from studies of the original drug in children, especially in children of the same ethnicity in other countries or regions, should be fully evaluated to determine the benefit–risk to Chinese children. If the benefit–risk analysis is positively supported, approval marketing with waiver of paediatric clinical trial can be considered to meet the urgent needs for paediatric drugs.

STRENGTHEN COMMUNICATION AND TECHNICAL GUIDANCE IN THE R&D STAGE OF INNOVATIVE PAEDIATRIC DRUGS

Although paediatric patients account for almost 20% of all patients in China, less than 2% of the drugs circulating in the market are approved for use in children.[11] To overcome the relatively slow research on paediatric drugs, the FDA and European Medicines Agency promulgated the *Best Pharmaceuticals for Children Act* (BPCA), the *Paediatric Research Equality Act* (PREA) policies[12 13] and *Regulation (EC) No 1901/2006*,[14] respectively, which require pharmaceutical companies to submit the clinical investigation plan for paediatric indications at the development stage. In the absence of special reason like paediatric waiver or paediatric deferral, which refers to that the requirement for paediatric assessments can be waived or the submission of the paediatric assessments can be deferred, paediatric drug investigation must be carried out. Once the drug is approved, it can be generally granted an additional 6 months of market exclusivity for the full drug programme. Table 2 shows the comparison of legislation in the European Union (EU), USA and China on drug R&D. The innovative drug R&D is still in development in China, and the mandatory requirements for paediatric indications have not yet been formulated. However, the necessity of putting forward paediatric drug investigation plans has been recognised. The *Drug Administration Law* implemented on 1 December 2019 clearly states that the state shall take effective measures to encourage and prioritise the development of new varieties, dosage formulations and specifications of paediatric drugs in line with the physiological characteristics of children. The regulatory agencies are currently formulating the guiding principles, strengthening communication and technical guidance, and ensuring high-quality resources and technical support for clinical trials on paediatric drugs.

Table 2 The comparison of legislation in the EU, USA and China on drug research and development

	EU	USA	China
Legislation	Paediatric Regulation (EC) No 1901/2006	Best Pharmaceuticals for Children Act (BPCA); Paediatric Research Equality Act (PREA)	Regulations for the Implementation of the Drug Administration Law of the People's Republic of China (Draft for Comments)
Instrument	PIP	BPCA: WR; PREA: PSP	Investigation plan
Rewards and incentives	1*: 6-month SPC extension 2†: 2 additional years of market exclusivity 3‡:10 years of data protection	6-month exclusivity	Up to 12-month market exclusivity

*Unauthorised medicinal products and authorised medicinal products covered by an SPC or eligible for an SPC.
†Orphan-designated medicinal products.
‡Paediatric-use marketing authorisation.
EU, European Union; PIP, paediatric investigation plan; PSP, paediatric study plan; SPC, supplementary protection certificate; WR, written request.

DISCUSSION

Paediatric drug R&D in China has been long hindered by the widespread off-label drug use caused by delayed extension of paediatric indications, lacking simultaneous international multiregional drug trials, low motivation in applying for paediatric indications from the original drug and generic drug enterprises, and the absence of paediatric drug investigation plans for innovative drugs. Since the regulatory strategies of other countries or regions cannot fully comply with local challenges, after nearly 10 years of practice, the China's drug regulatory agency has formulated a set of technical guidelines and evaluation strategies with Chinese characteristics for domestic R&D.

In the USA and the EU, the BPCA, PREA and Regulation (EC) No 1901/2006 have significantly increased the accessibility of paediatric drugs, indicating the impact of national policies in promoting paediatric drug development. The State Council of China issued '*The Outline on the Development of Chinese Children (2011–2020)*'[15] in 2011, which for the first time shed light on the national drug shortage for children. In addition, the National Health Commission regularly published the *List of Priority Drugs for Paediatric Population*,[16–18] which provides an incentive for further paediatric drug development. The *List of Priority Drugs for Paediatric Population* is a green channel to speed up approval of paediatric drugs, and can guide enterprises to organise production reasonably, promote the R&D of appropriate varieties, dosage forms and specifications for children so as to better meet the needs of paediatric clinical drug use. To effectively implement these policies, it is necessary to promote reforms in drug regulatory practices in addition to formulating new technical guidelines, such as setting up data and marketing protection periods, encouraging the development of

drugs applicable for children and incorporating paediatric indications into the routine R&D outlines for drugs.

The recent advances in our knowledge of paediatric physiology, pathology and pharmacology are expected to promote new research methods in the field of paediatric drug research.[19] For example, in order to extrapolate the dose–exposure–response relationship in children through modelling and simulation, it is crucial to understand the pathogenesis of the disease, the growth and development characteristics of children, changes in metabolic enzyme functions, organ maturation, etc. Furthermore, a greater push to basic research will indirectly promote the quality and efficiency of clinical studies on paediatric drugs.

Active participation in international exchanges is another effective way to improve regulatory quality. Chinese regulators are actively strengthening exchanges with academia globally after joining the ICH. The published and implemented ICH E11(R1) guidelines and the ICH E11A guidelines under development in China are important international platforms for sharing experience on R&D and scientific regulation of paediatric drugs. China has the largest population of children in the world, and the government has been committed to promote paediatric drug development and ensure accessibility to paediatric drugs through active drug policy reforms and technical support.

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REFERENCES

1 Report on the development of maternal and child health in China (2019), 2019. Available: http://www.nhc.gov.cn/fys/s7901/201905/bbd8e2134a7e47958c5c9ef032e1dfa2.shtml [Accessed September 2022].
2 Annual report of national childhood cancer surveillance 2020, 2020. Available: https://www.pcscn.org.cn/download [Accessed September 2022].
3 National medical products administration. Guideline on pharmacokinetic studies in paediatric population, 2014(in Chinese). Available: https://www.nmpa.gov.cn/xxgk/fgwj/gzwj/gzwjyp/20140711112001393.html [Accessed September 2022].
4 National medical products administration. Guideline on clinical trials in the paediatric population, 2016(in Chinese). Available: https://www.nmpa.gov.cn/xxgk/ggtg/qtggtg/20160307164401912.html [Accessed September 2022].
5 National medical products administration. Guideline on extrapolation from adults to paediatric patients, 2017(in Chinese). Available: https://www.nmpa.gov.cn/yaopin/ypggtg/ypqtgg/20170518163201802.html [Accessed September 2022].
6 National Medical Products Administration. Guideline on the use of real-world research to support development and regulatory evaluation for paediatric drugs, 2020(in Chinese). Available: https://www.nmpa.gov.cn/xxgk/ggtg/qtggtg/20200901104448101.html [Accessed September 2022].
7 U.S. Food and Drug Administration. General clinical pharmacology considerations for paediatric studies for drugs and biological products, 2014. Available: https://www.fda.gov/media/90358/download [Accessed September 2022].
8 Schrier L, Hadjipanayis A, Stiris T, *et al*. Off-Label use of medicines in neonates, infants, children, and adolescents: a joint policy statement by the European Academy of paediatrics and the European Society for developmental perinatal and pediatric pharmacology. *Eur J Pediatr* 2020;179:839–47.
9 Hao G-X, Yuan X-X, Guo W, *et al*. Paediatric drugs trials in China. *BMJ Paediatr Open* 2020;4:e000618.
10 Liu QH, Liu F. Current situation, problems and policy suggestions of Chinese pharmaceutical industry development and industrial policy. *Review of Economic Research* 2014:39–67.
11 Zhang J, Qin D, Jin HT. Preliminary thoughts of the safety evaluation system of paediatric drug. *Chinese Journal of Pharmacovigilance* 2017;14:657–61.
12 U.S. Food and Drug Administration. Best pharmaceuticals for children act (BPCA), 2018. Available: https://www.fda.gov/drugs/development-resources/best-pharmaceuticals-children-act-bpca [Accessed September 2022].
13 U.S. Food and Drug Administration. Paediatric research equity act (PREA), 2019. Available: https://www.fda.gov/drugs/development-resources/pediatric-research-equity-act-prea [Accessed September 2022].
14 Official Journal of the European Union. Regulation (EC) NO 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending regulation (EEC) NO 1768/92, directive 2001/20/EC, directive 2001/83/EC and regulation (EC) NO 726/2004, 2006. Available: https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=celex:32006R1901 [Accessed September 2022].
15 National Working Committee on Children and Women under State Council. *The outline on the development of Chinese children (2011-2020)*. People's Publishing House, 2011.
16 National Health Commission of the People's Republic of China. Circular on the Issuance of the first list of priority drugs for paediatric population, 2016(in Chinese). Available: http://www.nhc.gov.cn/yaozs/s3581/201605/b0ea217312314c5098d905094f7e67ee.shtml [Accessed September 2022].
17 National Health Commission of the People's Republic of China. Circular on the Issuance of the second list of priority drugs for paediatric population, 2017(in Chinese). Available: http://www.nhc.gov.cn/yaozs/s3581/201705/b9874725a6a04e2ebbc8a969a4604609.shtml [Accessed September 2022].
18 National Health Commission of the People's Republic of China. Circular on the Issuance of the third list of priority drugs for paediatric population, 2019(in Chinese). Available: http://www.nhc.gov.cn/yaozs/s7656/201908/9a10b2382fe94d84817d9044d90dda15.shtml [Accessed September 2022].
19 Zhao W, Le Guellec C, Benjamin DK, *et al*. First dose in neonates: are juvenile mice, adults and in vitro-in silico data predictive of neonatal pharmacokinetics of fluconazole. *Clin Pharmacokinet* 2014;53:1005–18.