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Overview of China Drug Review Annual Report (2015-2021)

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Since 2013, the National Medical Products Administration ("**NMPA**") Center for Drug Evaluation ("**CDE**") has been releasing a Drug Review Annual Report ("**Report**") each year, which summarizes its work on drug review of the previous year. The Reports have gradually covered key issues such as the acceptance of drug registration applications, the review and approval of drug registration applications, the expediting procedures, the communication mechanism, main issues on drug registration applications, the varieties in key therapeutic areas, and the review and approval of traditional Chinese medicines.

We have made a comprehensive analysis of the latest seven Reports (from 2015 to 2021), in order to provide an overview of the progress of CDE's work regarding drug registration and show the past achievements and future development trends in China's reform of the drug review and approval system. We hope this will provide some guidance for future drug development and registration activities.

Highlights of China's reform of the drug review and approval system

Each year, CDE lists and explains in the Reports its main work and progress regarding drug review. Therefore, we can find out the priorities of CDE's work and the focus of the reform of China's drug review and approval system for each year.

The following table extracts part of the keywords of the reform mentioned in the Reports over the past seven years. Among them, addressing the drug lag issue was the focus in 2015, while generic drug review (5 hits), ICH works (5 hits), clinical trial administration (5 hits), and procedures for prioritized/expedited review and approval (5 hits) were the keywords repeatedly mentioned in the past six years. According to these highlights, we summarize the development of China's drug review and approval system in the past seven years covering five topics including,

1. the time management of drug review and approval,
2. the modification in the registration classification and in the application requirements of chemical drugs,
3. the consistency evaluation of generic drugs,
4. the development of the registration of biologics, and
5. the review and approval of pediatric drugs and orphan drugs.

[1] Leyi Wang and Shuwen Sun have also contributed to this article.

Key Issues\Year	2015	2016	2017	2018	2019	2020	2021
Drug Lag	Solving the Drug Lag						
Administration of Drug Review and Approval	Reforming the administration system of drug review Enhancing the quality administration of drug review	Enhancing the establishment of drug review system Consolidating basic works of drug review	Enhancing the scientific basis of drug review	Further enhancing the scientific basis of drug review	Coordinating the establishment of quality management system of drug review Enhancing the scientific basis of drug review Constructing a scientific administration system oriented to the process of drug review	Promoting the establishment of a scientific administration system oriented to the process of drug review Further enhancing the scientific basis of drug review	Constructing a more scientific administration system oriented to the process of drug review
Policies		Enhancing the establishment of the technical guidelines and standard systems for drug review Enhancing the establishment of the quality			Being deeply involved in the revision of drug related laws and regulations Enhancing the establishment of a detailed technical standard system for drug review	Promoting the formulation and revision of the supporting documents of the *Measures for the Administration of Drug Registration*	Improving of the system of technical guiding principles for drugs

Key Issues\Year	2015	2016	2017	2018	2019	2020	2021
		management systems for drug review				Accelerating the establishment of the technical standard system for drug review	
Generic Drug Reviews	Improving the review of generic drugs		Achieving breakthroughs in the work of conducting consistency evaluation of generic drugs		Vigorously carrying out the consistency evaluation of generic drugs	Accelerating the work of conducting consistency evaluation of generic drugs	Promoting the work of conducting consistency evaluation of generic drugs
ICH Works			Taking a solid step forward on ICH works	Promoting the work of the ICH Office	Actively promoting and deepening ICH works	Continuously carrying out ICH works	Ensuring the re-appointment of members of the ICH Administration Committee Promoting the transformation and implementation of ICH Guiding Principles and the coordination

Key Issues\Year	2015	2016	2017	2018	2019	2020	2021
							of relevant issues
Clinical Trials / Studies			Implementing the regime of implied approval of clinical trials	Reforming the administration of clinical trials	Implementing risk administration during clinical trials	Fully implementing risk administration during clinical trials	Improving the administration system of clinical trials and improving the quality of drug clinical studies
Procedures for Prioritized / Expedited Review and Approval		Continuously advancing the prioritized review and approval system		Accelerating the review of overseas new drugs urgently needed in clinical settings	Accelerating the review of overseas new drugs urgently needed in clinical settings	Accelerating the review of overseas new drugs urgently needed in clinical settings Making full efforts to carry out emergency reviews	Taking multiple measures to meet the urgent clinical needs for pediatric drugs and promoting the R&D and innovation of pediatric drugs
Others	Encouraging the R&D of innovative drugs			Ensuring the pilot reform of government purchase in typical items			Guiding the Sub-Centers to carry out drug review

Main issues on drug registration applications

In the 2020 Report and the 2021 Report, CDE has respectively listed and analyzed the main issues on drug registration applications of the year. This article will summarize these main issues in order to offer some help and suggestions for those participating in the R&D and the registration of drugs.

I. Main issues and analyses

The following table summarizes the main perspectives and specific issues in drug registration applications:

Categories	Issues of 2021
Establishment of R&D projects	The clinical purpose and function of the drug R&D is unclear, and the selection of indications is not reasonable.
	The existing study data suggest that the pharmacodynamic effect is not obvious, the target and mechanism of action are not clear, and the risk for druggability is high.
	The use of concomitant drugs is contrary to the principles of clinical diagnosis and medication or lacks study data to support its efficacy and safety.
	The existing study data do not support the improvements to marketed varieties.
	The reference listed drugs ("**RLDs**") of the generic drugs have been withdrawn from the market due to safety and efficacy issues.
	The modifications in supplementary applications are reasonable.
Efficacy	The existing clinical study data cannot prove the efficacy of the varieties.
	The conducted clinical studies have issues regarding the protocols or quality control, and the efficacy of the studied varieties cannot be evaluated.
	The results of the consistency evaluation show that the generic drugs are not equivalent to the RLDs.
	The registration applications of Class 3 chemical drugs lack clinical data on domestic efficacy.
Safety	Early stage (IND phase) study results suggest that the toxicity is significant, or the "therapeutic window" is too narrow, so that it's hard to enter the phase of clinical development. Or, the results suggest that the benefit of clinical application may be very limited.
	The methods or quality control of preclinical safety studies cannot support subsequent clinical development, or the study data are not sufficient to support subsequent clinical development.
	The existing clinical study data indicate the presence of serious adverse effects and an unreasonable benefit-to-risk ratio for clinical application.
	The registration applications of Class 3chemical drugs lack clinical data on

Categories	Issues of 2021
	domestic safety.
Quality controllability	The pharmacological studies are seriously flawed and cannot demonstrate the quality controllability of the product.
	The application materials cannot prove the consistency of the quality of the generic drugs and the RLDs.
	Studied samples are inconsistent across each development phase of the study.
	The stability results of the samples and the selection of Active Pharmaceutical Ingredients ("**API**") starting materials do not meet the technical requirements for the marketing of generic drugs.
	Generic drugs have not used API from legitimate sources as required.
	The review tests of the samples do not meet the requirements, or the test methods have serious defects.
Compliance	Authenticity issues with the study data are identified in the registration examinations.
	Other major defects that affect product quality are identified in the registration examinations.
	The sampling inspections in the registration examinations have not been passed.
Others	Study data are not provided, or the study projects are not supplemented or improved in accordance with the requirements and standards set forth by the regulatory authorities at the time of communication.
	The contents of the studies are found incomplete and cannot support the registration applications during the drug review.
	The supplementary applications of the revise of instructions for users ("**IFUs**") do not meet the writing requirements and management specifications of IFUs.
	The literature or study data are not sufficient to support the supplementary applications.

Categories	Issues of 2020	
IND applications	The applicants have made no communication before formal applications.	
	The sources of the establishments of R&D projects are not sufficient, and there are serious defects on druggability.	
	The application materials are not sufficient to support the conducting of clinical trials, or to ensure the safety of the study subjects.	A serious lack of study materials is found after the filing of application due to failure to communicate, and supplementary research cannot be completed within the time limit.
		The available study results suggest weak efficacy and high toxicity, and the benefit-to-

Categories	Issues of 2020	
		risk ratio for clinical application is unreasonable.
		The purpose and function of the clinical development is contrary to the basic principles of clinical diagnosis and treatment, and use of drugs.
		The existing pharmaceutical and preclinical studies do not meet the requirements of clinical trials.
		The overall design of the clinical trial is seriously flawed, and the risk control measures are insufficient.
		The non-clinical study data of concomitant drugs are not sufficient.
		Insufficient data and/or inconsistent immunization procedures for single vaccines in combination vaccines are found.
NDA applications	The quality control and management of the studies have defects so that the available study results cannot prove the safety, efficacy and quality controllability of the drugs.	
	Non-Compliance	The design of key clinical studies has significant defects and fails to provide objective and robust evidence of efficacy and safety.
		The pharmacological studies are seriously flawed and cannot demonstrate the quality controllability of the product.
		Studied samples are inconsistent across each development phase of the study.
		Authenticity issues with the study data are identified in the registration examinations.
Applications of generic drugs (ANDA)	The establishments of generic drugs R&D projects are not reasonable.	
	The application materials cannot prove the consistency of the quality of the generic drugs and the RLDs.	The RLDs of generic drugs have been withdrawn from the market, and there already are newer products with better safety to meet clinical needs.
		The review tests of the samples do not meet the requirements, or the test methods have serious defects.

Categories	Issues of 2020	
		The results of the consistency evaluation show that the generic drugs are not equivalent to the RLDs.
		The stability results of the samples and the selection of API starting materials do not meet the technical requirements for the marketing of generic drugs.
		Generic drugs have not used API from legitimate sources as required.
Supplementary applications	The application materials have not sufficiently explained the scientificalness and reasonability of the changes, and thus cannot support the changes.	
	The available study results cannot ensure the safety, efficacy, and quality controllability of the products after the changes.	The changes will cause significant changes in the medicinal substance bases.
		The applications for the revision of IFUs do not meet the technical requirements of the writing of IFUs.
		The literature used to support the changes is biased, or the clinical safety and efficacy data are not sufficient.
Others	The development of biosimilars lacks data demonstrating the similarity to the reference drugs, or the selection of the reference drugs has defects.	
	The preclinical study results of the biosimilars are not sufficient to support the conducting of clinical trials.	
	The study materials of natural medicines do not meet the basic technical requirements of multi-regional clinical trials or the evaluation of natural medicines in China.	

According to the data provided in the 2021 Report, 542 applications were concluded as disapproved/recommended for disapproval after technical review, of which 66.3% were due to the applicants' failure to supplement materials within time limit, and 33.7% were due to the failure of application materials to prove the safety, efficacy or quality of the drugs. CDE has pointed out that, overall, the main issues in the registration applications in 2021 have great similarity with that in the previous years, but there are also some changes that deserve attention:

Firstly, new issues that emerged in 2021 include the failure of applicants to submit study materials as requested by the regulatory authorities during pre-IND communications, resulting in the lack of study materials during the review period of IND applications. According to Article 88 of the current *Measures for the Administration of Drug Registration*, the applicant shall not submit supplementary technical materials during the review period for an application for clinical trials or a supplementary application during the clinical trials. Therefore, if the applicant fails to submit the study materials that

have been requested by the regulatory authorities during the communications, the application will not be approved.

Secondly, the 2020 Report has listed 12 main issues and 19 specific issues, while the 2021 Report has listed 28 main issues but no specific issues. Although the classification of issues in the 2020 Report and the 2021 Report are not the same, CDE has implied that the number of drug varieties rejected due to certain reasons in 2021 has changed compared with in 2020: (i) there were no application rejected due to lack of communication in 2021; (ii) the number of applications of Class 3 chemical drugs rejected due to lack of clinical data on domestic efficacy and safety has increased significantly in 2021 compared to previous years; (iii) the number of applications rejected due to compliance issues was decreasing in 2021 compared to previous years; and (iv) the number of applications rejected due to the reasonability of the establishment of R&D projects has increased significantly in 2021.

II. Insights and suggestions

With reference to CDE's analysis of the aforementioned issues, participants in drug R&D and registration may consider the following recommendations:

Firstly, need to pay attention to the basis of drug R&D projects. In recent years, as more attention is paid to the regulatory compliance issues related to drug registration applications, the non-compliance issues have been relatively reduced. However, beside red lines, the reasonability of the drug R&D projects must also be taken seriously as CDE has been raising the quality requirements for drug R&D. The Reports emphasize that the R&D of drugs should be based on clinical needs, and should especially aim at fulfilling those unmet clinical needs. The R&D of drugs should be oriented by clinical value and should avoid low-level or repetitive development. The clinical value and advantages of Class 2 chemical drugs should be fully evaluated.

Secondly, the communication mechanism should be properly utilized. Relevant parties should be aware that the communication mechanism not only offers important facilities for registration applications, but also may provide specific regulatory requirements to registration applications. On one hand, the applicants can make full use of the communication mechanism to strengthen their communication with regulatory authorities in all aspects of drug development, so to eliminate information asymmetry and reach consensus. On the other hand, the applicants must pay attention to and follow the requirements provided by regulatory authorities during the communication; otherwise, the registration applications may fail.

Thirdly, updates of the filing requirements for drug registration made by regulatory authorities should be timely followed. As mentioned above, after the implementation of the current *Measures for the Administration of Drug Registration*, the requirements for the registration applications of Class 3 chemical drugs have been adjusted, and the 2020 *Clinical Technical Requirements for Drugs Marketed Overseas but Not Marketed in China* clearly stipulates the requirements of the clinical trials for the registration of Class 3 chemical drugs. Understanding and following these latest regulatory requirements helps to avoid issues such as the failure of registration of Class 3 chemical drugs for lack of clinical data on domestic efficacy and safety.

Finally, basic research of innovative drug development in the early stage should be strengthened. The Reports have mentioned that it is advisable to do sufficient assessment on the druggability for certain new mechanisms of action and new targets and to carry out as many proof-of-concept studies as possible to reduce the risk of subsequent development, so that the waste of research resources can be avoided.

Time management of drug review and approval

I. Drug Lags and its causes

The backlog of drug review and approval ("**Drug Lags**") has long been a serious issue for China's drug administration department. The 2015 Report clearly states that "the large amount of backlog of review tasks has become a huge obstacle to the achievement of scientific supervision and healthy development of the industry". At its peak in 2015, CDE had a backlog of over 22,000 review tasks. Therefore, it has become an arduous task for the authorities to solve the Drug Lag issue.

There are many reasons for the Drug Lags: First, there is an unbalance between the review workload and the review capacity. After the year of 2000, the authority of drug review and approval was taken over by the central government. As a result, review and approval tasks that were originally scattered in the provincial governments become centralized. The huge increase in review workload severely challenges the meager resources of drug review. Second, review timelines are lengthy and continually delayed. According to statistics, between the year of 2013 and 2015, the average delay period for the review and approval of the applications for innovative drug clinical trials in China is 14 months[2]. Finally, serious problems of poor-quality and duplicate fillings and incomplete, untrue and non-standardized filling materials have further led to the Drug Lags.

II. Main countermeasures

According to the *Opinions of the State Council on Reform of the Review and Approval System of Drugs and Medical Devices* ("**Notion No.44**"), settlement of Drug Lags is one of the primary goals of the system reform. Notion No.44 proposes to "clear the backlog by the end of 2016, achieve yearly balance between registration applications and reviewed cases as soon as possible, and reach the goal of reviewing and approving in accordance with prescribed time limit by 2018."

In order to solve the Drug Lags, China has adopted, including but not limited to, the following measures in recent years：

First, to conduct self-examination and verification of drug clinical trial data. As mentioned above, untrue and non-standardized filings is one of the reasons for the Drug Lags. To this end, the former State Food and Drug Administration of China ("**CFDA**") issued the *Notice on the Self-examination and Verification of Drug Clinical Trial Data* ("the **Notice**") on July 22, 2015, to verify the clinical trial data of received registration application for drugs that are applying for manufacturing or importation. The Notice requires 1,622 clinical trial projects to conduct self-examination and voluntarily withdraw itself

[2] Zhou Q, Chen XY, Yang ZM, Wu YL (2017), The Changing Landscape of Clinical Trial Approval Processes in China, Nature Reviews Clinical Oncology 14:577–583.

in case of any problem discovered. If failing to submit a report or withdraw the application within prescribed time limit, unannounced inspections would be conducted. Once any problem were discovered, the relevant applicant, clinical trial institution and personnel related would face serious administrative penalties. As of December 31, 2015, 1,009 drug registration applications had been voluntarily withdrawn by the applicants, representing 62.2% of the total drug registration applications, involving hundreds of drug companies. Subsequently, *Working Procedures for Drug Clinical Trial Data Verification (Interim)*, *Drug Administration Law*, *Measures for the Administration of Drug Registration*, *Start-up Working Procedures for Verification and Inspection of Drug Registration*, *Working Procedures for Drug Registration Verification (for Trial Implementation)*, *Key Points and Principles for Drug Registration Verification (Drug Clinical Trial) (for Trial Implementation)*, and other relevant regulations were issued one after another. Self-examination and verification of drug clinical trial data changes from an unexpected regulatory storm to a sophisticated, long-term regulatory system. Implementing the self-examination and verification of drug clinical trial data has both decreased the quantity of low-quality registration applications and improved the overall quality of registration applications, significantly assisting in the reduction of application backlog.

Second, to establish the implied approval policy for clinical trials. As mentioned above, the delay of review and approval, especially in clinical trial application is one of the reasons for the Drug Lags. In this regard, *Opinions on Deepening the Reform of the Review and Approval Systems and Encouraging Innovation on Drugs and Medical Devices* proposes to optimize the approval procedures for clinical trial application. Accordingly, drug administration department shall be deemed to have approved if it does not give a denial or doubting opinions within a given period after accepting an application for clinical trial, and the registration applicant may conduct the clinical trial in accordance with the submitted protocol. Later in 2019, Article 19 of the revised *Drug Administration Law* formally established the implied approval policy for clinical trial applications in China, significantly shortening the review and approval time limit to 60 working days. This greatly accelerates the review and approval process of drug clinical trials in China.

Third, the establishment of expediting registration procedures for drug marketing. Chapter IV of the *Administrative Measures for Drug Registration* revised in 2020 provides principal provisions on the procedures for breakthrough therapy designation, conditional approval, prioritized review and approval and procedures for special approval. The follow-up legislations including the *Working Procedures for Breakthrough Therapy Designation (for Trial Implementation)*, *Working Procedures for the Review* and *Approval Procedures for Conditional Approval of Drug Marketing Applications (for Trial Implementation)* and the *Working Procedures for the Prioritized Review and Approval Procedures for Drug Marketing Applications (for Trial Implementation)* further promote the implementation of expediting registration procedures.

Fourth, the expansion of the review capacity. The 2019 Report proposes “to expand review capacity through multiple channels including but not limited to large-scale recruitment of personnel and secondment of provincial bureau personnel”. Later in 2021, the Report emphasizes to promote team building by “actively coordinating and increasing staffing, promoting the recruitment of talent based on review needs, and reinforcing the professional review capacity”. It is thus clear that promoting team

building has always been the focus of CDE in recent years.

III. Achievements and progress

According to the data from annual Reports, the Drug Lags was progressively reduced from 2015 to 2018. In 2015, the number of applications for review was reduced from more than 22,000 at the peak to less than 17,000 at the end of the year; in 2016, the number of applications for review dropped to nearly 8,200; In 2017, the number of applications for review dropped to 4,000, basically reaching the goal of eliminating the Drug Lags stipulated in Notion No.44. In 2018, the number of applications for review dropped to 3,440, further consolidating the requirement of Notion No.44.

The 2019 Report points out that the Drug Lags was basically eliminated in 2019, and the work focus of CDE has gradually shifted from resolving Drug Lags to improving the percentage of drug registration application received and approved in time ("**Timeliness Percentage**"). According to the data annually published by CDE, the overall Timeliness Percentage throughout the whole year increased year by year from 2019 to 2021. Timeliness Percentage for traditional Chinese medicine, chemical medicine and biological products reached 90% in 2019, 94.48% in 2020 and 98.93% in 2021.

Amendment to chemical drug registration classification and application

I. Amendment to chemical drug registration classification

China modified the registration classification of chemical drugs in 2016, in which the definitions of new drugs and generic drugs have been amended, thus the scope of new drugs is narrowed down and that of generic drugs is expanded. Compared with the registration classification requirements in 2007, the definition of new drugs in China has changed from "new in China" to "new worldwide", i.e., new drugs must have not been marketed in China or overseas, and new drugs are further divided into Class 1 (innovative drugs) and Class 2 (modified new drugs).

"Drugs manufactured by domestic applicants by imitating the patent drugs that have been marketed overseas but not yet in China ", which used to be classified as new drugs, are now identified as generic drugs. Amendments to the registration classification are listed in the table below.

Previous registration classification	Current registration classification
According to the 2007 *Requirements for Registration Classification and Application Dossiers of Chemical Drugs* ("**the Registration Requirements**"), chemical drugs are classified into 6 categories, Class 3 drugs, "drugs that have been marketed overseas but not yet in China", fell under the category of new drugs and should be filed in accordance with the procedures for new drugs.	In 2015, the State Council issued Notion No.44, which stated that the registration classification of drugs shall be reformed and adjusted. The definition of new drugs is adjusted from **"drugs that have not been marketed in China" to "drugs that have not been marketed in China and overseas"**. The definition of generic drugs is adjusted from "drugs manufactured in reference to existing national drug standard" to "drugs that have proven consistency of quality and efficacy with the patent drugs". In 2016, CFDA issued the *Work Plan for the Reform of Chemical Drugs Registration Classification*, which

Previous registration classification	Current registration classification
	modifies the registration classification of chemical drugs to 5 categories and clarifies the regulatory requirements for chemical drugs registration of various categories. Class 3 drugs, "drugs manufactured by domestic applicants by imitating the patent drugs that have been marketed overseas but not yet in China" shall be filed in accordance with the procedures for generic drugs. After the promulgation of *2020 Measures for the Administration of Drug Registration* and to facilitate its implementation, NMPA formulated and issued the new version of the *Requirements for Registration Classification and Application Dossiers of Chemical Drugs*, in which the provisions on the registration classification of chemical drugs are basically consistent with those in the 2016 reform work plan.

II. Consistency of requirements for application dossiers and international standards

Compared with the version 2007 and 2020 of the Registration Requirements, China's regulatory requirements for application dossiers on the registration of chemical drugs have also changed. Version 2020 of the Registration Requirements requires to clarify the requirements for application dossiers with reference to the technical guidance of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use ("**ICH**").

ICH is an international institution for the harmonisation of technical requirements for pharmaceuticals for human use of global significance. In 2017, China officially joined the ICH and in 2018, China's health regulatory authority was elected as a member of the ICH Management Committee. To promote the alignment of technical standards for drug registration with international standards, CFDA issued the *Announcement on Application of the Second Level Guiding Principles of the ICH*, which clarifies that since 1 February 2018, the registration applications for Chemical Drug of Class 1 and 5.1, therapeutic biologics of Class 1 and prophylactic biologics of Class 1 shall subject to the *M4: Common Technical Document for the Registration Application of Pharmaceuticals for Human Use* ("**Document M4**").

Version 2020 of the Requirements requires that while filling for drug clinical trials, drug marketing registration and chemical APIs, the applicants shall conduct the study in accordance with requirements of relevant technical guidance promulgated by NMPA, collate and submit the application dossiers as per the format number and item order of the current version of Document M4.

III. Impact of changes in classification and application dossiers requirements on chemical drugs registration

1. Overall impact

Firstly, the registration threshold of R&D and innovation level for new drugs has been raised. The new registration classification has narrowed the scope of new drugs and raised the requirements for companies' R&D capabilities. And for modified new drugs under the new classification, they are required to have a "definitive clinical advantage" over the patent drug, which will effectively curb the possibility of drugs registering as new drugs with a low level of innovation, such as a change in dosage form or a change in route of administration.

Secondly, the registration of generic drugs faces stricter regulatory requirements. Current registration classification defines generic drugs more precisely and provides stricter regulatory requirements, emphasizing the consistency in quality and efficacy between generic drugs and reference preparations. Class 3 drugs that were classified as new drugs under the old classification are classified as generic drugs under the new classification, and the corresponding new drug observation period has been abolished. However, regulatory requirements for the drug review have been increased rather than decreased, requiring consistency evaluation with the patent drugs. Therefore, companies who manufacture Class 3 drugs that have been marketed overseas, but not yet in China, will be subject to stricter and higher regulatory standards.

2. Impact on registration application of class 3 drugs

Changes in the requirements of application dossier for chemical Class 3 drugs have affected the results of their registration applications. The 2021 Report points out that "the number of marketing registration applications for chemical Class 3 drugs, which were not approved due to the lack of domestic clinical data regarding efficacy and safety, has increased significantly compared with previous years." It is worth noting that the application for marketing registration of chemical Class 3 drugs is not completely exempt from the domestic clinical trial requirements, which was stipulated in *Clinical Technical Requirements for Drugs Marketed Overseas but Not Marketed in China*, stating that, based on factors such as racial sensitivity analyses, the accessibility of complete clinical data of patent drugs and pharmaceutics factors of generic drugs, drugs marketed overseas but not marketed in China still requires clinical trials in China to assess the safety and efficacy of drugs in Chinese patients.

The development of generic drug consistency evaluation system

I. The establishment and development of consistency evaluation system

The modified definition of generic drugs, from "drugs manufactured in reference to existing national drug standard" to "drugs that have proven consistency of quality and efficacy with the patent drugs", emphasizes that generic drugs should be able to achieve the same level of quality and efficacy as the patent drugs. The establishment and development of the consistency evaluation system for generic drugs is conducive to improving the quality of generic drugs, promoting the pharmaceutical industry, and effectively maintaining the medication safety.

1. Policy BASIS

Since 2015, China has issued a series of policy documents to promote the establishment and development of generic drug consistency evaluation system.

Effective date	Issuing authority	Name of policy	Key points
2015.08.09	State Council	*Opinions of the State Council on Reform of the Review and Approval System of Drugs and Medical Devices*	**Improve the quality of generic drugs. Expediting the quality consistency evaluation of generic drugs** and aiming to complete the quality consistency evaluation of oral preparations and reference preparations in national essential medicines list by the end of 2018.
2016.02.26	General Office of State Council	*Opinions of the State Council on Performing Consistency Evaluation of the Quality and Efficacy of Generic Drugs*	Put forward a series of opinions on how to perform the consistency evaluation, including: **to specify the objects and time limit of evaluation, to determine the principle for reference preparations selection, to adopt reasonable evaluation methods, to require enterprises to assume responsibility, to strengthen the management of consistency evaluation and to encourage companies to conduct consistency evaluation**.
2017.08.25	NMPA (CFDA)	*Announcement of State Food and Drug Administration on Matters Relating to the Consistency Evaluation of Quality and Efficacy of Generic Drugs*	Prescribe the **selection of reference preparations, registration of bioequivalence tests, time limits for evaluation and approval of the consistency evaluation**, and other issues, and further clarifies **application methods** for the consistency evaluation of generic drugs.
2018.12.28	NMPA	*Announcement on Matters Concerning the Consistency Evaluation of the Quality and Efficacy of Generic Drugs*	Put forward requirements, including: "**strict evaluation standards, strengthened post-market supervision**", "**reasonable adjustment of time limits and evaluation requirements**".

Effective date	Issuing authority	Name of policy	Key points
2020.05.12	NMPA	*Announcement on Performing Consistency Evaluation of the Quality and Efficacy of Generic Chemical Injections*	Initiate the consistency evaluation of **Generic Chemical Injections**.

2. Progress of generic drug consistency evaluation

CDE has officially undertaken the overall work of consistency evaluation since August 2017. Since then, vigorously performing and promoting the consistency evaluation of generic drugs has been included in the CDE's annual priorities. The main achievements of CDE in promoting the evaluation in recent years are listed in the following table.

Main achievements	Specific performance
Continuous Performance and Regulation of Selection of Reference Preparations	On March 25, 2019, NMPA released the *Procedures for Selection and Determination of Reference Preparations for Chemical Generic Drugs* to regulate the selection procedures for reference preparations.
	On October 16, 2020, CDE released the *Requirements on Application Materials for Selecting Reference Preparations of Chemical Generic Drugs*, which further emphasizes the self-examination of applicants and improves the efficiency of reference preparation selection.
	The 2021 Report points out that, since the implementation of the consistency evaluation started in August 2017, there have been 49 batches catalogues of RLDsissued in total, involving 4,677 specifications (1,967 varieties), including 1,253 specifications (477 varieties) for injections, involving 850 specifications (527 varieties) issued in 2021.
Continuous Improvement and Optimization of Consistency Evaluation	Completing the collection of relevant data on marketed chemical drugs in China. According to the 2021 Report, in order to better perform the consistency evaluation, CDE has conducted analyses and studies on drug varieties with clear clinical value but without reference preparations, domestic innovative drug varieties and peculiar drug varieties of China, providing guidance for the further work.
	Draft a series of technical requirements and guidance to gradually improve the review standard system: According to the 2021 Report, CDE has developed technical requirements of pharmacological research for 75 varieties and has drafted 27 guidelines for bioequivalence study of individual drugs.
Information Disclosure & Communication	Establish "Generic Drug Consistency Evaluation Column" on the website to disclose policies, regulations and technical guidelines, instruction of various specifications, research paper of enterprises, various data including trial data of bioequivalence tests and other information. Accept consultations and launch "100

Main achievements	Specific performance
	Q&As of Consistency Evaluation".
	Actively hold communication meetings, seminars, symposiums, etc., publicize various technical requirements, application materials requirements, etc., answer queries from the industry and to listen to the comments and suggestions from enterprises.

3. Postponement of consistency evaluation of 289 essential list

Before the definition modification of generic drugs, generic drugs approved for marketing in China did not have mandatory requirements of consistency evaluation with patent drugs, resulting in certain gaps between some generic drugs and patent drugs in quality and efficacy.

To perform consistency evaluation for generic drugs that have been approved for marketing before the implementation of the new registration classification, General Office of State Council issued the *Opinions of the State Council on Performing Consistency Evaluation of the Quality and Efficacy of Generic Drugs*, stipulating that oral solid dosage forms of chemical drugs, approved for marketing before October 1, 2007, in the *National Essential Medicine List (2012 Edition)* ("289 Essential List") should complete consistency evaluations by the end of 2018 while specifications requisite for clinical effectiveness test or under special circumstances should complete consistency evaluations by the end of 2021. In case of overdue evaluation, the re-registration will be denied.

However, due to the small size and weak economic strength of many generic pharmaceutical enterprises in China, consistency evaluation constitutes a heavy burden for these SMEs.

On December 28, 2018, NMPA issued the *Announcement on Matters Concerning the Consistency Evaluation of the Quality and Efficacy of Generic Drugs*, proposing that for generic drugs that have been included in the national essential medicines list, the consistency evaluation timelines are no longer uniformly set, and companies are allowed to apply for an appropriate extension. Considering the importance of essential medicines to the public, the postponement of the consistency evaluation of 289 Essential List in 2018 is a scientific and reasonable adjustment.

II. Increasing specification of consistency evaluation

According to the Reports, the specifications evaluated and approved by CDE continued to rise between 2017 and 2021. In 2017, a total of 17 specifications (13 varieties) was evaluated and approved; while by 2021, the number of specifications evaluated and approved reached 331, achieving a significant growth.

The diversification of RLDs, on the one hand, expands the public's choice of generic drug and effectively reduces drug costs, and on the other hand, promotes the competitive development of pharmaceutical enterprises and facilitates centralized drug procurement.

III. Overall high percentage of consistency evaluation performed in time

The 2017 *Announcement of State Food and Drug Administration on Matters Relating to the*

Consistency Evaluation of Quality and Efficacy of Generic Drugs specifies the time limits of consistency evaluation: (a) formal review of application materials shall be conducted within 15 working days from the date of receipt of such documents to determine whether to accept the materials or not; (b) after the acceptance, filling reviews shall be conducted by the CDE and applications that meet the requirements shall be filed within 45 working days; (c) In case applicants are required to submit supplementary materials, all the supplementary materials should be submitted within four months at once. In the aforementioned case, follow-up technical evaluation shall be conducted in 40 working days while administrative evaluation within 20 working days.

Due to the great importance attached to the performance of generic drug consistency evaluation, CDE concentrates review resources and prioritizes the consistency evaluation. According to the statistics as of the end of 2019, the overall percentage of consistency evaluation performed in time is above 90%, with a median review time frame of approximately 124 working days[3]. According to 2021 Report, the percentage of consistency evaluation performed in time in 2021 reaches 98.80%.

The Rapid development of biopharmaceutical industry

With the continuous development of biotechnology, global biopharmaceuticals have entered a stage of rapid development. Although China's biopharmaceutical industry started relatively late than the global market, it has shown a vigorous development trend and its market scale has continued to expand in recent years. In the Reports, we can see China's gratifying achievements in the development of biopharmaceuticals, including the growing number of registration applications and approvals of biologics, the active R&D of biosimilars, and the strong development of biotech companies.

I. The registration applications and reviews of biologics in the past 7 years

From 2015 to 2021, the number of registration applications of biologics increases every year and is over 1,000 since 2019. Moreover, the number of review completions, together with the number of approvals/recommended for approvals is also growing during these 7 years.

Year	Application received	Review completed	Approvals / recommended for approvals			
			Biologics IND	Innovative biologics IND	Biologics NDA	Innovative biologics NDA
2015	567	543	150	-	19	-
2016	410	646	271	-	17	-
2017	632	678	227	50	29	2
2018	944	971	349	103	41	4
2019	1179	1104	312	120	74	5
2020	1867	1410	500	225	89	7
2021	2113	1920	764	537	149	23

[3] Chen X, Wu Q, Wen BS (2020), Progress and Prospects of Consistency Evaluation of Quality and Efficacy of Chemical Generic Drugs, China Journal of New Drugs: 2185-2189.

In addition, in each years' Reports, a number of biologics have been listed as approved varieties in key therapeutic areas, such as 13-valent pneumococcal conjugate vaccines, recombinant Ebola vaccines (adenovirus vector), 9-valent human papillomavirus vaccines (saccharomyces cerevisiae), 13-valent pneumococcal polysaccharide conjugate vaccines, recombinant zoster (CHO cell) vaccines, bivalent human papillomavirus vaccines (E. coli), nasal spray live attenuated influenza vaccines, COVID-19 vaccines, etc.

II. Biosimilars development period

Biosimilars are therapeutic biologics that are similar in quality, safety and efficacy to those approved reference biologics. Biosimilars can help increase access to and reduce prices for biologics, which help satisfying the public demand for biotherapeutic products. To promote the development of biosimilars, China has issued a series of policies and guidelines since 2015 to standardize the registration administration and support the R&D of biosimilars.

1. The development of policies related to biosimilars

Issue date	Authorities	Policies	Key contents
2015.02.28	NMPA	*Technical Guideline for the Research, Development and Evaluation of Biosimilars (for Trial Implementation)*	Clarifying the definition of biosimilars for the first time and stipulating the basic principles for the R&D, pharmaceutical studies, non-clinical studies, clinical studies, IFUs, pharmacovigilance and other aspects of biosimilars.
2017.07.19	CDE	*Notice of Solicitation of Public Comment on Consideration of Clinical Study Design and Review of Biosimilars of Bevacizumab Injection*	It was the first time for CDE to formulate the key points of review for a single variety. This help to provide reference for the development of this variety.
2017.10.08	General Office of the Central Committee of the CPC and the General Office of State Council	*Opinions on Deepening the Reform of Review and Approval System and Encouraging the Innovation of Drugs and Medical Devices*	Explicitly proposing to support the development of biosimilars.
2017.12.13	National Development and Reform Commission	*Three-year Action Plan to Enhance the Core Competence of the Manufacturing Industry (2018-2020)*	Encouraging the development and industrialization of first generic drugs and first biosimilars with high market potential and high clinical value; clarifying that the first biosimilars are high-end drugs.

Issue date	Authorities	Policies	Key contents
2020.01.22	State Administration for Market Regulation (SAMR)	*Measures for the Administration of Drug Registration* (2020)	Further standardizing the registration classification of biosimilars.
2020.06.29	NMPA	*Requirements for Registration Classification and Application Dossiers of Biological Products*	Further specifying the registration classification and requirements of applications for biosimilars.
2021.02.10	CDE	*Technical Guidelines for the Evaluation of Similarity and the Extrapolation of Indications of Biosimilars*	Further supplementing the guidance on the evaluation of similarity and the extrapolation of indications of biosimilars, aiming to provide technical references for the industry.
2022.01.20-2022.04.01	CDE	*Technical Guidelines for Clinical Pharmacology Research of Biosimilars*	Providing further regulation and guidance for the R&D and review of biosimilars.

In addition, in January 2021, the deputy director of the National Healthcare Security Administration clearly indicated that biosimilars will be included in the centralized procurement of drugs in the near future. As for now, some provinces, such as Guangdong, have already included biosimilars into the centralized procurement[4].

Moreover, in recent years, CDE has successively issued a series of technical guidelines for specific varieties based on their characteristics, which provides great guidance for the R&D of relevant biosimilars.

2. The application and approval of biosimilars

On February 22, 2019, NMPA has approved the marketing registration application for HLX01, which is developed by Henlius and provides an alternative treatment option for patients with non-Hodgkin's lymphoma (NHL). Henlius's HLX01 is the first biosimilar approved in China. According to incomplete statistics, by the end of 2020, NMPA has approved the marketing of 14 biosimilars, involving 7 reference biologics. The number of biosimilars on the domestic market is continuously growing since 2021.

3. The application procedure for biosimilars

It is worth noticing that, unlike generic drugs, the registration applications for biosimilars shall be under the procedures of NDA instead of ANDA. This has been stated in the 2007 *Measures for the Administration of Drug Registration* and the 2015 *Technical Guideline for the Research, Development and Evaluation of Biosimilars (for Trial Implementation)*. Comparing with chemical drugs, biological

[4] https://www.gdmede.com.cn/announcement/announcement/detail?id=1496341402903121920.

products have more complex structures and more complicated manufacture processes. Therefore, it is difficult to make complete replications of biological products. This is the reason why the registration applications for biosimilars must be under the procedures of NDA instead of ANDA.

III. Biotech companies are growing fast

In recent years, a number of biotech companies with biologics as their main business have grown rapidly and have completed their IPOs. For example, Henlius (HK.02696), CARsgen (HK.2171), JW Therapeutics (HK. 2126) and Immunotech Biopharm (HK.6978) have been listed in Hong Kong; Gracell (GRCLO) and Legend Biotech (LEGN.O) have been listed on Nasdaq; Chongqing Zhifei Biological Products Co., Ltd. (300122.SZ), Kexing Biopharm (688136.SH), CanSinoBIO (688185.SH), and Sunshine Guojian (68833.SH) have been listed on Shenzhen Stock Exchange or Shanghai Stock Exchange.

The review and approval of pediatric drugs and orphan drugs

I. Achievements in the review and approval of pediatric drugs and orphan drugs

In recent years, benefited from the development of the prioritized review and approval system for pediatric drugs and orphan drugs, great progress has been achieved in the review and approval of pediatric drugs and orphan drugs

1. Data on the review and approval of pediatric drugs from 2016 to 2021

A. Number and proportion of registration applications included in the prioritized review and approval system

Year	Objects	Number	Proportion in all applications included in the prioritized review and approval system
2016	Pediatric drugs	17	9.0%
2017		30	13.0%
2018		35	11.2%
2019		24	9.5%
2020[5]		14	9.7%
	New varieties, formulations and specifications of pediatric drugs that meet the physiological characteristics of children	7	9.3%
2021		34	29.6%

[5] The 2020 *Measures for the Administration of Drug Registration* modified the name of the types of drugs included in the prioritized review and approval system. This table analyzed relevant data regarding "pediatric drugs" (before July 1, 2020) and "new varieties, formulations and specifications of pediatric drugs that meet the physiological characteristics of children" (after July 1, 2020).

B. Number and proportion of varieties passing the prioritized review

Year	Objects	Varieties	Proportion in all varieties passing the prioritized review
2016	Pediatric drugs	4	57.1%
2017		1	2.0%
2018		9	10.8%
2019		7	8.5%
2020		8	7%
	New varieties, formulations and specifications of pediatric drugs that meet the physiological characteristics of children	9	6.92%
2021		9	10.11%

2. Data on the review and approval of orphan drugs from 2016 to 2021

A. Number and proportion of registration applications included in the prioritized review and approval system

Year	Objects	Number	Proportion in all applications included in the prioritized review and approval system
2016	Orphan drugs	8	4.1%
2017		11	5.0%
2018		28	8.9%
2019		28	11.1%
2020[6]		21	14.6%
	Drugs urgently needed in in clinical settings and in shortage, innovative drugs and improved new drugs for the prevention and treatment of major infectious diseases and rare diseases	14	18.7%
2021		5	4.35%

[6] The 2020 *Measures for the Administration of Drug Registration* modified the name of the types of drugs included in the prioritized review and approval system. This table analyzed relevant data regarding "orphan drugs" (before July 1, 2020) and "drugs urgently needed in in clinical settings and in shortage, innovative drugs and improved new drugs for the prevention and treatment of major infectious diseases and rare diseases" (after July 1, 2020).

B. Number and proportion of varieties passing the prioritized review

Year	Objects	Varieties	Proportion in all varieties passing the prioritized review
2016	Orphan drugs	—	—
2017		—	—
2018		3	3.6%
2019		6	7.3%
2020		11	9.0%
	Drugs urgently needed in in clinical settings and in shortage, innovative drugs and improved new drugs for the prevention and treatment of major infectious diseases and rare diseases	13	10.0%
2021		9	10.11%

II. The development of policies related to the prioritized review and approval system for pediatric drugs and orphan drugs

The R&D of pediatric drugs and orphan drugs usually takes long time and high costs and is full of difficulties. Therefore, many companies are not willing to develop these drugs, and these drugs are often in shortage. In order to encourage the R&D and manufacture of pediatric drugs and orphan drugs, China has issued a series of policies in recent years to improve the prioritized review and approval system for pediatric drugs and orphan drugs.

Issue date	Authorities	Policies	Key contents
2015.11.11	NMPA (CFDA)	*Announcement on Several Policies for Drug Registration, Review and Approval*	Separately processing the registration applications of innovative orphan drugs and pediatric drugs and accelerating the review and approval of these drugs.
2016.01.29	NMPA (CFDA)	*Basic Principles of Evaluation for Applications of Pediatric Drugs Included in the Prioritized Review and Approval System and in Urgent Clinical Need*	Providing basic guidelines for the prioritized review and approval of pediatric drugs that are urgently needed in clinical settings.
2016.02.26	NMPA (CFDA)	*Opinions on the Implementation of the Prioritized Review and Approval System to Resolve Backlogged Drug Registration*	Including registration applications of pediatric drugs and orphan drugs with obvious clinical advantages into the scope of the prioritized review and approval system.

Issue date	Authorities	Policies	Key contents
		Applications	
2017.12.21	NMPA (CFDA)	*Opinions on Encouraging Drug Innovation and Implementing the Prioritized Review and Approval System*	The same as above.
2020.01.22	SAMR	*Measures for the Administration of Drug Registration* (2020)	Article 68 indicated that innovative drugs and improved new drugs for prevention and treatment of rare diseases and new varieties, formulations and specifications of pediatric drugs that meet the physiological characteristics of children may apply for application of procedures for prioritized review and approval.
2020.07.07	NMPA	*Priority Review and Approval Procedures for Drug Marketing Authorizations (for Trial Implementation)*	Providing specific and detailed information on the conditions of application, procedures, requirements of the prioritized review and approval.

III. Other highlights on the reform of the review and approval system for pediatric drugs and orphan drugs

1. Highlights on the reform of the review and approval system for pediatric drugs

In the 2021 Report, CDE has listed its work in promoting pediatric drugs. The measures include improving the mechanism for the review of pediatric drugs, establishing working groups, and improving the standards and guidelines for pediatric drugs, etc.

2. Highlights on the reform of the review and approval system for orphan drugs

The 2020 *Measures for the Administration of Drug Registration* stipulates that under the prioritized review and approval system, the time limit for review of orphan drugs marketed overseas but not in China that are urgently needed in clinical settings is 70 days. According to the 2020 Report, the reviews of orphan drugs urgently needed in clinical settings were all completed within the time limit, and all reviews of orphan drugs was completed within 3 months.

In 2021, CDE has issued the *Technical Guidelines for the Clinical Development of Orphan Drugs*, intending to promote the R&D of more orphan drugs in China and bring more hope to those patients suffering rare diseases.

Conclusion

This article provides an overview on the Reports from 2015 to 2021, sorts out the current situation and future trend of registration applications and reviews and approvals of various types of drugs, and

summarizes the gratifying achievements made by CDE in the reform of the drug review and approval system in recent years. China's pharmaceutical industry is experiencing a period of rapid development. The reform of the drug review and approval system can better support the innovation of drugs and meet the public demand for drugs, thus making China's development and regulation of drugs reach the international leading level. With the continuous improvement of China's drug registration system and the joint efforts of the industry, we believe that drug reviews in China will be more high-quality and efficient in the future.

Important Announcement

This Legal Commentary has been prepared for clients and professional associates of Han Kun Law Offices. Whilst every effort has been made to ensure accuracy, no responsibility can be accepted for errors and omissions, however caused. The information contained in this publication should not be relied on as legal advice and should not be regarded as a substitute for detailed advice in individual cases.

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