



Thoughts on the Construction of Pediatric Exclusivity Policy in China

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Abstract

Objective To study the 6-month patent exclusivity rule in the US and provide reference for designing pediatric exclusivity policy in China. **Methods** In this paper, summarize the development history and status of pediatric exclusivity in the US was summarized to analyze its effect for pediatric drugs research and development incentive and information improvement. Then, we can learn from its experience to construct pediatric exclusivity policy in China. **Results and Conclusion** Pediatric exclusivity policy in the US has obvious incentive effects, but the scope is limited to patented or other data protected drugs. Based on the successful experience of the United States, we can fully evaluate the impact of patents and other data protection policies on the exclusive marketing rights. In addition, we should conduct in-depth study on the applicable objects, authorization scope, protection mode and time limit of the pediatric exclusivity so that we can introduce supporting measures for China's pediatric exclusivity as soon as possible.

Keywords: pediatric drug; data protection; market exclusivity

The difficulty in drug development for children has always been a major problem in China. Since The State Council issued the "Outline for the Development of Chinese Children (2011–2020)" in August 2011 and proposed to "encourage the research and development and production of children's drugs", the relevant ministries and commissions of the state have successively issued more than 30 policies related to the research and development of children's drugs. Besides, three batches of lists were published to encourage the research and development of pediatric drugs. The new version of the "Drug Administration

Law" encouraged children's drug research and development to the legal level for the first time. In May 2022, the State Food and Drug Administration issued the "Regulations for the Implementation of the Drug Administration Law (Draft)" (hereinafter referred to as the "Regulations"), and children's drugs were mentioned once again as an important topic. The regulations proposed that new drugs for children should be given a market exclusivity period of no more than 12 months, which greatly encouraged pharmaceutical companies to develop pediatric drugs.

The United States has established a relatively perfect market exclusivity system for pediatric drugs, which has a significant incentive effect. This paper briefly reviewed the development history and current situation of the market exclusivity system

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of pediatric drugs of the United States Food and Drug Administration (FDA), and put forward some suggestions for improving the market exclusivity system of pediatric drugs in China.

1 Policy background of the pediatric exclusive period system in the United States

In the early 20 century, a number of adverse drug events in the United States promoted its regulation of the safety and efficacy of drugs, such as the sulfa drug event (1937) prompted Congress to introduce the “Federal Food, Drug and Cosmetic Act” (FDCA), which for the first time required that new drugs must be tested by manufacturers and approved by the FDA before they were marketed. The thalidomide event (1957–1961) prompted the adoption of the Kefauver-Harris Drug Amendment, which mandated that enterprises should conduct safety and efficacy assessments before drugs were marketed^[1].

However, the limitations of the above policies were also evident, because the U.S. drug law did not distinguish between children and adults. Due to the complexity of clinical trial design in children and complicated consent procedures, most enterprises choose to carry out clinical trials only in adults. At the same time, to avoid legal responsibilities, pharmaceutical enterprises emphasize in the label that drugs “have not been studied in children”, potentially depriving children of access to and use of new drugs, and forcing doctors to use drugs not labeled for children to treat children’s diseases, which leads to an increase in adverse drug events^[2]. The frequent occurrence of adverse drug events and the development of pediatric pharmacology have made US authorities realize the necessity of carrying out pediatric clinical studies. In 1979, the FDA issued a “Labeling Requirement”, demanding that drugs for pediatric use should add pediatric medication information to the label^[3]. The regulation is intended to urge enterprises to carry out pediatric clinical trials to obtain the effectiveness and safety information of the active ingredients in drugs used in pediatric population. However, due to the complexity of

pediatric drug research, high R&D cost, difficulty in subject recruitment and other factors, most enterprises are reluctant to carry out the study in the pediatric population, resulting in that the industry intentionally avoids this therapeutic field. In 1994, the FDA issued the “Pediatric Labeling Rule”, requiring pharmaceutical companies should voluntarily change or supplement pediatric medication information in drug labels, but the effect of this regulation is not obvious. According to statistics, 77% of drugs remain unchanged^[4].

In order to further promote the research and development of pediatric drugs, the FDA has intensified its incentive and successively issued a series of regulations and policies, of which the pediatric drug market exclusivity has played a significant role.

2 Implementation process of exclusive period system of pediatric drugs in the United States

When the US Congress first passed the pediatric exclusivity provision (Section 505A) of the “Food And Drug Administration Modernization Act” (FDAMA) in 1997, it granted 6 months of market exclusivity to new drugs that have been initiated and completed in pediatric studies in accordance with a written request letter issued by the FDA^[5]. According to the terms, the market exclusivity system of pediatric drugs in this stage is only applicable to the marketing application of drugs containing new chemical entities (NCE), and it is not applicable to the marketed drugs with new pediatric research. Therefore, the incentive effect is limited^[6].

In 2002, the “Best Pharmaceuticals for Children Act” (BPCA), approved by Congress, retained Section 505A of the FDAMA and provided specific provisions for pediatric exclusivity. At the same time, the Act added a five-year “sunset clause”, which was amended every 5 years^[7]. In 2007, the BCPA was reauthorized through 2012 by the “Food and Drug Administration Amendments Act” (FDAAA), in addition to a provision to increase transparency in pediatric research. In 2012, the “Food and Drug Administration



Safety and Innovation Act” (FDASIA) made the FDA’s BPCA program permanent. The FDA’s BPCA program does not need to be authorized by Congress every 5 years. In 2017, the FDA “Reauthorization

Act” continued the National Institutes of Health (NIH) BPCA program with further amendments (with permanent authorization of the FDA component of the program). See Table 1 for details of the revisions.

Table 1 History of revisions to the FDA market exclusivity system for pediatric drugs

Release time	Act	Specific provisions on the market exclusivity system for pediatric drugs
1997	FDAMA	Section 505A: Grant of protection of the 6-month market exclusivity period for new drugs that conducted and completed pediatric studies by written request letters issued by the US FDA
2002	BPCA	(1) Authorize FDA and NIH to jointly implement the BPCA program; (2) Expand the scope of incentives for pediatric exclusivity by providing for NIH to update the priority list of marketed Off-Patent drugs requiring additional pediatric indication studies every 3 years, and FDA to draft written recommendations with reference to the priority list; (3) Strengthen the management of drugs that have obtained market exclusivity protection, and require pharmaceutical companies to submit all adverse event reports of related drugs within one year of obtaining exclusivity and to publicly submit safety evaluation reports to the Pediatric Advisory Committee (PAC). PAC will evaluate non-clinical, clinical reviews, and other relevant information. Determine whether the company needs to continue reporting more adverse events, add additional clinical trials, or modify labeling information. In addition, under the Act, the BCPA will be amended every five years thereafter ^[8]
2007	FDAAA	(1) Reauthorize the BCPA until 2012; (2) FDA may require firms that have completed a pediatric study plan in accordance with written recommendations to make the results of a pediatric study public; (3) Publicizing the drugs obtained in the pediatric drug market during the exclusive period, and tracking the subsequent changes in the instructions; (4) A Pediatric Review Committee (PRC) is established to evaluate written requests for drug use studies in children, the results of clinical trials conducted based on written requests, and to determine whether an exclusivity period is recommended ^[7]
2012	FDASIA	(1) Make FDA’s BPCA program permanent; (2) NIH’s BPCA program for generic drugs will need to be licensed every 5 years; (3) Newborn babies should be given priority when NIH selects drug list ^[9]
2017	FDA Reauthorization Act	(1) Extend the BPCA Program for generic pediatric drug trials through fiscal Year 2022; (2) NIH prioritizes research to identify biomarkers for pediatric diseases and conditions; (3) Specifically allow NIH to post data from its funded pediatric studies on its public website when reporting to the FDA, as required by potential labeling changes ^[9]

3 Overview of the US pediatric exclusivity system

3.1 Purpose of the system

The purpose of the exclusive market system of pediatric drugs in the United States is not only to promote the research and development of pediatric drugs, but also to stimulate enterprises to carry out pediatric studies to obtain the effectiveness and safety information of the active ingredients in drugs used in pediatric groups and improve pediatric labels, so

as to achieve the fundamental purpose of improving the accessibility and safety of pediatric drugs and promoting children’s health.

3.2 Features of the system

Firstly, market exclusivity for pediatric medicinal products is an incentive policy that encourages sponsors to conduct voluntary pediatric studies for all indications of new chemical entities or the active ingredients of marketed drug, not just those that have been declared for marketing. It is consistent with the

mandatory provisions of the Pediatric Research Equity Act (PREA), which authorized the FDA to mandate that eligible drugs submit an agreed-upon Pediatric Study Plan (PSP) and pediatric evaluation before marketing. They are independent and complementary to each other, and together constitute the FDA's strategy to improve pediatric information^[10].

Secondly, the market exclusivity for pediatric drugs, also known as the data exclusivity protection system for pediatric drugs, is the administrative protection of some special clinical trial data granted by the FDA, regardless of whether the drug has patent protection^[11]. Meanwhile, unlike other data protection systems, the market exclusivity for pediatric drugs cannot take effect alone, it must be extended to the end of the valid patent or other protection period. Combined with the purpose of the market exclusivity system for pediatric drugs, it can be seen that the pediatric exclusivity only takes effect after the end of patent protection and other exclusive protection periods for the active ingredients.

3.3 Applicant

The scope of application of the pediatric market exclusivity includes new chemical entity drugs, marketed drugs for new pediatric studies and

marketing applications for the first generic drugs^[12].

3.4 Application procedure

In the United States, obtaining pediatric exclusivity protection involves several steps (Fig. 1). (1) FDA issues written requests (WR) to drug sponsors such as pharmaceutical companies or third-party non-drug sponsors interested in pediatric research, including research institutions and universities. (2) Subjects who have received WRs have voluntarily made written responses to conduct pediatric research. (3) The sponsor of the pediatric study enters into a written agreement with FDA regarding the specifics of the pediatric study. (4) The sponsor of the pediatric study conducts all studies in accordance with written requests and written protocols (if no written agreement is established, in accordance with accepted scientific principles), and produces a pediatric study report that meets the requirements (minor deviations allowed). (5) The sponsor of a pediatric study submits an application to FDA under Section 505 and ensures that at the time the drug is approved, the remaining period of protection of the patent or other exclusivity is at least nine months. (6) Drug labels contain pediatric applicable information obtained from studies and are approved by FDA^[13].

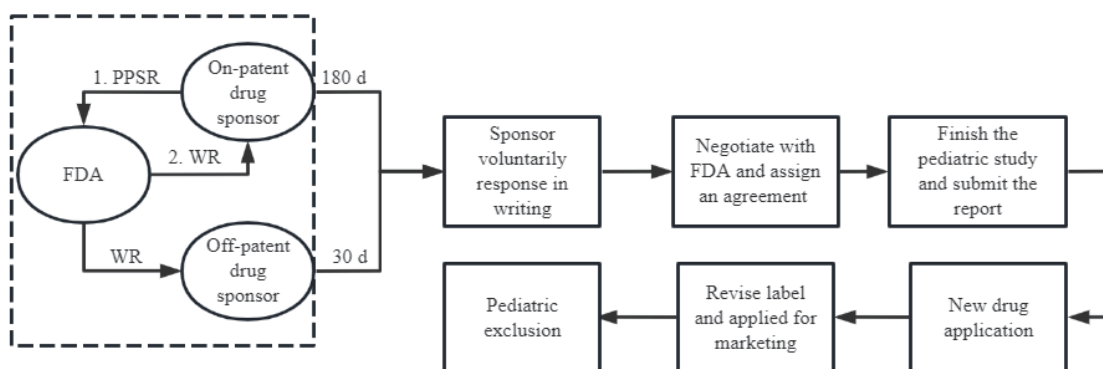


Fig. 1 Application for market exclusivity protection procedure for pediatric drugs

Specifically, on-patent and off-patent drugs with patent or exclusive protection (or eligible for protection) have some differences in the application process.

Obtaining a written request. Proposers of

pharmaceutical products that have patent or exclusive protection (or are eligible for protection) should proactively submit a proposed pediatric study request (PPSR) to FDA, based on which FDA will decide whether to issue a written request, it should also



be noted that PSP submissions and protocols are not a substitute for submission of PPSRS^[14]. For marketed drugs that have lost or have no patent or exclusive protection, NIH will place some drugs on the “priority list” based on the drug use needs of the child population, and then send a PPSR to FDA for the drugs on the “priority list”, and FDA will issue a WR to the drug holder. Non-drug sponsors such as research institutes or universities can also send PPSRS to FDA on the priority list to obtain the WR of the drug product^[15]. If enterprises reject WRs, NIH will provide funding through the “Pediatric Research Program” and organize members of the pediatric trials network (PTN) to conduct research.

Written response. Sponsors of pharmaceutical products with patent or exclusive protection (or eligible for protection) have 180 natural days from the date of receipt of FDA’s WR to respond in writing to FDA, while sponsors of pharmaceutical products without patent or other exclusive protection and third parties wishing to conduct pediatric studies have 30 days to respond^[13].

Conditions for obtaining exclusive protection of pediatric drug use. The purpose of the exclusive

market system for pediatric drug use is to improve pediatric information by encouraging the development of pediatric research to obtain pediatric experimental data of the active ingredients of drugs. Therefore, pediatric exclusivity is given to the pediatric test data of one or several active ingredients of a drug, rather than a drug or a pediatric indication. That is, in principle, for a drug that has completed pediatric research according to WR and has been approved for marketing, pediatric exclusivity protection can be obtained regardless of whether the pediatric research is successful (It doesn’t matter whether the drug has pediatric use or not)^[14]. However, considering the nature that the period of pediatric exclusivity protection cannot be applied in isolation, for marketed medicinal products without patent or exclusive protection, the right of pediatric protection cannot be applied after other periods of protection if the pediatric studies fail. It means they are not approved for a new pediatric use (including pediatric indications and pediatric dosage forms) (Table 2). However, if the results of pediatric studies show that the application of the drug in some aspects is harmful to children, it must be marked in the label^[7].

Table 2 Conditions to obtain exclusive pediatric protection

Drug type	Clinical study (Indication A)	Pediatric studies required by WR (Indication B)	Protection period (months)
	×	NA	×
On-patent	√	×	$X + 6$
	√	√	$X + 6$
Off-patent	NA	×	× (6 months cannot exist alone)
	NA	√	3 years (new clinical trial data protection) + 6

Note: × – Fail to be marketed; √– Be marketed; NA – Not applicable; X – The effective patent period or other protection period (in months) after the drug is marketed.

3.5 Other provisions

FDA will publish all study information and revised labels in the journal “Federal Registry” within 180 days of the filing of study results, regardless of whether a 6-month pediatric exclusivity is granted. Holders of pediatric exclusivity must also report all adverse event information within 1 year of the drug’s marketing

approval to the Office of Pediatric Therapy^[15].

4 Implementation effect

4.1 Overall

Since the implementation of the market exclusivity incentive for pediatric drug use in 1997,



520 WRs were issued by FDA as of June 8, 2022 (Fig. 2). As of December, 288 drugs were granted pediatric exclusivity protection, which actually increases the use

information of 274 active ingredients in the pediatric population. Among them, 277 drugs are under patent or exclusive protection^[16], as shown in Fig.3.

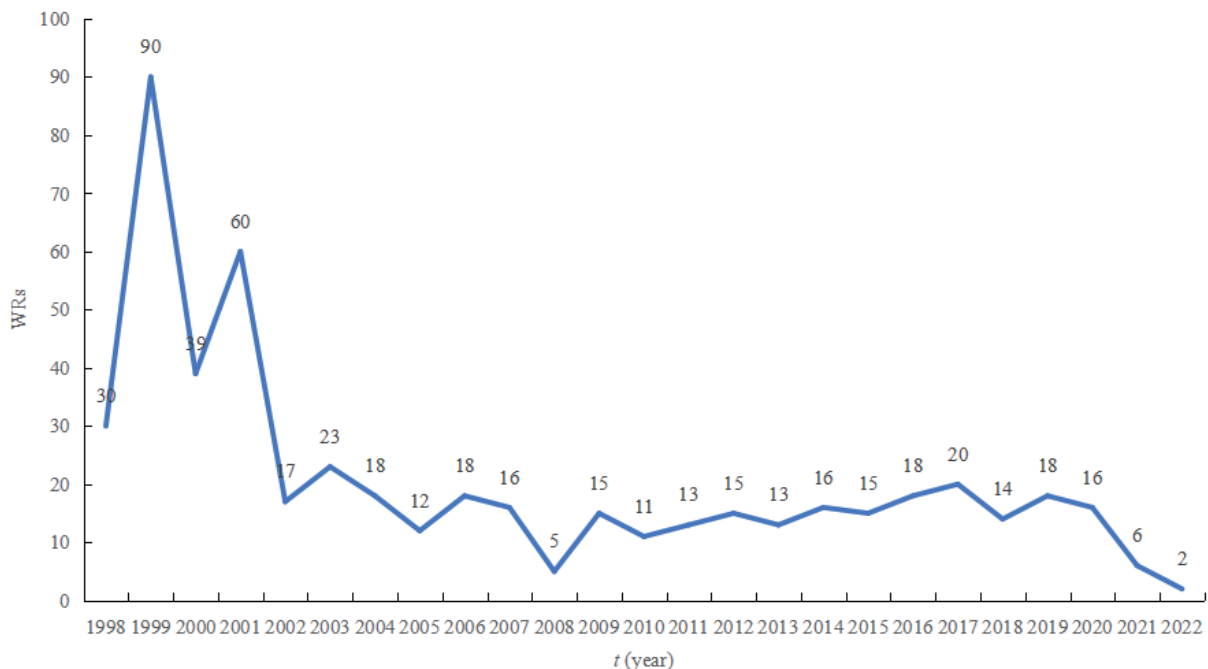


Fig. 2 FDA written requests from 1998 to 2022



Fig. 3 Pediatric exclusivity drugs granted by FDA from 1998 to 2022

4.2 BPCA plan for off-patent

For generic drugs, as of the last update to the priority list (2020–2021), the NIH BPCA program had

prioritized over 150 drugs and treatment areas, funded over 40 clinical studies, and revised the labeling of 11 drugs^[17]. The priority list in 2020 consists of 16 categories, 49 treatment areas, and 79 drugs, among



which the following points should be focus on.

Firstly, among the currently listed treatment fields, the drugs for neonatal infection are the most included (9), followed by childhood epilepsy (6) and childhood hypertension (5), suggesting that these three diseases are common in pediatric population, and have a great demand for drugs.

Secondly, there are few drugs for migraine, type I diabetes, chronic kidney disease, acute kidney injury and nephrotic syndrome, suggesting that pediatric drugs in the above 5 areas are scarce.

Thirdly, most of the drugs in the list are eventually carried out pediatric research by PTN, indicating that most holders of generic drugs are unwilling to bear the consequences of not recovering the R&D investment after the failure, so pediatric research is rarely carried out.

5 Discussion and recommendations

Through the above analysis, it can be seen that although the exclusive market policy of pediatric drugs in the United States has some disadvantages. For example, the scope of incentive is limited to drugs that have patent or other exclusive protection (including first-imitation drugs). For off-patent drugs, even though FDA and NIH jointly issued some auxiliary policies, such as pediatric research plan, pediatric research fund, etc., the incentive effect is still limited, and many drugs on the market still lack pediatric information. But it is undeniable that the market exclusivity system of pediatric drugs not only promotes the research and development of pediatric drugs, but also greatly improves the information of pediatric drugs, which plays an important role in improving the accessibility and safety of pediatric drugs. Therefore, it is imperative to establish the market exclusivity system of pediatric drug that is suitable for China. Based on the provision in the “Regulations” that “the first new varieties, dosage forms and specifications specially for children approved for market, as well as the indications or usage and dosage of children increased, the longest period of market exclusivity shall not exceed 12

months, during which the same varieties will not be approved for market”, this paper puts forward some suggestions from the following aspects.

5.1 Incentive range

According to the “Regulations”, the incentive objects of the market exclusivity system of pediatric drugs include innovative drugs and improved new drugs. However, as no official regulations have been issued, there is a lot of controversy on whether to include improved new drugs in the scope of incentive. Compared with developed countries, there is a big gap in the level of pediatric research and development ability of pharmaceutical enterprises in China. Granting exclusive rights to newly listed drugs in pediatric research may enable the foreign pediatric drugs to occupy the Chinese market for a long time, affecting the enthusiasm of domestic enterprises to research and develop pediatric drugs.

However, from the perspective of policy, the purpose of market exclusivity system for pediatric drugs is not only to encourage pharmaceutical enterprises to actively carry out pediatric research, but also to improve the accessibility and safety of pediatric drugs for children’s health. Therefore, if pediatric exclusive protection is not provided for improved new drugs, foreign enterprises may consider that it is difficult to recover the research and development investment when formulating the marketing strategy of improved new drugs with pediatric indications. They will not choose to market these drugs in China, which potentially deprives Chinese children of the opportunity. Incentivizing the research and development of innovative drugs only for children will also lead to the lack of pediatric information for a large number of drugs already on the market in China. Therefore, we suggest that improved new drugs should be included in the incentive scope.

5.2 Conditions for exclusivity protection for pediatric drugs

According to the market exclusivity period clause of the “Regulations”, the National Medical



Products Administration (NMPA) grants exclusive protection to new drugs successfully marketed for pediatric use (including pediatric varieties, dosage forms, specifications, indications, usage and dosage). Drugs that have been studied in pediatrics but not marketed for pediatric use are excluded from the scope of protection. Referring to the implementation effect of the generic drug BPCA program in the United States, we can find that most enterprises may be unwilling to bear the consequences of pediatric research failure, thus avoiding the research and development of pediatric drugs.

Therefore, we should refer to the provisions of the United States when formulating follow-up supporting measures, and grant pediatric exclusive protection to drugs that have completed pediatric research in accordance with the requirements as long as they are approved for marketing, regardless of whether they have pediatric indications.

5.3 Mode and duration of protection

Different from the pediatric exclusive period

of 6 months determined by the FDA, the maximum market exclusive period of 12 months is currently stipulated in China for the pediatric drugs, but the basis and standard for determining the specific time limit are not yet clear. It is suggested that the State Food and Drug Administration fully consider the actual clinical needs of pediatric patients, the spectrum of diseases in children, the availability of drugs and other factors when promulgating supporting measures.

At the same time, it is not clear whether market exclusivity of the pediatric drugs will be effective alone or after the end of other patent or exclusive protection on the active ingredient, as in the United States. The role of pediatric exclusivity in extending the period of drug market exclusivity in the United States is based on the mature patent protection and drug data protection system, in which the data protection system flexibly covers new chemical entities, new clinical trials (such as adding new indications), and generic drugs (Table 3), so that pediatric exclusivity protection applies to improved new drugs and even generic drugs.

Table 3 Type and duration of drug data protection in the United States and China (Draft)

FDA		NMPA (draft)	
Type	Protection time	Type	Protection time
NCE data protection ¹	5 years	Protection of innovative drugs	6 years (12 years for innovative therapeutic biologics)
New clinical trial data ²	3 years	Pediatric specific drug protection	6 years
Rare drug data	7 years	Rare drug protection	6 years
Patent challenge success	180 days	Patent challenge success	12 months
Pediatric data	6 months (not separate)		

Note: 1 – New drugs containing new chemical entities (NCEs) first approved by FDA; 2 – New indications or dosage forms for clinical trials of approved drugs.

However, at present, the system of intellectual property rights, especially the system of drug test data protection, is still in its initial stage in China. In 2018, the NMPA published the “Measures for the Implementation of Drug Test Data Protection

(Interim) (Draft)” (hereinafter referred to as the “Measures for Implementation”) ^[18]. Innovative drugs, innovative therapeutic biological products, drugs for rare diseases, special drugs for children and drugs successfully challenged by patent (first



imitation drugs) are included in the scope of trial data protection. But no progress has been made in the “Measures for Implementation”, and no other supporting regulations have been issued. In 2021, the “Implementation Measures for the Early Settlement Mechanism for Drug Patent Disputes (Trial)”^[19] jointly issued by the NMPA and the State Intellectual Property Office only specified the 12-month market exclusivity period of the first imitation drug (Table 3). In addition, according to research evaluation^[20], the valid patent period of Chinese innovative drugs after approval is longer than the protection period of drug trial data. It means that the data protection period is included in the patent period and does not play an extended role.

It is suggested that we should further improve the provisions on the protection period of drug trial data on the basis of the “Measures for Implementation”, fully evaluate the impact of patent and other data protection systems on the market exclusivity period, and determine the protection mode and time limit of the market exclusivity system of pediatric drugs.

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