# A Comparison of Pediatric Drug Policy and Development in China and the United States

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## Abstract

**Objective** To find the shortcomings of children's drug research and development policy in China, and to put forward feasible suggestions for encouraging China's children's drug research and development by drawing the experience from the United States. **Methods** To compare the similarities and differences between the policies guiding the use of children's medicines issued by China and the United States. **Results and Conclusion** In recent years, the Chinese government has introduced a number of policies, but there is still a big gap in clinical trial design and drug review system compared with the policies of the United States. China should further improve the laws and regulations related to children's medication, promote the development of clinical trials, develop pricing programs, and expand international cooperation, so as to formulate more scientific and comprehensive guiding principles for the research and development of children's medication.

**Keywords:** children's medication; policies and regulations; implementation effectiveness

China has a large population of children, and according to the data of the seventh national census, the population of children aged 0−14 years in China was 250 million in 2020, accounting for 17.95% of the total population [1]. However, pediatric medication in China has such problems as the lack of drug varieties, the prevalence of over-specification of medication, and the lack of suitable dosage forms [2]. Many diseases that occur in adults also occur in children, who usually use the same drugs as adults. The effects of many medications can differ between adults and children. The instructions of many drugs currently on the market omit information of safe and effective use in all or some pediatric age groups. In fact, the instructions of many drugs widely used for pediatric patients clearly state that their safety and effectiveness in pediatric patients have not been determined. Based on the comparative policies on children's medications in the United States and China, and drawing lessons from international experiences, we explored appropriate policies and measures that are consistent with the actual development of China's pharmaceutical industry.

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## 1 The development and implementation effects of relevant policies on the research and development of medicines for children at home and abroad

### *1.1 Development of policies on R&D of medicines for children in the United States and effects of implementation*

#### *1.1.1 Development of policies related to pediatric drug use in the United States*

The United States is a pioneer in the research and development of children's drugs. In response to the shortage of children's drug varieties, the U.S. FDA took the lead in adopting legislation to fundamentally improve the accessibility and safety of children's drugs. As early as 1979, FDA introduced the subsection of "pediatric use" into the instruction manual of medicines. After the introduction of the "Food and Drug Administration Modernization Act (FDAMA)" in 1997, the government of the U.S. has gradually established a comprehensive regulatory system for children's medication and related measures. The U.S. policy on children's medication is shown in Table 1.

**Table 1 The evolution of major U.S. policies on children's medication**

| Time | Policy name | Main content |
|---|---|---|
| 1979 | Pediatric Information Requirements | The US FDA has issued regulations requiring pediatric information to be indicated on drug labels and packaging instructions |
| 1994 | Rules for Pediatric Instruction Manuals | Standardized language to be used in children's drug instructions |
| 1996 | Pediatric Drug Labeling | If a company establishes a pediatric medication plan, the FDA allows it to obtain pediatric drug labels |
| 1997 | Food and Drug Administration Modernization Act (FDAMA) | If the pharmaceutical company conducts testing and determines pediatric indications and doses, provide a 6-month extension of the drug patent |
| 2002 | Best Pharmaceuticals for Children Act (BPCA) | Establish a voluntary incentive plan, granting a 6-month "pediatric exclusivity period" if the study initiator conducts pediatric research in accordance with FDA written requirements |
| 2003 | Pediatric Research Equity Act (PREA) | If the submitted product application involves new active ingredients, indications, dosage forms, methods of administration, or routes of administration, unless FDA approves exemptions or postpones the application, pediatric evaluation information for the product must be included in the new drug application or biological product licensing application |
| 2007 | Food and Drug Administration Amendment Law | Reauthorize BPCA and PREA as legal basis for conducting pediatric research |
| 2012 | Food and Drug Administration Safety and Innovation Act (FDASIA) | Authorized BPCA and PREA to be permanently effective, and compiled a "Pediatric Research Plan (PSP)" template |
| 2017 | Food and Drug Reauthorization Act (FDARA) | Reauthorize FDA's various user payment plans, develop and approve rare disease and pediatric medications |

The policies introduced by the United States covered a wide range of aspects, including encouraging research and development and production, strengthening regulation, the popularization of science and publicity, and clinical research, and improving the system of guaranteeing the use of medicines for children. The implementation of these policies in the United States aimed at strengthening the regulation of research and development and clinical trials of medicines for children, ensuring the safety and effectiveness, and at the same time emphasizing the protection of children in clinical trials.

#### *1.1.2 Effectiveness of the implementation of policies related to children's medications in the United States*

The first was the increasing number of pediatric

clinical trials. Over the decades, the dominant policy incentive for children's medications in the United States has shifted from protecting children from pediatric research to protecting children through research. From 2002 to 2019, more than 8 000 children participated in 40 clinical trials at more than 200 pediatric research sites for generic drugs alone, and from 2007 to 2019, the total number of clinical trials related to Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA) was 1 105, involving 323 964 patients [3].

The second was the continuous improvement of pediatric medication information. From 1998 to 2020, a total of 854 medicines had improved pediatric medication information [4]. More than half of them were initiated by PREA, which indirectly reflected that mandatory sticks were more powerful than incentivized carrots in promoting the development of children's medications in the United States. The number of drugs with changes in pediatric drug information was also increasing year by year, and more drugs had improved pediatric drug information, which provided more supportive and reliable bases for diagnosis, treatment, and drug administration.

Besides, there was the expanding pediatric patient population for existing drugs. According to FDA's annual new drug approval report and drug database data, 18 (75%) of the 24 drugs approved by the FDA under the new or expanded use category were approved to cover a wider range of pediatric patients from 2017 to 2020. The percentage of new drugs approved in the U.S. in recent years that included pediatric indications has also fluctuated between 16% and 30% of the total number of new drug approvals. In 2020 alone, 17 (32%) of the 53 new drugs approved by the FDA contained a pediatric indication.

Finally, it was a model for global research on medicines for children. As a global pioneer and leader in the development of medicines for children, U.S. incentives have served as a model for the rest of the world. From the 1997 Roundtable to the first "EU Pediatric Medicines Act" in 2007 and its "Pediatric Investigation Plans (PIPs)", the European Medicines Agency has facilitated the rapid development of pediatric medicines in the EU. The Pharmaceutical and Medical Devices Agency of Japan and the Ministry of Health, Labor and Welfare of Japan have also formulated a number of strategies to promote the development of medicines for children, including the establishment of the Japanese Pediatric Clinical Trial Network, the Pediatric Medicines Working Group, incentives for additional premium reimbursement for medicines for children, and pharmacy consultative councils [5]. In addition, member countries of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use have adopted the ICH guideline E11, "Guidelines for Clinical Studies of Medicinal Products for Pediatric Use", to varying degrees.

### *1.2 Development of China's policies on R&D of pediatric drugs and implementation effects*

#### *1.2.1 Development of China's policies related to pediatric drug use*

Compared with the U.S, China's legislation on children's medication started late. However, with the government's gradual attention to children's medication and the efforts of relevant practitioners, some policies and guidelines have been launched. China's pediatric medication-related policy system is becoming better. The development of China's policies on pediatric medicine is shown in Table 2.

**Table 2 Development of major policies on pediatric medicine in China**

| Time | Policy name | Main content |
|---|---|---|
| 2003 | Good Clinical Practice | First inclusion of children in clinical trials |
| 2005 | Technical Guidelines for Clinical Pharmacokinetic Research of Chemical Drugs | Independent population pharmacokinetic research methods for pediatric populations |

(to be continued)

**Continued Table 2**

| Time | Policy name | Main content |
|---|---|---|
| 2013 | Opinions on Deepening Drug Review and Approval Reform to Further Encourage Innovation | Encourage the development of children's drugs, and encourage enterprises to actively develop child specific dosage forms and specifications; Registration applications with sufficient evidence and clinical trial data support for opposing questions will be subject to accelerated review |
| 2014 | Several Opinions on Ensuring Medication for Children | Accelerate application review and promote research and development innovation; Strengthen policy support to ensure production supply; Improve system construction and enhance the comprehensive evaluation ability of clinical use |
| 2014 | Technical Guidelines for Pharmacokinetic Research in Pediatric Population | Systematically explain the pharmacokinetic characteristics of the pediatric population and analyze and explain the key technical points on how to safely, effectively, and ethically conduct pharmacokinetic research in the pediatric population |
| 2015 | Notice of the General Office of the National Health and Family Planning Commission on the Establishment of the National Health and Family Planning Commission Expert Committee on Children's Medication | Establish an expert committee on pediatric medication to provide assurance for the approval and use of pediatric drugs |
| 2015 | Announcement on Several Policies for Drug Registration Review and Approval | Including children's drugs in the "clinically urgently needed drugs" directory management and implementing a separate queue for their registration applications can accelerate the review and approval process |
| 2016 | Technical Guiding Principles for Clinical Trials of Drugs for the Pediatric Population | Provide guidance for the implementation of clinical trials of pediatric drugs |
| 2017 | Opinions on Encouraging Drug Innovation to Implement Priority Review and Approval | Clearly include pediatric drugs with significant clinical advantages in priority review, and propose relevant procedures for priority review |
| 2017 | Technical Guidelines for Extrapolating Adult Medication Data to Pediatric Populations | Encourage research and development enterprises to communicate with regulatory authorities on data extrapolation in the early stages of pediatric drug development |
| 2019 | Drug Administration Law of China | Take relevant measures to encourage the development and innovation of children's drugs, and implement priority review and approval |
| 2020 | Technical Guidelines for Real-World Research Supporting the Development and Evaluation of Pediatric Drugs | Encourage RWE to support the research and evaluation of pediatric drugs, including new drug registration, expansion of pediatric indications, and improvement of pediatric dosage plans |
| 2020 | Pediatric Drugs Clinical Pharmacology Research Technical Guidelines | Propose the use of clinical pharmacology and quantitative pharmacology methods to make reasonable and scientific extrapolation of existing data, providing a basis for medication in pediatric populations while avoiding unnecessary clinical research |
| 2020 | Children's Drugs (Chemical Drugs) Pharmacy Development Guidelines (for Trial Implementation) | Elaborate on the characteristics of pediatric pharmaceutical development from the aspects of drug delivery routes and dosage forms, raw materials, excipients, packaging systems and delivery devices, patient acceptability, etc., aiming to provide research and development ideas and technical guidance for pediatric pharmaceutical development |
| 2021 | Technical Guidelines for Clinical Trials of Modified New Chemicals for Children (Trial) | Encourage the development/expansion of pediatric applications based on known active ingredient drugs, guided by the clinical needs of pediatrics in China, and in accordance with the growth and development characteristics of children and the needs of pediatric clinical practice |
| 2021 | Technical Guidelines for Writing Children's Medication Related Information in the Instructions of Chemical Drugs and Therapeutic Biological Products (Trial) | Promote the orderly drafting and improvement of pediatric medication information in drug instructions by enterprises, and better guide the rational use of drugs in clinical practice |

The policies on children's medicines issued by China covered such aspects as encouraging research and development, improving the standardization, strengthening the supervision and improving the accessibility. Since 2011, documents issued by China's government at different levels have illustrated that the development of children's medicines were jointly promoted by multiple sectors and disciplines, and that the government attached great importance to the research and development, supply and rational use of children's medicines, aiming to promote the research, development and application, improve the safety and efficacy, and safeguard children's health.

*1.2.2 Effectiveness of the implementation of policies related to children's medication in China*

Children's drugs are categorized as urgently needed clinical drugs, and their registration applications are queued separately, as well as measures such as accelerated review and approval and inclusion in the green channel of centralized bidding and purchasing of medicines [6]. In terms of funding, preferential tax policies were given to children's drug research and development and production enterprises that met the relevant conditions. The Ministry of Industry and Information Technology (MIIT) also gave financial support to the project of Capacity Building for Development and Industrialization of Specialized Technologies for Pediatric Drugs [7].

### *1.3 Comparison of policy development gaps between China and the United States*

The policies introduced by the United States covered such aspects as encouraging the research and development and production, strengthening the regulation, the popularization, and the clinical research, and improving the system of guaranteeing children's medicines. There are some gaps between China and the U.S. in terms of children's drug policy, which are mainly reflected in the following aspects.

(1) Regulatory bodies and regulatory systems: The United States in the 1990s had introduced a series of policies and regulations, such as the "Rules for Pediatric Instruction Manuals" "FDA Modernization Act" and the "Pediatric Code", etc. These regulations provided clear guidance for the research and development, approval and listing of children's drugs. China, on the other hand, has relatively few regulations in this area, and the approval process for children's drugs may be the same as that for adult drugs, with priority review and approval of children's drugs implemented only in the past two years.

(2) Pediatric clinical research: The U.S. has changed its mindset from "avoiding clinical trials to protect children" to "protecting children through clinical trials", and encourages pharmaceutical companies to conduct pediatric research. In China, the system of pediatric research has not yet been perfected, and there are relatively few clinical trials on children's medication.

(3) Incentive policies and measures: The United States and the European Union have mainly adopted pediatric exclusivity policies to increase the incentives for pharmaceutical companies to conduct R&D on drugs for children. However, the pediatric exclusivity policy of the EU also includes generic drugs, while the U.S. is limited to patented drugs. In terms of incentives, the U.S. provides financial incentives for pharmaceutical companies to develop drugs for children, while China has relatively few incentives.

(4) Drug review and approval: The U.S. is more rigorous in reviewing and approving pediatric drugs, including strict approval standards and procedures, as well as comprehensive assessments of the safety, efficacy, and quality of the drugs. China is also gradually improving in this area, but there is still a gap compared with that in the United States.

(5) Drug information and regulation: Both the U.S. and the EU have established comprehensive drug information systems to provide the public with detailed drug information and guidance on drug use. At the same time, their regulation of drugs is also strict to ensure the safety and effectiveness of drugs. In China, the drug information and regulatory system is still under continuous improvement.

## 2 Comparison of the content of pediatric medication policies in China and the United States

The two pillar bills for children's medication in the U.S. are BPCA and PREA. By comparing our policies with these two pillar bills in the U.S., we are able to learn from international advanced experiences, meet common challenges and promote policy innovation, with a view to contributing to the development of children's medication in China.

### *2.1 U.S. policies for pediatric drug development*

The BPCA is an incentive bill. To promote research on pediatric drugs and improve information on pediatric drugs, FDAMA first introduced the concept of PE in 1997, which was a kind of add-on exclusivity to the existing market exclusivity period or patents. the BPCA enacted in 2002 retains and improves the system. the FDA's PE for children's drugs has the following three major features. (1) Wide scope of application: PE not only applies to drugs under development, but also covers all other drugs of the company containing the same active ingredient. (2) Double preference: Drugs approved for pediatric indications may also be granted a second six-month exclusivity period on top of the original PE. (3) Lenient conditions: PE can be obtained only by conducting the study, submitting the study report, and fulfilling the written request within a specified period of time after receiving a written request (WR) from the FDA, regardless of whether the study results are successful or unsuccessful [8-10].

The BPCA required the National Institutes of Health (NIH) to establish a mechanism for research on medications used in children. In 2003, it published the first Priority Research List of Medications for Children, identifying priority medications for development in children, which has been updated almost annually since 2006. As of 2020, the BPCA program had prioritized 200 drugs in 50 therapeutic areas, conducting 44 pediatric clinical trials, and submitting 28 clinical study reports to the FDA for use in changing pediatric drug information in the specification [11]. Meanwhile, to encourage drug companies to voluntarily conduct pediatric studies, the BPCA stipulated that sponsors could also take the initiative to submit a "Proposed Pediatric Study Request (PPSR)", urging the FDA to issue a WR to them, which in turn could lead to a PE.

PREA, on the other hand, is a mandatory act. For new drugs and existing drugs that are not marketed in the United States, PREA requires mandatory pediatric research and corresponding legal requirements for adding new active ingredients, new indications, new dosage forms, new drug administration schemes or new routes of administration [3]. The "Initial Pediatric Study Plan (iPSP)" applies to "New Drug Applications (NDA)" and "Supplemental New Drug Applications (sNDA)" that have not received orphan drug designation. NDA of molecular targeted drugs applicable to adult tumors after August 18, 2020 must be submitted to iPSP regardless of whether they have received orphan drug status. Biosimilars that are not approved as replaceable qualify as new active ingredients and are also submitted to the iPSP.

In addition, in some cases, PREA has established flexible procedures, such as waivers and deferrals, which allow sponsors to submit some or all of the required pediatric medication assessments after the submission of an NDA, a biologics license application (BLA) or sNDA, or a Supplemental Biologics License Application (sBLA). However, regardless of whether a waiver or deferral has been granted, every drug application, except for those with orphan drug status, must include a pediatric medication assessment report.

While the two regulations of BPCA and PREA have facilitated the development of pediatric medications in the U.S., they cannot cover specific types of pediatric diseases. In order to fill the loopholes and improve the legislation, multiple levels of supporting regulations have been created. At the same time, FDA is actively developing a variety of research methods to assist in the development of pediatric drugs. For example, the "Accelerated Cures and Equity in Research for Children Act" was for pediatric oncology drugs, the "Animal Regulations"

was for pediatric critical or infectious diseases, the "Rules for Pediatric Instruction Manuals" was the extrapolation of efficacy, and the "21st Century Cures Act" was on real-world basis.

In May 2023, FDA also released an updated guidance document, "Pediatric Drug Development Under the Children's Research Equity Act and Best Pharmaceuticals for Children Act: Scientific Considerations" [12], which was intended to help the industry develop the data and obtain the information needed to support the approval of medications in pediatric populations, as well as the ethical issues associated with pediatric drug development. It specifically covered requirements related to dosage forms for pediatric drugs, collection of nonclinical information, study design in clinical pharmacology, safety information regarding drug delivery to children, and aspects of pediatric drug development, which provided detailed descriptions of several of these areas.

### *2.2 Policies for R&D of pediatric drugs in China*

China attaches great importance to children's medication, but the research on pediatric medication started late, and the risk of clinical pediatric medication is serious. Therefore, we still need to work hard on pediatric medication. In 2011, the State Council issued the "Outline of China's Children's Development (2011–2020)", which explicitly proposed to encourage the research, development, and production of medicines for children. In 2012, the "Twelfth Five-Year Plan for National Drug Safety" proposed to encourage the research and development of drugs for rare diseases and appropriate dosage forms for children. To ensure the safety of children's drugs, in recent years, National Medical Products Administration has strictly reviewed and approved children's drugs, actively carrying out adverse drug reaction monitoring for children, and modifying the drug information for children in the drug instructions. In 2017, National Medical Products Administration issued the "Opinions on Deepening the Reform of Drug Review and Approval and Further Encouraging Drug Innovation" [13] to encourage the development of children's drugs. From the aspects of bidding, pricing, and medical insurance, enterprises are encouraged to actively research and develop special dosage forms and specifications for children. From the aspect of improving the relevant system of children's medication management, the clinical medication specification for children has been improved. Besides, enterprises are encouraged to improve the information on children's medication in the instruction manuals, and to strengthen the monitoring of adverse reactions and reevaluation of children's medication, which enhance the management of children's medication. The 2016 "Thirteenth Five-Year National Drug Safety Plan" [14] prioritized pediatric drug use. The "Technical Guiding Principles for Clinical Trials of Drugs for the Pediatric Population" and the "Opinions on Encouraging Drug Innovation to Implement Priority Review and Approval" were released from 2016 to 2017 [15], which reasonably guided clinical trials of pediatric drugs and safeguarded the rights of subjects, and played a role in pediatric clinical trials.

National Medical Products Administration in recent years issued the "Children's Drugs (Chemical Drugs) Pharmacy Development Guidelines (for Trial Implementation)" "Pediatric Drugs Clinical Pharmacology Research Technical Guidelines", and "Children's Chemical Drugs Clinical Trials of Improved New Drugs Technical Guiding Principles (for Trial Implementation)", which were the latest guiding principles for children's medicines. They aimed to better promote the development of children's drugs by domestic pharmaceutical enterprises and improve the quality of children's drugs. The "Children's Drugs (Chemical Drugs) Pharmacy Development Guidelines (for Trial Implementation)" provided detailed recommendations based on the key routes of administration and dosage form selection, APIs, excipients, packaging systems and delivery devices, patient acceptability, frequency of administration, and instructions that need to be focused on for the use of medicines in children [16]. According to the "Pediatric Drugs Clinical Pharmacology Research Technical Guidelines" [17], through data extrapolation, some pediatric clinical trials could be reduced or exempted

to optimize clinical trials in the pediatric population. "Children's Chemical Drugs Clinical Trials of Improved New Drugs Technical Guiding Principles (for Trial Implementation)" [18] encouraged the development/ expansion of pediatric applications based on known active ingredient drugs in accordance with the characteristics of children's growth and development and the needs of pediatric clinical practice in China.

In the "Guiding Principles of Real World Evidence to Support Drug R&D and Review (for Trial Implementation)" [19] released in 2020, it clearly pointed out that real-world study, as a new research methodology, could be used to support the research and development and review of children's medicines. Besides, it could provide support for the registration of new medicines, expansion of children's indications, and improvement of children's dosage regimens. It was used to promote the R&D of drugs for children in China mainly in the following four situations: (1) It is used to study the clinical effects of drugs after they are listed on the market, and to observe the long-term efficacy of the drugs and their effects on children's growth and development. (2) For drugs approved for use in both adults and children outside China, and approved for use in adults in China, extrapolation is used to study the effects of the drugs on children's treatment. (3) Using the data of drug instructions to support their application to children can reduce the cost of drug research and development to a certain extent. (4) For drugs for rare diseases, real-world data can be used as an external control.

### *2.3 Comparison of children's medication policies in China and the United States*

#### *2.3.1 Similarities of children's drug use policies between China and the U.S.*

Similarities of policies guiding the research and development of medicines for children between China and the U.S. included the followings. (1) Policy objectives: both countries are committed to ensuring the safety, efficacy and accessibility of medicines for children, and encourage the research, development and production of medicines for children through policies. (2) Encouragement of innovation: Both countries recognize the importance of innovation in the development of medicines for children, and therefore encourage pharmaceutical companies to increase R&D investment and develop new varieties, dosage forms and specifications of medicines for children. (3) Safety assessment: Both countries require strict safety assessment of medicines for children to ensure that they are not harmful to children's health. This includes clinical trials, adverse reaction monitoring and other aspects. (4) Strengthening of supervision: Both countries have strengthened the supervision of medicines for children to ensure the quality and safety of medicines. This includes drug approvals, production licenses, and market supervision. (5) International cooperation: The United States is actively engaged in international cooperation in the research and development of medicines for children, conducting clinical trials and sharing research and development results with other countries. China is also strengthening cooperation with international organizations and other countries to jointly promote the R&D and progress of medicines for children. (6) Encouraging the use of real-world study: Both China and the United States encourage the use of real-world evidence generated by real-world study to support the review and approval of pediatric drugs.

#### *2.3.2 Differences of policies on children's medications between China and the U.S.*

Differences included the followings. (1) Incentive mechanism: the United States has explicitly introduced economic incentives such as pediatric exclusivity period (PE) in the form of legislation to encourage pharmaceutical companies to carry out research and development and clinical trials of children's drugs. While China has also proposed incentives, there are relatively few specific economic incentives. (2) Mandatory requirements: The United States, through regulations such as the PREA Act, has mandatory pediatric research requirements for new drugs and new indications and dosage forms

of existing drugs. While China also emphasizes the R&D of pediatric drugs, it does not explicitly put forward mandatory requirements. (3) R&D guidance: The United States provides detailed R&D guidance for pharmaceutical companies by issuing a priority research list for children's drugs and formulating technical guidelines for pediatric clinical trials. China, on the other hand, has relatively less guidance in this regard, but it has been gradually improved. (4) Regulatory efforts: The United States has greater regulatory efforts in drug R&D and listing, which is more stringent in the approval and management of pediatric drugs. Although China has strengthened its drug supervision in recent years, there is still a certain gap compared with the international advanced level. (5) Drug pricing and health insurance policies: The U.S. is more market-oriented in drug pricing, and its health insurance policies are relatively flexible, but high drug prices may lead to limited access to drugs for children. China pays more attention to fairness and universality in drug pricing and health insurance policy, and reduces drug prices through government pricing and health insurance negotiation, which can improve the accessibility of medicines for children.

At present, China is still facing difficulties in the research and development of children's drugs and clinical trials. Besides, the implementation process due to poor cost-effectiveness, informed consent difficulties, poor compliance, access to information difficulties, children's clinical trials are also generally less active. The main reason is that children's drug research and development incentive is insufficient in China. Although new drug R&D investment is huge, the profit is not proportional to the children's group. Clinical treatment generally adopts drugs beyond the drug instructions and reduces the dosage. Therefore, it is difficult to increase the motivation for research and development of medicines for children. Secondly, it is hard to recruit children as subjects, and the participation of children in clinical trials requires the consent of their guardians. Although the review conditions of clinical trials for children's drugs are more stringent, guardians generally maintain a refusal attitude, and often refuse to participate in clinical trials when other treatment methods are available. Thirdly, few medical institutions in China conduct pre-market clinical trials for pediatric drugs.

## 3 Policy recommendations

### *3.1 Promoting the development of clinical trials of medicines for children*

Based on the comparison of incentives and children's clinical research, it can be seen that China has deficiencies in children's clinical trials. Therefore, China should accelerate the diversification of the distribution of institutions with conditions for children's clinical trials. Then, these institutions can be expanded more widely from children's hospitals, women's and children's hospitals, and maternal and child health hospitals to other general hospitals, which is convenient for children's patients to seek medical treatment. Besides, ongoing children's clinical trial programs should be followed up throughout the entire process. Projects that have not yet begun should be organized to discuss and give guidance to experts, so as to speed up the progress of the projects. As to the society, relevant publicity and education can be carried out to encourage child subjects to participate in the trials, which can provide a broader participation base. In terms of policy and economy, the government should provide policy as well as economic support for the research and development of medicines for children [20] in order to solve the problems related to benefits as well as risks.

### *3.2 Improving the policy system of children's medication*

Based on R&D guidance and regulatory aspects, we can see that there is still a gap in the system of children's medication in China. In recent years, China's drug supervision and management departments have been increasing the strength of the reform of the drug review and approval system, which has made positive efforts to accelerate the review and approval of children's drugs. However, only relying on

the priority review and approval policy is not enough to support the research and development of medicines for children. Real-world research can be utilized to identify drugs suitable for children and conduct clinical trials. In addition, companies are required to conduct safety and efficacy studies on suitable drugs for children's indications. This will accelerate the transformation of real-world data into real-world evidence, which will ultimately be applied to the review and approval of pediatric drugs [21]. We can also learn from the experience of the United States, the European Union and other countries to improve children's information as an obligation of enterprises.

### *3.3 Developing pricing programs for children's medicines*

Based on the comparison of drug pricing and medical insurance policies, it can be seen that there are still deficiencies in drug pricing in China. It is recommended to refer to the pricing principles of the United States and Japan for children's drugs, and provide direct incentives to children's drugs through the initial pricing of new children's drugs to make up for the addition, and the addition of new children's indications in the catalog. China can give a certain range of price markups to innovative children's drugs that enter the medical insurance catalog for the first time. Besides, children's drugs can be taken as a separate factor for examination in the process of access and price measurement of our negotiated medicines, and consider them as markups on the basis of the affordability of payment by China's medical insurance fund.

### *3.4 Expanding the international cooperation*

Based on the comparison of the aspects of international cooperation, although China is also trying its best to expand international cooperation, it still needs to be strengthened. International cooperation is an important part of promoting the development of the field of pediatric medication and improving data on pediatric medication. Through international cooperation, we can learn advanced experience in clinical trial design, implementation, summary report writing, and other multi-dimensional and multi-level experiences [22]. International cooperation can share best practices and successful cases of pediatric medication with other countries, promote multinational cooperation in conducting multicenter clinical trials of pediatric medication, facilitate the sharing and exchange of data on pediatric medication, as well as strengthen the enhancement of norms and standardization.

## 4 Conclusion

The healthy development of children is the key to the future of the country and the nation, so the issue of children's medication is urgent, and the development of children's medication has a long way to go. The United States has introduced two sets of specialized bills, as well as a variety of guiding principles and related legal incentives in the field of children's medication. Yet, China's policies and regulations are still far from the United States. Therefore, China should learn from foreign experience, further improve the laws and regulations related to children's medicines, establish a review mechanism in line with the characteristics of children's medicines, publish a priority research catalog for pediatric drugs, which helps to guide children's drug research and development enterprises to conduct research in an orderly manner [23]. At the same time, we should promote the development of clinical trials for children's medicines, formulate pricing programs for children's medicines, and expand international cooperation to further improve the research and development of children's medicines, which will promote the safety, efficacy, and accessibility of children's medicines.

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