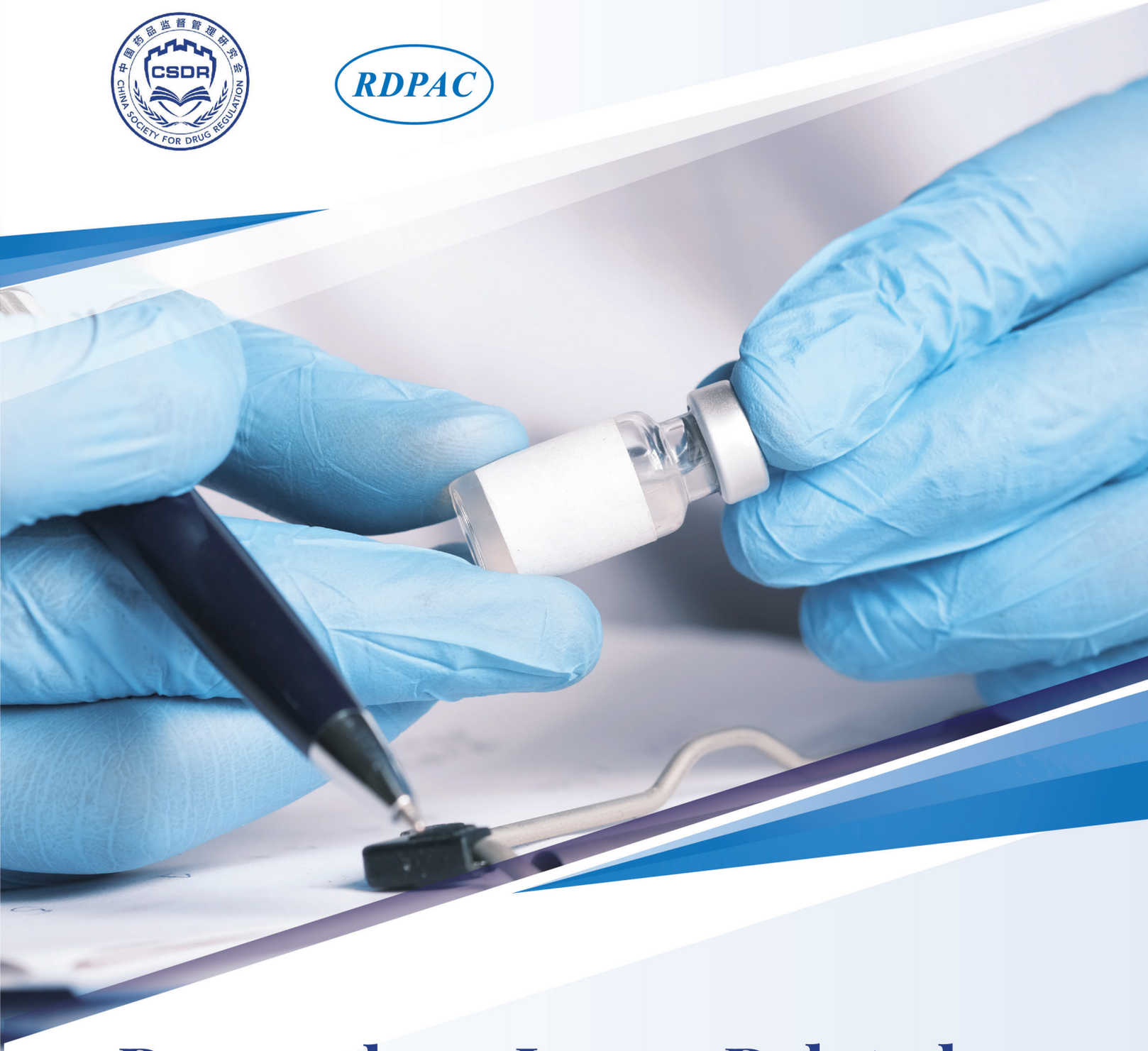


Research on Issues Related to the Management of Drug Registration Testing

China Society for Drug Regulation

R&D-based Pharmaceutical Association Committee (RDPAC)

December 2023

Research on Issues Related to the Management of Drug Registration Testing

China Society for Drug Regulation

Professional Committee on International Exchange and Cooperation in Drug Regulation

R&D-based Pharmaceutical Association Committee (RDPAC)

Research on Issues Related to the Management of Drug Registration Testing

Table of Contents

Chapter I Introduction ····· 01

1. Research Objectives and Background ····· 01
2. Comparison of Chinese and Foreign Regulations on Drug Registration Testing ····· 02
3. Issues in China's Drug Registration Testing ····· 02
4. Recommendations for Improvement in China's Drug Registration Testing ····· 03

Chapter II Research Plan and Methods ····· 05

Chapter III Overview of Main Regulations or Documents on Drug Registration Testing in China and Overseas and Analysis of the Differences ····· 07

1. Evolution and Development of Regulations on Drug Registration Testing in China ····· 07
2. Comparison of Requirements for Drug Registration Testing Between China and Other Major ICH Member States and Regions ····· 10
3. Enlightenment of Foreign Experience on China's Drug Registration Testing Management ····· 13

Chapter VI Analysis of Main Issues and Their Causes in China's Drug Registration Testing ····· 16

1. Issues and Causes in 2nd-Round Drug Registration Testing ····· 16
2. Issues and Causes in Drug Registration Testing for Post-Marketing Changes ····· 18
3. Issues and Causes in Optimizing the Specifications for Drug Registration Testing ····· 19
   - 3.1 Issues with Requirements for Samples and Standard Substances ····· 19
   - 3.2 Testing Related to Inter-Provincial Contract Manufacturing of MAHs ····· 22

Chapter V Reflections and Recommendations on Chinese Drug Registration Testing Management System ····· 23

1. Strengthen Communication among All Parties Involved in Drug Registration Testing ····· 25

1.1 Establish Efficient Communication Mechanism ····· 25

1.2 Establish Information Platform for Communication to Enhance Communication Efficiency ····· 26

2. Avoid 2nd-Round Drug Registration Testing and Optimize the Process to Accelerate Drug Marketing ····· 27

2.1 Strengthen Business Training to Enhance Mutual Understanding Among All Parties Concerned ····· 27

2.2 Establish Mechanism for Risk-Based Initiation of 2nd-Round Drug Registration Testing ····· 28

2.3 Optimize 2nd-Round Drug Registration Testing Related Procedure and Rationally Allocate Testing and Sample Resources ····· 28

3. Improve Drug Registration Testing Mechanism for Post-marketing Changes ····· 29

3.1 Clarify Drug Registration Testing Initiation Conditions for Post-marketing Changes and Flexibly Conduct Advance Testing ····· 29

3.2 Recommend to Clarify the Initiation Conditions for Drug Registration Testing for Post-marketing Changes and Relevant Documents ····· 29

4. Optimize Specification for Drug Registration Testing Procedure ····· 32

4.1 Issues Regarding Samples and Standard Substances ····· 32

4.2 Testing Issues in MAH Cross-Provincial Contract Manufacturing ····· 34

Chapter I Introduction

1. Research Objectives and Background

In accordance with Article 51 of the Provisions for Drug Registration: "Drug registration testing consists of specification verification and sample testing. Specification verification refers to laboratory assessment of the scientific basis of items included in the drug specifications submitted by the applicant, the feasibility of testing methods and the rationality of quality control criteria. Sample testing refers to laboratory testing conducted on samples according to the drug specifications submitted by the applicant or approved by CDE." Therefore, drug registration testing, as a critical part of drug review and approval, serves as an essential basis for China's Center for Drug Evaluation (CDE) to conduct drug review, and provides technical support to ensure the smooth conduct of post-marketing drug supervision and testing.

Following the implementation of the new Provisions for Drug Registration, China's regulatory authorities have been striving to boost regulatory efficiency and accelerate review and approval, with a view to enhancing the overarching landscape of drug R&D and manufacturing in China from multiple perspectives. However, as a crucial part, drug registration testing currently runs into various issues in China during the coordination and cooperation between multiple parties. These issues affect the efficiency and effectiveness of drug registration testing, and sometimes even become bottlenecks in drug approval and registration, so there is an urgent need to optimize drug registration testing. In this regard, the China Society for Drug Regulation (CSDR), adhering to the guiding principles of the document Implementing Opinions on Comprehensively Strengthening the Capacity Building of Drug Supervision issued by the General Office of the State Council and the principles of reinforcing the foundation, addressing weaknesses, overcoming bottlenecks, and fostering advancements in drug review and approval, deems it necessary to conduct relevant research in an effort to align with internationally recognized standards to further enhance a scientific, law-based, international and modern drug regulatory system. Hence, the project team was established in March 2023 to undertake the research on issues related to the management of drug registration testing.

In this research, the management of drug registration testing in the EU, the US and Japan was first summarized to analyze the similarities and differences in management between China and foreign countries; at the same time, adequate surveys were conducted among the parties involved in drug registration testing to identify and make an in-depth analysis of main issues in China's current drug registration testing management system. The ultimate objective was to provide relevant authorities with recommendations for short-term and long-term improvement in line with China's national conditions and the current development stage of drug registration testing.

2. Comparison of Chinese and Foreign Regulations on Drug Registration Testing

Since the 1980s, China has established a robust and professional drug regulatory workforce. Registration testing has undergone rounds of reform. Initially, drug registration testing was required for both clinical trial applications (CTAs) and marketing authorization applications (MAAs). Currently, except for vaccines, other drugs at the clinical research stage are exempted from drug registration testing, but drug registration testing is still required for MAAs, and for post-marketing major CMC changes based on the needs of review. In addition, drug registration testing has gone through the shift from initial sequential testing, subsequent parallel testing, to the current advance testing allowed for eligible applications. In the context of encouraging innovation, China has been exploring an efficient and feasible pathway for drug registration testing to support the goal of simultaneous global R&D and submission of MAAs with a view to benefiting Chinese patients.

The current regulations in China, the US, and the EU are similar in terms of the requirements for drug registration testing for drug registration applications. However, there are slight differences. In the US, the decision to initiate drug registration testing is made by the Center for Drug Evaluation and Research (CDER)/ Center for Biologics Evaluation and Research (CBER). In the EU, it is determined by the Committee for Medicinal Products for Human Use (CHMP), and the applicant is required to retain samples for testing. In China, drug registration testing is initiated by CDE based on the needs of registration review, with sampling and testing by regulatory authorities. In Japan, there is no requirement for drug registration testing in its current regulations.

In practice, the US Food and Drug Administration (FDA) rarely initiates drug registration testing during MAA review, except batch release procedures possibly initiated for some high-risk biological products (e.g., vaccines, blood products). In for-cause cases, FDA may request on-site sampling for testing at FDA laboratories during on-site inspection as part of review. The EU is like the US in that it has cause-triggered drug registration testing practices. In Japan, there is no drug registration testing process set for MAAs; however, marketing authorization holders (MAHs) are required to complete batch testing and release in Japanese laboratories (MAHs' own laboratories or contract laboratories), and MAHs are accountable for laboratories conducting the release. In China, drug registration testing is generally initiated for MAAs and most post-marketing major CMC changes; whether drug registration testing is conducted smoothly has a great impact on the final timeline for registration approval.

3. Issues in China's Drug Registration Testing

While acknowledging the importance of drug registration testing in registration review, it is challenging to successfully completing the transfer of testing methods between different laboratories and to obtain accurate and impartial results within the specified timeline. The conduct of testing is affected by multiple factors, including sample preparation, transportation, customs clearance (for imported drugs), standard writing of the submitted specifications, scientificity and operability of testing items, compatibility of instruments and equipment, and access to reference standards and special reagents. It is evident that drug registration testing is a systematic endeavor requiring effective collaboration among multiple parties to achieve the objectives.

By means of surveys among and qualitative interviews with testing institutions as well as Chinese and foreign companies, the project team collected several prominent common issues in drug registration testing: (1) Three parties (sponsors, the testing party, and the review party) all raised the issue of excessive "2nd-round drug registration testing". It burdens the parties involved, requiring additional financial and material resources, significantly reducing work efficiency, and delaying the review and approval timeline. Moreover, it gives rise to many secondary issues such as the provision of samples for testing and reference standards, which need to be resolved urgently. (2) Another issue raised by the parties involved is the excessive initiation of drug registration testing for supplementary applications related to post-marketing changes of drugs, in particular, for

supplementary applications arising from companies' efforts to optimize and enhance marketed products. The high frequency of drug registration testing prolongs the review timeline for CMC changes, which in turn impacts the continuous supply of drugs on the market and undoubtedly hinders the swift implementation of companies' optimization and enhancement. (3) The communication among the parties involved in drug registration testing is not smooth, with a lack of established communication mechanisms and an efficient and transparent information communication platform. (4) The requirements for providing registration samples and standard substances are not entirely reasonable. (5) Another issue is related to drug registration testing involving inter-provincial contract manufacturing of MAHs in China.

4. Recommendations for Improvement in China's Drug Registration Testing

With the development of the pharmaceutical industry and the alignment with international standards, the gap between Chinese and foreign companies is increasingly narrowing in terms of the technical level of R&D, manufacturing, and quality control. The MAH system, introduced in the amended Drug Administration Law issued and implemented in 2019 and the Provisions for Drug Registration issued and implemented in 2020, aligns with internationally recognized management models. MAHs should dutifully fulfill their responsibilities and obligations and be responsible for product management throughout the lifecycle, including manufacturing and quality release testing among other critical tasks. From a national regulatory perspective, the responsibilities of MAHs should be strengthened. The deterrence of regulatory testing should be enhanced by intensifying inspection and risk-based testing.

(1) Further refine the drug registration testing mechanism

It is undeniable that drug registration testing remains an integral part of registration review and functions as a crucial step in establishing China's drug registration specifications, completing the transfer of testing methods, and preparing for future marketing release testing (biological products, vaccines, and initial import of chemical drugs) and for sampling and testing for market surveillance. To better align with this objective, drug registration testing may be conducted flexibly. For example, advance testing is a good initiative. However, excessive constraints are placed on advance testing, greatly limiting its value in shortening the review timeline. Therefore, it is necessary to establish scientific and flexible requirements for advance testing. For instance, advance testing may be conducted under the conditions of well-established specifications and analytical methods as well as appropriately representative samples for testing, rather than the rigid requirement to be consistent with the final application dossiers or to use process validation samples for testing.

In terms of drug registration testing for post-marketing changes, the proportion of initiating drug registration testing should be reduced against the backdrop of companies' enhanced ability to manage risks and assume responsibilities. It is recommended to clarify the conditions for initiating drug registration testing for post-marketing changes, establish and publicize a list of post-marketing changes requiring the initiation of testing, and open the channel of advance drug registration testing for post-marketing change applications that necessitate drug registration testing. For post-marketing changes that have drug registration testing initiated, it is recommended that the review and approval timeline be 60/80 business days to ensure the advantages of advance testing in continuously optimizing the processes for post-marketing changes.

Furthermore, for post-marketing CMC changes, companies may employ a bracketing approach to determine the batches to be re-evaluated and validated based on change-related risks and scientific considerations, even if multiple manufacturing sites are involved. Therefore, the number of sample batches obtained for change research and validation is difficult to meet China's requirements for the batches for drug testing. That is, 3 batches of samples per strength and packaging form from different manufacturing sites are usually

not immediately available. As such, companies often have to wait for some time to accumulate sufficient batches before submitting change applications in China. This has somewhat impeded the post-marketing continuous optimization of processes and the implementation of quality control changes for some products. It is recommended to consider the validation batches of a product that pass the scientific risk assessment as the batches for drug testing for post-marketing changes and to avoid the rigid requirement for submitting 3 batches under all circumstances.

In summary, it is recommended to implement for-cause drug registration testing based on risks and review needs and initiate such testing for changes in analytical methods and post-marketing changes of high-risk products to minimize unnecessary drug registration testing.

(2) Enhance the communication among the parties involved in drug registration testing to minimize 2nd-round drug registration testing and accelerate drug marketing

Drug registration testing is complex and requires multi-party collaboration. A transparent and trustworthy communication mechanism is an effective means for smoothly conducting the testing and for minimizing "2nd-round" or "multiple round" drug registration testing. According to the feedback obtained from surveys, 2nd-round drug registration testing is a common pain point for the three parties, which not only increases the human and material resources for testing, but also greatly affects the review and approval timeline. In addition, it dilutes the dividends of simultaneous global R&D, and makes it difficult to achieve the goal of simultaneous marketing to benefit Chinese patients. Various issues encountered in drug registration testing, such as the adjustment of testing items and limits proposed for registration specifications, non-standard textual expression of specifications, and poor reproducibility due to non-smooth method transfer, may be resolved through communication during initial drug registration testing to avoid 2nd-round drug registration testing. More than 98% of the respondents acknowledge the importance of communication during drug registration testing. Communication should be promptly initiated and organized for issues that arise during the testing by a drug testing institution or during the Certificate of Analysis (CoA) review by CDE. For issues that arise during the testing, direct communication between the testing institution and the applicant will be more efficient. To this end, the project team believes that the most urgent and important initiative is to build a drug registration testing information platform for communication among the three parties as early as possible. We are delighted to learn that the building of this communication platform is already underway.

To sum up, it is urgent to improve the management of drug registration testing, although the process will be challenging and complicated, involving the construction of superordinate regulations and operational details. With a focus on the big picture, attention should also be paid to small steps. Consideration should be given to not only medium- and long-term directions of reform, but also short-term objectives. Considering the development of the industry and the progress in China's regulatory model, there is a need to expedite the internationalization of drug registration testing to align with global standards. Internationally recognized risk-based and for-cause testing should be the direction of development, with testing resources to be used where they are most needed. However, prior to the adjustment of superordinate regulations, efforts can be first directed towards streamlining the operational details of drug registration testing, optimizing workflows, fostering efficient communication, and scientifically setting the requirements for samples and materials subject to drug registration testing. Such efforts can contribute to efficient drug registration testing, support review needs and ultimately achieve simultaneous global marketing of drugs urgently needed in clinical settings to better serve Chinese patients.

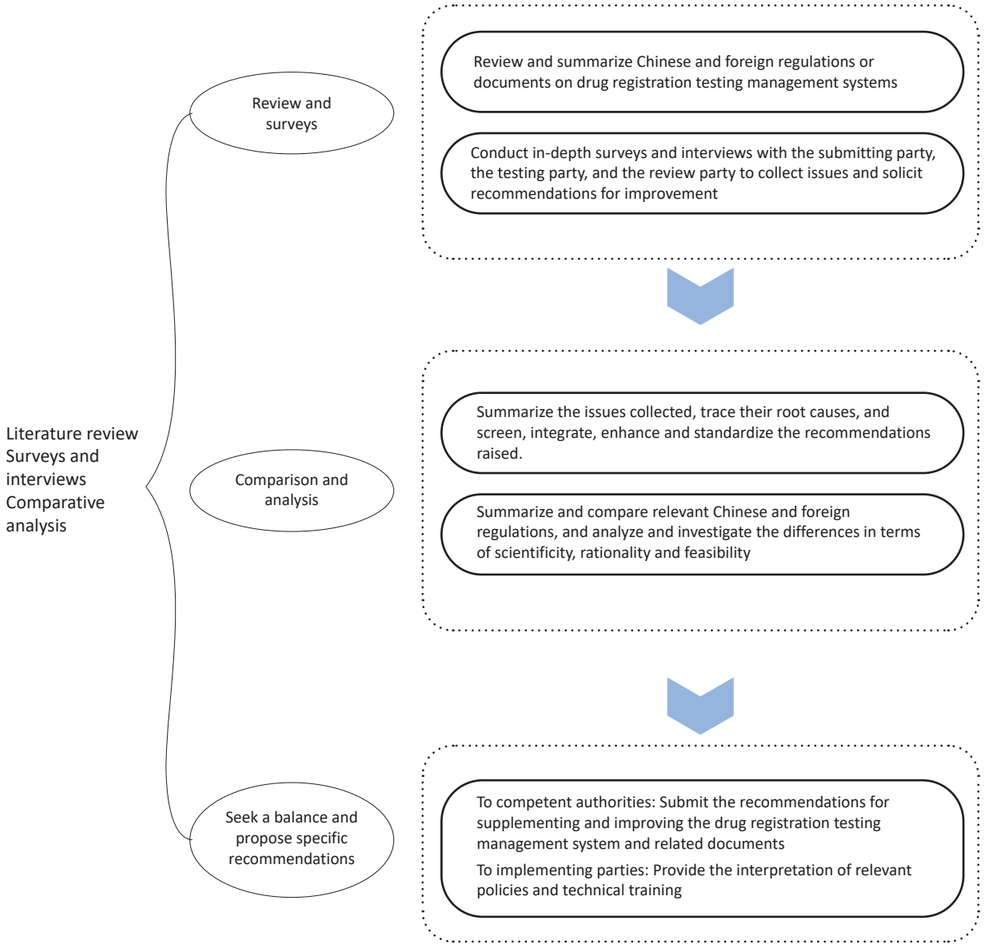
Chapter II
Research Plan and Methods

Guided by the social survey methodology theory, the project team adopted the following plan and methods to conduct the project's research (see Figure 1):

1) Literature review. First of all, a review of the literature was conducted. Chinese and foreign regulations or documents on drug registration testing and its management were retrieved and compared.

2) Surveys and interviews. Based on the knowledge of Chinese and foreign regulations and documents on drug registration testing, survey questionnaires and interview outlines were designed respectively for the three parities mainly involved in drug registration testing: Chinese and foreign companies, drug testing institutions, and CDE. Interviews or symposiums were organized among relevant authorities, experts, as well as representatives from companies, drug testing institutions and CDE to widely collect main issues at various stages of drug registration testing and to solicit their recommendations for improvement to address the issues identified in drug registration testing from different perspectives.

3) Summarization and comparative analysis. Various issues and recommendations for improvement collected from symposiums, interviews and survey questionnaires were summarized, and the root causes underlying these issues were traced and analyzed. The recommendations collected were screened in terms of rationality and feasibility, and were then integrated, standardized, and enhanced.



Chapter III

Overview of Main Regulations or Documents on Drug Registration Testing in China and Overseas and Analysis of Their Differences

Drug registration testing plays a crucial role in review and approval of drug registration applications in China. New insights can be gained through reviewing old materials. To better align drug registration testing with China's regulatory landscape for drug registration and to facilitate coordinated development, the project team conducted a longitudinal review of the origin and evolution of regulations on drug registration testing as well as the development history of testing management in China, and made a horizontal comparison of current requirements for drug registration testing between China and other major ICH member states and regions. On the basis of understanding the formation of China's requirements for drug registration testing and with reference to reasonable elements of supervision in other countries, this research was intended to contribute to continuous adjustment and optimization of China's requirements for the management of drug registration testing.

1. Evolution and Development of Regulations on Drug Registration Testing in China

China's administrative licensing measures for drug manufacturing and marketing, i.e., "drug registration", originated in 1963. *Several Provisions on the Management of Drug Regulatory Affairs* [1] stipulated a regulatory practice in which provincial health departments (bureaus) were tasked with establishing drug review committees to receive, review and approve drug application dossiers. However, there were no unified requirements for performing drug testing corresponding to review and approval. The requirements for drug testing corresponding to review and approval, i.e., "drug registration testing", can be traced back to the *Regulations on the Management of Drug Regulatory Affairs (Interim)* [2] issued in 1978. Pursuant to the Regulations, newly-developed drugs must have their application dossiers submitted for inspection and samples submitted for testing by drug testing institutions at the provincial, municipal, and autonomous regional levels. The *Measures for the Management of New Drugs (Interim)* [3] issued in 1979 further stated that drug testing institutions should actively collaborate in and support the research on testing methods and the establishment of specifications for new drugs; that clinical trials, validation, or trial use of new drugs must undergo inspection and testing as per clinical specifications and clinical trial use criteria established by drug testing institutions; and that drug testing institutions making significant achievements in the establishment of specifications should be rewarded. It is evident that, since

the inception of China's drug supervision and management system, the drug testing institutions established or designated by the drug regulatory authorities have been playing a crucial role in providing regulatory and technical support. Most drug testing institutions at or below the provincial level have been established since the 1960s, forming a professional and technical force for official drug testing covering the whole country, and the drug testing institutions at all levels provide professional and technical guidance to the testing departments of drug manufacturers and suppliers to help them improve the technical level of drug testing [2]. During the review and approval of drug R&D and manufacturing, the drug testing institutions that shoulder the responsibility for approving and establishing drug specifications not only act as the approver of drug specifications but also as the actual writer of drug specifications. The industry situation at the time was that, following the nationalization and state-operation of the pharmaceutical industry in the early 1950s, the whole industry was directed under the national plan to engage in drug research, manufacturing, and supply. The professional and technical personnel from the drug testing institutions were deeply involved in various activities in the pharmaceutical industry, playing a pivotal role in ensuring drug quality control. The aforementioned responsibilities and functions of the drug testing institutions were an inevitable choice given the development of the pharmaceutical industry in China prior to the 1980s.

Since the 1980s, with the development of diverse forms of ownership, the pharmaceutical industry has gained more driving forces, necessitating a more specialized and standardized approach to its administrative management, review and approval. The *implementation of the Provisions for Drug Registration (Interim)* [4] in 2002 marked China's standardization of its administrative management for drug manufacturing and marketing as "drug registration", followed by the standardization of its management of drug registration testing, including sample testing and specification verification. Drug registration testing was required for drug registration applications involving clinical research of new drugs, manufacturing of new drugs, drugs with national specifications, and imported drugs. If sample testing failed to comply with specifications for the drug under application, or the results of specification verification concluded that specifications for the drug under application were inadequate for quality control, registration approval wouldn't be granted. Following registration approval, the specifications issued to the applicant were the drug registration specifications for the specific drug, and the manufacturer of this drug must comply with the registration specifications. The *Provisions for Drug Registration* (2005) [5] further specified the drug registration testing requirements for supplementary applications. Drug registration testing was required for supplementary applications when drug manufacturers holding the new drug certificate applied for approval number, changes in drug strengths, changes in pharmaceutical excipients required in the drug formulation, changes in manufacturing processes affecting drug quality, amendment to drug registration specifications, replacement or removal of toxic or endangered medicinal materials from the formulation with national drug specifications, changes in the packaging materials or containers in direct contact with drugs, new drug technology transfer, changes in manufacturing sites of imported drugs, changes in drug manufacturing sites within Chinese drug manufacturers and changes in manufacturing sites of drug substances of drug products manufactured in China. At the time, drug registration testing was required for nearly all types of drug registration applications. As the total number of drug registration applications rapidly increased in China (from 8,472 registration applications of various types handled by CDE in 2003 to 22,255 in 2006 [6]), it was difficult for the national testing institutions to meet the rapidly-growing demand for drug registration testing, which became one of key factors to delay review and approval.

In this regard, the *amended Provisions for Drug Registration* (2007) [7] eliminated drug registration testing for clinical trial registration applications (except for biological products) and eliminated drug registration testing for

[1] 原卫生部 , 原化工部 , 原商业部 . 关于药政管理的若干规定 . (1963-10-25).
[2] 国务院 . 药政管理条例（试行）[EB/OL]. (1978-07-29). https://law.lawtime.cn/d550697555791.html.
[3] 原卫生部 . 新药管理办法（试行）[EB/OL]. (1979-02-20). https://law.lawtime.cn/d551461556555.html.
[4] 原国家药品监督管理局 . 药品注册管理办法（试行）[EB/OL]. (2002-12-01). https://law.lawtime.cn/d392371397465.html.
[5] 原国家食品药品监督管理局 . 药品注册管理办法 [EB/OL]. (2005-05-01). https://law.lawtime.cn/d353831358925.html.
[6] insight 数据库 . https://db.dxy.cn.
[7] 原国家食品药品监督管理局 . 药品注册管理办法 [EB/OL]. (2007-10-01). https://law.lawtime.cn/d664862669956.html.

the manufacturing of new biological products, thereby mitigating the issues of drug registration testing affecting the review timeline. However, in procedures, drug registration testing was still required to be conducted during the review following registration acceptance, resulting in the impossibility of conducting the testing and review in parallel. Furthermore, without the CoA, technical review couldn't be completed to proceed to comprehensive evaluation. In practice, a notice on supplementary dossiers would not be issued prior to the receipt of the CoA, and the period spent awaiting the CoA was not included in the review timeline [8].

With the rapid shift of China's pharmaceutical industry from the repeated over-development of generic drugs towards global innovation, the increasing emergence and application of new technologies have continually refreshed and evolved both the concept and practice of drug quality research and quality management. This evolution is reflected in the changing definition of drug registration specifications. The definition was adjusted from "specifications approved for a specific drug of the applicant by NMPA and followed by the manufacturer of this drug" [4] in 2002 to "specifications approved by CDE, the drug regulatory department under the State Council, upon proposal by the drug registration applicant, and issued to the drug MAH during the approval of the drug marketing authorization or supplementary applications by the drug regulatory department under the State Council" [9] in 2023. It means that the applicant is the main body of drug R&D. The formation of drug registration specifications should not merely involve technical guidance, review, and modification by drug testing institutions, nor should these institutions act as the "actual writer" of the registration specifications. In response to the new trends and needs of the industry, drug regulatory reforms have also continuously adjusted the management methods for drug registration testing in recent years. The *amended Provisions for Drug Registration* (2020) [10] reflects a change in the concept of "drug registration testing based on review needs". A related supporting document [11] explicitly stipulates that the drug testing institutions should "verify and provide comments, but not modify the submitted specifications". "Advance" drug registration testing has optimized the testing procedures for marketing registration applications.

After nearly three years of practice, a number of prominent issues in drug registration testing are yet to be further adjusted and improved. For instance, drug registration testing is excessively initiated for supplementary applications for post-marketing CMC changes, especially with a too high frequency of initiating drug registration testing for CMC changes that don't alter testing methods or generate new critical quality attributes beyond the current control range (such as changes in processes, changes in supply sources of drug substances and excipients, changes in manufacturing sites); there is an urgent need to establish a "review needs-based" drug registration testing technology exchange and issue solving mechanism among the drug review divisions, drug testing institutions and drug registration applicants; and issues involve the one-time handling of approval letters for imported drugs that have not been marketed in China or overseas, the rationalization of the requirements for receiving and testing samples submitted, and representativeness of differences in sample batches/strengths/packaging presentations. In enhancing the drug registration testing system established over the past four decades, it's crucial to acknowledge the continuity and gradualness of adjustment and improvement as well as the necessity and urgency of meeting the needs of the industry's development.

[8] 国家药监局药品审评中心 . 药品审评中心审评任务管理规范（试行）[EB/OL]. (2011-10-11). https://www.cde.org.cn/main/news/viewInfoCommon/a5d3d977820ac1bd5a1729d93c471bd5.
[9] 国家药品监督管理局 . 药品标准管理办法 [EB/OL]. (2023-07-05). https://www.nmpa.gov.cn/xxgk/fgwj/xzhgfxwj/20230705191500136.html.
[10] 国家市场监督管理总局 . 药品注册管理办法 [EB/OL]. (2020-01-22). https://www.samr.gov.cn/zw/zfxxgk/fdzdgknr/fgs/art/2023/art_3275cb2a929d4c34ac8c0421b2a9c257.html.
[11] 中国食品药品检定研究院 . 药品注册检验工作程序和技术要求规范（试行）[EB/OL]. (2020-07-01). https://www.nifdc.org.cn//nifdc/xxgk/zcfg/flfg/20200701134238784.html.

2. Comparison of Requirements for Drug Registration Testing Between China and Other Major ICH Member States and Regions

In this project, differences in drug registration testing were identified by comparing the current regulations and regulatory practices between China and other major ICH member states and regions, represented by the US, the EU, and Japan, to provide reference for China to continuously adjust and improve its management of drug registration testing. To highlight relevant information and factors, the differences are summarized in the table below.

Table 1. Comparison of Requirements for Drug Registration Testing in China, the US, the EU, and Japan

	China	US	EU	Japan
Drug registration testing-related authorities	**CDE** decides whether to initiate drug registration testing. **The National Institutes for Food and Drug Control (NIFDC) or NMPA designates drug testing institutions** to conduct the testing [10].	**CDER/CBER** decides whether to initiate drug registration testing. FDA laboratories conduct the testing [12].	**CHMP** decides whether to initiate drug registration testing. **Official Medicines Control Laboratories (OMCLs) or laboratories designated in member states** conduct the testing[13][14]	**Not available [15].** There is no requirement for drug registration-related testing.
Regulatory references for regulations on drug registration testing	***Provisions for Drug Registration*** [10]: Having completed CMC-related studies supporting drug marketing, establishment of specifications, and commercial-scale manufacturing process validation, the applicant may apply for drug registration testing to NIFDC or the drug regulatory departments of the provinces, autonomous regions or municipalities directly under the Central Government before the drug registration application is accepted; where the applicant does not request drug registration testing before the drug registration application is accepted, the drug registration testing shall be initiated by CDE within 40 days after accepting the drug registration application.	**21 CFR** 314.50 (e) [12]: Upon request from FDA, the applicant must submit the samples to the places identified in the Agency's request. FDA generally will ask applicants to submit samples directly to two or more Agency laboratories that will perform all necessary tests on the samples and validate the applicant's analytical procedures. Representative samples of the drug product proposed for marketing, the drug substance used in the drug product from which the samples of the drug product were taken; and reference standards and blanks (except that reference standards recognized in an official compendium) should be provided to perform three times each test described in the NDA to determine whether the drug substance and the drug product meet the specifications given in the NDA. Samples of the finished market package should be provided, if requested by FDA. **21 CFR** 601.2 (a) [16] ... sample(s) representative of the product for introduction or delivery for introduction into interstate commerce; summaries of results of tests performed on the lot(s) represented by the submitted sample(s) ...	**Regulation (EC) No 726/2004** [13]: CHMP may request that an OMCL or a laboratory that a Member State has designated for that purpose test the medicinal product for human use, its starting materials and, if need be, its intermediate products or other constituent materials in order to ensure that the control methods employed by the manufacturer and described in the application documents are satisfactory. Samples for testing the proposed medicinal product are not required at time of submission of the application. CHMP may however request the testing of samples of the medicinal product. In this case the reviewer and/or co-reviewer will specify a test protocol (type of samples, number of samples, number of batches, testing to be performed and methods and specifications to be used) and agree with EMA which OMCL or other laboratories designated for this purpose by a member state will carry out the required testing. Sampling and testing will be coordinated by the EMA in collaboration with the European Directorate for the Quality of Medicines and Healthcare (EDQM). The results of the tests are reported to EMA, reviewer and/or co-reviewer and CHMP for consideration in finalizing the CHMP Assessment Report [14].	**Not available [15].** There is no requirement for drug registration-related testing.

[12] FDA. Code of Federal Regulations Title 21[EB/OL]. (2023-11-11). https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-314/subpart-B/section-314.50.
[13] European Parliament. Regulation (EC) No 726/2004[EB/OL].(2022-01-28). https://eur-lex.europa.eu/eli/reg/2004/726/oj.
[14] EMA. European Medicines Agency pre-authorisation procedural advice for users of the centralised procedure[EB/OL].(2023-11-13). https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agency-pre-authorisation-procedural-advice-users-centralised-procedure_en.pdf.
[15] Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices - English - Japanese Law Translation.
[16] FDA. Code of Federal Regulations Title 21[EB/OL]. (2023-11-11). https://www.ecfr.gov/current/title-21/chapter-I/subchapter-F/part-601/subpart-A/section-601.2#p-601.2(a).

	China	US	EU	Japan
Management practices and initiation of drug registration testing	**CTAs:** To ensure that clinical trials are reviewed and approved within 60 business days, drug registration testing has generally not been initiated since 2018 [17], except special situations like vaccines.	**CTAs:** Under the US investigational new drug application (IND) system, the review timeline is only 30 days. With no drug registration testing initiated, the review is only based on application dossiers.	**CTAs:** Taking the simultaneous review of application dossiers I and II as an example, the total review timeline is 60 days. With no drug registration testing initiated, the review is only based on application dossiers.	**CTAs:** Under Japan's clinical trial reporting system, the review timeline is either 30 or 14 days. With no drug registration testing initiated, the review is only based on application dossiers.
	MAAs: Drug registration testing is required to be initiated, and the applicant may request advance testing. When testing items and methods are consistent with those for similar drugs included in the national drug specifications, only sample testing is required, with specification verification exempted. In addition, sampling and testing may be conducted during the registration on-site inspection [10] [18]. In practice, applications are often subject to verification comments and review comments on 2nd-round drug registration testing.	**MAAs:** Applicants must retain samples (for method verification/validation [19]). Based on risks, FDA generally does not initiate drug registration testing. For chemical drugs, CDER generally does not require testing during the NDA review (except in very few cases, such as botulinum).	**MAAs:** Based on risks, EMA (CHMP) generally does not initiate drug registration testing. Samples are only requested if, during the review, the reviewer or co-reviewer determines it necessary based on risks. This is equivalent to the decision-making procedures on whether to initiate testing during the review.	**MAAs:** Drug registration testing is not initiated. Drug registration testing is not included in the marketing authorization registration procedures.
	Post-marketing changes: Drug registration testing is initiated for supplementary applications for changes in processes/manufacturing sites/specifications, but no normative document is released. A Notification on Testing is issued upon acceptance.	**Post-marketing changes:** Drug registration testing is not initiated, unless testing is required for major changes in biological products subject to batch release as per the batch release process.	**Post-marketing changes:** Drug registration testing is not initiated.	**Post-marketing changes:** Drug registration testing is not initiated.

As shown in the comparison above, China has long used the experimental research of drug registration testing as the technical support for approving drug registration specifications. In current regulatory practice, the research on verification of specifications of imported drugs is of historical significance for providing a scientific experimental basis for drug testing at ports to ensure that pharmaceutical companies follow China's regulatory requirements [20]. However, in other ICH member states and regions, drug registration testing is not considered as a general requirement for registration management; testing is only required under special circumstances involving batch release or for-cause concerns, during the registration assessment; the approval of registration specifications is primarily based on technical review of application dossiers, rather than on laboratory testing of samples.

On the other hand, post-marketing drug supervision in China is based on drug registration specifications for identifying counterfeit drugs and substandard drugs. The quality testing conclusions from drug testing institutions should be legally documented in the decision on penalties for such drugs [21], as the testing by official drug testing institutions constitutes a crucial measure of post-marketing drug supervision in China. Thus, during the drug registration review, particular emphasis is placed on the applicability of the approved drug registration specifications in laboratories for post-marketing regulatory testing conducted by official drug testing institutions. As can be seen, in the discussion of the implications of regulatory practices of other ICH member states and regions in adjustment and improvement made to the management of drug registration testing, it is necessary to further investigate their requirements for post-marketing drug testing, as summarized in the following table:

[17] 国家药品监督管理局 . 国家药品监督管理局关于调整药物临床试验审评审批程序的公告 [EB/OL]. (2018-07-27). https://www.nmpa.gov.cn/xxgk/ggtg/ypggtg/ywlchshyjgrdgg/20180727172901286.html.
[18] 国家药监局药品审评中心 . 药品注册核查检验启动工作程序（试行）[EB/OL]. (2021-12-17). https://www.cde.org.cn/main/policy/regulatview/eec23c3baabc7b94666001ddf87c29d9.
[19] FDA. Analytical Procedures and Methods Validation for Drugs and Biologics, Guidance for Industry[EB/OL]. (2020-04-21). https://www.fda.gov/files/drugs/published/Analytical-Procedures-and-Methods-Validation-for-Drugs-and-Biologics.pdf.
[20] 中国食品药品检定研究院 . 我院召开首次进口化学药品标准复核专家会审会议 [EB/OL]. (2019-04-24). https://www.nifdc.org.cn//nifdc/gzdt/ywdt/20190424142517322.html.
[21] 全国人民代表大会常务委员会 . 中华人民共和国药品管理法 [EB/OL]. (2019-08-27). https://www.nmpa.gov.cn/xxgk/fgwj/flxzhfg/20190827083801685.html.

Table 2. Comparison of Requirements for Post-Marketing Drug Testing in China, the US, the EU, and Japan

	China	US	EU	Japan
Requirements for post-marketing drug testing by official drug testing institutions	Drug testing institutions at various levels perform sampling and testing on drug quality, while imported drugs are sampled and tested by port drug testing institutions. Drugs sold in China for the first time and biological products specified by NMPA should be tested at designated drug testing institutions [22]. In 2018, the requirement for customs clearance testing for non-initial import of chemical drugs was eliminated [22]. However, testing is stilled required by port drug regulatory authorities for changes in formulation processes, specifications and manufacturing sites, akin to that for initial import of drugs [23]. Vaccines and blood products are subject to batch release [24].	FDA has the authority to collect samples for testing during on-site inspection/investigation. Pursuant to 21 CFR 610.1 and 21 CFR 610.2 [16], pre-marketing batch-by-batch testing, also known as batch release, by FDA laboratories was mandated for biological products, with exemptions granted at the discretion of the Director of CBER. Since 1995, well-characterized biological products (e.g., recombinant protein products, monoclonal antibodies) have been exempted from batch release, while only certain biological products (e.g., vaccines, blood plasma products) are subject to batch release.	Following marketing approval via the EU centralized procedure, official testing is typically conducted in the post-marketing third year. Typically, 40 products are tested annually. Besides, the official annual testing plan is formulated based on risks. In accordance with Directive 2001/83/EC and relevant guidelines for the management of batch release, preventive biological products and human blood products must be subject to testing by an OMCL prior to marketing, i.e., batch release. Upon batch release in a member state, such products can be sold in all EU member states.	After a product is marketed, drug testing institutions will collect samples from the market distribution channels for specification verification [15].
Requirements for post-marketing drug testing by companies	Drug manufacturers shall conduct the testing of drug quality, and those that do not conform to national drug specifications shall not be released [22]. Selling drugs that shall be tested but have not been constitutes a legal violation involving the connection between administrative and criminal proceedings [22]. MAHs shall audit drug products released by drug manufacturers. Drugs shall not be released until signed off by a qualified person, and those that do not conform to national drug standards shall not be released [22].	Companies are not required to conduct post-marketing drug registration testing [25] As specified in 21CFR Part 211 §211.165 Testing and Release for Distribution, for each batch of drug product, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release. The accuracy, sensitivity, specificity, and reproducibility of testing methods employed by the firm shall be established and documented. Drug products failing to meet established standards or specifications and any other relevant quality control criteria shall be rejected.	Pursuant to EU GMP Annex 21 (Importation of medicinal products) [26], after physical importation and custom clearance from member states, the Qualified Person of the MAH certifying the batch for release must ensure that all the medicinal products were manufactured in accordance with the EU GMP standards, and lab testing in the EU demonstrates that the medicinal product meets the specifications that are set out in the marketing authorization, unless there is a Mutual Recognition Agreement (MRA) or Agreement on conformity assessment and acceptance of industrial products (ACAA) in place.	In accordance with the GQP Ministerial Ordinance [27], the MAH, i.e., the manufacturer and marketer of the drug (drug manufacturer and marketer) must be an entity located within the territory of Japan (with the exception that the overseas holder is required to designate a Japanese agent to assume manufacturing and marketing responsibilities), and either the MAH or its designated GMP site is responsible for the certification of batch release for its drug. Drug batch testing is conducted by the MAH or its designated site, with the testing laboratory specified in the MAA and managed directly or indirectly by the MAH. As per Japan's GMP FAQs, testing can be reduced when appropriate conditions are met (this pertains to the exemption strategy in plant stability studies, and since HA principles are not publicized, it may not apply to HA's supervision of the quality of marketed drugs); testing can be exempted when a mutual recognition agreement is in place between Japan and the origin country of the imported drug, provided that appropriate conditions are met.

China has allocated substantial administrative and technical resources to allow official drug testing institutions to conduct sampling and testing for the quality of marketed drugs. In contrast, except drugs such as vaccines and blood products that are subject to batch release management, other ICH member states and regions request MAHs to shoulder the responsibility for batch release of marketed drugs to ensure drug quality.

[22] 国家药品监督管理局 . 国家药品监督管理局关于进口化学药品通关检验有关事项的公告 [EB/OL]. (2018-04-26). https://www.nmpa.gov.cn/xxgk/ggtg/ypggtg/ypqtggtg/20180426144301235.html.
[23] 广东省药品监督管理局 . 广东省药品监督管理局关于优化药品进口备案工作的指导意见 [EB/OL]. (2023-02-20). http://mpa.gd.gov.cn/zwgk/gzwj/content/post_4097687.html.
[24] 国家市场监督管理总局 . 生物制品批签发管理办法 [EB/OL]. (2020-12-11). https://www.samr.gov.cn/zw/zfxxgk/fdzdgknr/fgs/art/2023/art_44550c0842eb4e848ec197cd5fb5f49a.html
[25] 21CFR Part 211§ 211.165 Testing and release for distribution. [EB/OL]. (2023-12-14) eCFR :: 21 CFR 211.165 -- Testing and release for distribution.
[26] European Commission. The Rules Governing Medicinal Products in the European Union Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use[EB/OL]. (2022-02-16). https://health.ec.europa.eu/system/files/2022-03/vol4_annex21_en.pdf.
[27] MHLW. 医薬品、医薬部外品、化粧品及び再生医療等製品の品質管理の基準に関する省令 [EB/OL].(2021-08-01). https://elaws.e-gov.go.jp/document?lawid=416M60000100136.

3. Enlightenment of Foreign Experience on China's Drug Registration Testing Management

By comparing the similarities and differences in the aforesaid drug registration testing requirements between China and other ICH member countries, the following enlightenment can be drawn:

- **At the clinical trial application stage,** China is basically consistent with the United States, Europe, and Japan, all not requiring drug registration testing in the process of clinical trial application review (vaccines and other special cases excluded), otherwise it is difficult to achieve rapid review and approval of clinical trials. China has begun to require conducting drug registration testing for drug clinical trial applications since 1978[3]. In 2007, the drug registration testing for drug clinical trial applications, excluding biological products, was exempted [7]. Then in 2018, the drug registration testing for all drug clinical trial applications, except vaccines, was exempted [18]. This is a process of gradual exploration and gradual release based on risk considerations. This process is not only the development of drug regulatory science, but also relevant to the overall compliance level of the pharmaceutical industry in China and the rectification results of regulatory compliance.

The more orderly development of the industry has enabled the adoption of more efficient regulatory measures based on risk considerations. The elimination of drug registration testing has significantly sped up the review and approval process for clinical trial applications (from an average of approximately 120 working days [28] in the first round of review and approval in 2017 to within 60 working days at present), greatly enhancing the R&D of new drugs and China's involvement in the simultaneous global R&D of new drugs and better meeting the medication needs of patients.

- **At the marketing authorization application stage,** China has always taken drug registration testing, especially the experimental study of specification verification, as the technical basis for the verification of drug registration specifications during the review of marketing authorization applications since 1978[3]. Although through adjustments and optimizations of working procedures, the registration review and drug registration testing are adjusted from sequential operation to roughly concurrent operation, and drug registration testing is allowed to be conducted prior to the submission of marketing authorization application [10]. However, due to the objectively time-consuming period of experimental study, especially the inevitable laboratory applicability exploration process in the transfer of new analytical methods, drug registration testing remains a critical step restricting the acceleration of marketing authorization application review and approval. In comparison, the regulatory practices of the United States, Europe, and Japan are of reference significance:

  1) **The United States** Although the laws stipulate that the FDA has the authority to initiate drug registration testing and that applicants must retain samples for testing, the FDA seldom initiates such testing during the marketing authorization review process, except for biological products that initiate the batch release procedure at the review stage. FDA's practices, such as not initiating drug registration testing based on the risk, requesting on-site testing or delivery of sampling to FDA laboratories during on-site inspection in the review process for the causal situation, and conducting batch release-related work through FDA laboratory testing during the marketing authorization application review period, are worthwhile for China to learn from it.

  2) **European Union** Similar to the United States, European Union has a legal basis for drug registration testing, but in practice, drug registration testing is not a routine measure, but a special measure triggered by specific causes. In the review process, the severity of initiating testing for identified issues

[28] 国家药监局药品审评中心 . 2017 年度药品审评报告 [EB/OL].(2018-03-23). https://www.cde.org.cn/main/news/viewInfoCommon/4e5464e8c98de4a48ecfc560ea7f175f.

is comparable to initiating inspection for identified issues, and once drug registration testing is initiated based on review requirements, reviewers must formulate specific testing requirements and protocols, which is worthwhile for China to learn from it.

China has established normative documents for initiating testing and inspections based on risk and review needs during the registration review process [29]. However, currently, consideration is only given to the risk factors and risk levels for initiating inspections. The guidelines for product-related risk factors and risk level judgment involved in testing, as well as that for compliance factors and risk level management of the R&D and manufacturing entities, are still soliciting comments [30]. There is still a lack of detailed regulations for determining the risk factors and risk levels for initiating drug registration testing. It is necessary to refer to the practices of the European Union for drug initiating registration testing based on explicit review considerations. Once drug registration testing is initiated, specific testing requirements and protocols should be formulated for the specific testing issues required for review.

3) **Japan** The process for drug registration testing is not set in Japan's marketing authorization registration procedure. Japan requires that after a drug is approved for marketing, MAHs must complete batch testing release in a laboratory within Japan (either the MAH's own laboratory or a third-party laboratory). The MAH is responsible for managing the laboratory conducting the batch testing release, and specifies the practices of this laboratory in the marketing authorization application. This approach offers valuable insights for China.

- **At the post-marketing change stage,** China has explicitly stated the drug registration testing requirements for post-marketing supplementary application items since 2005 (Inspection and sampling of test samples in supplementary application for changes in drug manufacturing sites, application for new drug approval number with the new drug certificate, and specification verification where necessary in supplementary application for modifying drug registration specifications) [5]. However, after the revision and implementation of new regulations upon regulatory reform, detailed requirements have not yet been formulated for initiating drug registration testing in supplementary applications for post-marketing changes. The released guidelines for CMC changes of marketed drugs [31][32]require the provision of CoA in the study data for most CMC changes, but this requirement should be applicable to MAH's self-testing of drugs after changes, and should not necessitate the initiation of drug registration testing for all supplementary applications for such changes.

As mentioned above, the United States, the European Union, and Japan do not require initiating drug registration testing for post-marketing changes. Based on risk considerations and for the purpose of initiating drug registration testing, it is recommended to reduce the initiating drug registration testing required for post-marketing changes. Particularly for changes in testing items and methods that do not modify the drug registration specifications and for CMC changes that do not result in new critical quality attributes beyond the existing drug registration specification's control scope (such as process changes, changes in the source of drug substances, excipients and packaging materials, and changes in manufacturing sites), it can be considered not to initiate drug registration testing.

For cases where existing drug registration specifications have changed and require verification of the scientificity and rationality, or where existing drug registration specifications are insufficient to detect new critical quality attribute changes resulting from the changes, if experimental study is indeed necessary to support drug review through drug registration testing, it is recommended to propose targeted drug registration testing requirements

[29] 国家药监局药品审评中心 . 药品注册核查检验启动工作程序 (试行)[EB/OL].(2021-12-20). https://www.cde.org.cn/main/news/viewInfoCommon/c1dd9f7df30d686a2adab91f7f34587e.
[30] 国家药监局药品审评中心 . 药品注册研发生产主体合规信息管理与审查指导原则 (试行) (征求意见稿) [EB/OL].(2023-11-15). https://www.cde.org.cn/main/news/viewInfoCommon/f03df8e7c4321a46ceaa9e7d9dbc1afa.
[31] 国家药监局药品审评中心 . 已上市化学药品药学变更研究技术指导原则 (试行) [EB/OL].(2021-02-10). https://www.cde.org.cn/main/news/viewInfoCommon/4ec3dca752a82347bdf24ad3d3e85113.
[32] 国家药监局药品审评中心 . 已上市生物制品药学变更研究技术指导原则 (试行)[EB/OL].(2021-06-25). https://www.cde.org.cn/main/news/viewInfoCommon/7ef3a0d630aea8a49186f49f31a6fd3c.

based on review needs, formulate detailed rules for structured testing requirements, so that MAHs can foresee the testing items and content that may require specification verifications accordingly and can propose advance testing before submitting supplementary applications for changes, thus mitigating the impact of drug registration testing on the review and approval timeline.

Moreover, in addition to the aforementioned quality control technical factors, it is also recommended to incorporate the compliance factors of drug R&D and manufacturing entities into the consideration for initiating drug registration testing, especially for initiating drug registration testing for post-marketing changes[33], establish credit records based on the compliance of companies in the review process, and reduce drug registration testing for companies with good compliance.

- **During the process of drug marketing and distribution,** China relies more on drug testing institutions at all levels to carry out random sampling for quality testing of marketed drugs, and on port drug testing institutions to perform random sampling for testing of import drugs for customs clearance. By contrast, the United States, the European Union and Japan place more emphasis on the responsibility of the drug MAHs, including the completion of the testing of the marketed drug by MAHs to ensure the quality of drugs. Following the full implementation of the drug MAH system under the *Drug Administration Law* in 2019, a series of drug life cycle management measures, including the annual drug report, are being increasingly modified and improved, the regulatory requirements for principal responsibilities of MAHs are being gradually formulated and implemented, the concept and system of qualified person are being continuously implemented and improved, and the quality awareness and management level of companies are being continuously enhanced. In the current regulatory framework and industry level, the testing requirements for the drug marketing and distribution process can be further adjusted. It is recommended that regulatory authorities should pool limited testing resources, strengthen ongoing and ex-post supervision of MAHs, adjust regulatory measures through implementation of the responsibilities of MAHs, and alleviate the quality supervision pressure during the drug registration review.

[33] 蔺娟 , 乔利涛 , 李源等 . 现阶段药品注册检验启动工作要求及面临的挑战 [J]. 中国药事 ,2023,37(03):245-249. DOI:10.16153/j.1002-7777.2023.03.001. _

Chapter VI

Analysis of Main Issues and Their Causes in China's Drug Registration Testing

The project team conducted surveys among the parties involved in drug registration testing, and analyzed current issues in drug registration testing using both qualitative and quantitative approaches. In the qualitative interviews, there were 10 testing institutions, 12 Chinese companies, and 12 overseas companies. In the quantitative surveys, responses to questionnaires were received from 18 testing institutions, 58 Chinese companies, and 55 overseas companies. Moreover, the project team held on-site discussions with personnel from multiple divisions of CDE (including Division of Compliance, Division of Quality, Division I of Chemical Drugs, Division II of Chemical Drugs, CMC Division of Biological Products, and CMC Division of Traditional Chinese Medicine) to identify and analyze the causes of issues from the review perspective. The project team summarized and analyzed the survey results, with main issues and their causes presented as follows:

1. Issues and Causes in 2nd-Round Drug Registration Testing

[Current status and existing issues]

Testing institutions, Chinese companies, foreign companies, and the drug review divisions all raised issues concerning 2nd-round drug registration testing in their feedback during the surveys.

Feedback from testing institutions: Sometimes, notifications on 2nd-round drug registration testing are received before the initial drug testing is completed. However, the initial drug testing and 2nd-round drug registration testing involve different registration samples for testing, so re-testing is required, demanding separate review comments on each. This results in an unnecessary waste of both human and materials resources. Furthermore, non-standard and inaccurate writing of the submitted registration specifications is a primary cause for drug testing institutions' misunderstanding of the submitted specifications, hindering the smooth conduct of experimental verification.

The main issues raised by companies regarding 2nd-round drug registration testing include the process and time of 2nd-round drug registration testing as well as the provision of samples.

Survey results of overseas companies: The time of 2nd-round drug registration testing (from sample submission to testing completion) in the drug registration testing process is excessively lengthy. According to the feedback from 48% of respondents, it takes 6-9 months to complete 2nd-round drug registration testing, extending the approval timeline for new drugs and consequently delaying benefits to patients. Based on the feedback from companies, the main issues that trigger 2nd-round drug registration testing can be divided into the following

categories: 1) the proposed registration specifications contain incomplete testing items (64.29%), improper methods (46.43%) or limits (32.14%); 2) the testing institutions are unable to complete the testing due to incomplete testing methods submitted by applicants (53.57%) or non-conforming samples, reagents, and standard substances (14.29%); 3) the writing of registration specifications is neither standard nor complete (35.71%).

Feedback from the drug review divisions: The submitted specifications don't cover all items, resulting in the failure to effectively control the characteristics and quality of products. The experimental verification comments submitted by drug testing institutions is sometimes overly simplistic, offering insufficient support for the drug review divisions' evaluation of the specifications. Furthermore, there are even unclear comments and inconclusive reports, and there is no formal communication channel, making resolution achievable only be means of 2nd-round drug registration testing.

In summary, the drug testing institutions, the drug review divisions and companies encounter different issues in 2nd-round drug registration testing. Compared with Chinese companies, foreign companies experience more inconvenience.

[Causes of the issues]

Upon the summary and further analysis of the survey results by the project team, it is agreed that the causes of the aforementioned issues are as follows:

(1) Insufficient communication is most likely to lead to 2nd-round drug registration testing. Survey results on the current status of communication: 56% of the testing institutions surveyed consider it to be so-so, 27.8% consider it to be not smooth, and 16.7% consider it to be smooth; among Chinese companies surveyed, 60% find it smooth, 31% find it so-so, and 8.6% find it not smooth; among foreign companies surveyed, 60% hold that there are many communication issues between the companies and testing institutions, and 51% hold that there are many communication issues between testing institutions and drug review divisions. Regarding the necessity of establishing a tripartite communication platform among the drug review divisions, testing institutions, and applicants, all the parties surveyed consider it extremely important. Among them, the foreign companies surveyed hold that communication during drug registration testing for post-marketing changes is more important (93%) than that for MAAs for innovative drugs (56%).

The causes of non-smooth communication may include: 1) Resource constraints such as short testing timeline and heavy workload result in insufficient communication between testing institutions and companies and the failure to solve technical issues during the testing in a timely manner; 2) Due to the lack of procedures or platforms for communication with review divisions as raised by testing institutions in qualitative interviews, it is impossible to consult reviewers when issues arise; the drug review divisions are also unable to discuss testing-related issues with testing institutions in a timely fashion during the review; 3) The lack of a prompt communication mechanism among drug review divisions, testing institutions and applicants as raised by a number of testing institutions and companies leads to testing tasks and issues circulating only between the two parties or being resolved through 2nd-round drug registration testing during the supplement period.

(2) Applicants have insufficient capabilities or fail to fulfill responsibilities thoroughly. According to the statistics of the survey, the items or limits of registration specifications summited by applicants are incomplete or irrational. The submitted specifications are required to be improved when issues are identified during the review.

(3) Others: 1) Owing to the varied requirements of pharmacopeias, relevant guidance documents, and regulatory authorities concerning drug specifications across different countries, the testing items, methods, or limits included in the specifications submitted by some foreign companies diverge from those required in China. 2) As some requirements are unclear, applicants are unable to establish the specifications as required for testing, resulting in the submitted specifications failing to meet the requirements for drug registration testing.

3) For some products under application for advance drug registration testing, there is a higher likelihood of inconsistent testing and review comments on specification verification due to the simultaneous conduct of testing and review, thus triggering the review requirement for 2nd-round drug registration testing after testing completion or even prior to completion.

2. Issues and Causes in Drug Registration Testing for Post-Marketing Changes

[Current status and existing issues]

According to previous feedback from the industry, post-marketing CMC changes are likely to trigger drug registration testing, making the timeline for applications for CMC changes comparable to that for MAAs. As such, the project team conducted a survey on this issue, with the results as follows:

(1) Issues with the scope of advance testing. It is agreed in qualitative interviews among reviewers from CDE's Division of Traditional Chinese Medicine, some drug testing institutions and companies that the scope of advance testing should be expanded, allowing supplementary applications and drug substances to fall within advance testing and allowing applicants to choose advance testing to expedite the review and approval process.

(2) Issues with the initiation of drug registration testing. Feedback from international companies mainly involves changes in drug registration specifications (94%), changes in manufacturing sites (83%), and changes in manufacturing processes (72%); followed by changes in sources, processes, and specifications of drug substances (56.36%), packaging (45.45%), and excipients (30.91%); and finally, the extension of shelf life and changes in storage conditions (18.18%). This feedback is consistent with that raised by CDE on the initiation of supplementary applications for specification verification due to changes in formulation processes, changes in manufacturing sites and changes in specifications, with a high frequency of initiation.

(3) Issues with the *Notification on Testing* for post-marketing changes According to the survey, companies consider the information in the template of Notification on Testing to be inadequate, without clarifying whether sample testing, specification verification, or both are required (96%); without clarifying whether testing for changes involves full testing items (94%) or specific items (78%), making drug registration testing conducted as per full testing items rather than as needed.

In summary, the main issues in drug registration testing for post-marketing changes are related to the conditions for initiating drug registration testing, time of initiation, and the specific requirements outlined in the *Notification on Testing*.

[Causes of the issues]

More feedback from the industry focuses on the initiation of drug registration testing for post-marketing changes. Because post-marketing changes of drugs, especially major CMC changes, may affect the safety and efficacy of drugs, regulatory authorities generally require the initiation of drug registration testing for major CMC changes. However, companies generally conduct full in-house assessment to decide whether changes require drug registration testing, aiming to effectively meet the medication needs of Chinese patients.

Regarding the expansion of the scope of advance testing, in practice, some companies are already able to assess whether supplementary applications require testing. Therefore, some companies request advance testing for supplementary applications. However, as the current scope of advance testing primarily covers MAAs for new drugs rather than supplementary applications, reviewers find it difficult to handle subsequent compliance issues upon receipt of relevant dossiers, which may lead to a waste of resources in some supplementary applications with advance testing.

Additionally, the principles of initiating drug registration testing are unclear, so applicants involved in importing samples (including samples, equipment/instruments and materials required for pre-defined testing) are unable to prepare adequately in advance. For drugs manufactured overseas under global supply management, samples of such drugs for drug registration testing have a longer cycle of ordering, significantly hindering the progress of drug registration testing. This delay impacts the timeline for change review and approval, and further leads to the failure in supplying marketed products. Especially, during force majeure events like pandemics and wars, which impede the transportation and customs clearance of drugs manufactured overseas, the drug supply is easily disrupted, thus jeopardizing patient access to drugs.

There is no specific description of the requirements for testing in the Notification on Testing issued at the time of acceptance of supplementary applications for post-marketing changes and the notification on supplementary dossiers issued during the review, with only indication for initiating drug registration testing or conducting specification verification. In addition, there is no explanation for situations where only "single item testing" may be conducted. It is also unclear whether changes in drug substances/active pharmaceutical ingredients will trigger the initiation of formulation registration testing. In such cases, drug testing institutions use the most rigorous full testing items and specification verification by default, leading to unnecessary addition of testing items. This consumes additional regulatory resources and delays the review, approval, and implementation of changes.

3. Issues and Causes in Optimizing the Specifications for Drug Registration Testing

3.1 Issues with Requirements for Samples and Standard Substances

[Current status and existing issues]

According to the project team's survey results, more feedback focuses on issues in the drug registration testing of samples in question and reference standards. The issues are mainly related to the batches, shelf life, and packaging of the samples.

Survey results of drug testing institutions: (1) 89% of drug testing institutions hold that for drug registration testing focusing on specification verification, if the remaining shelf life of samples is less than 180 days (two testing cycles), but the stability of the product to be registration is still under investigation, and the company declares that it will assume full responsibility, such samples may be accepted as appropriate; 89% of drug testing institutions hold that during the review by CDE, if supplementary dossiers provided by a company need specification verification and the company declares that it will assume full responsibility and the CoA will only be used in response to the feedback from CDE, samples near the end of shelf life or expired samples from initial drug registration testing may be accepted as appropriate; 61% of drug testing institutions hold that if there is a specified re-testing period for drug substances and the company provides a declaration that the drug substances remain eligible for re-testing beyond this period, they may also be accepted as appropriate. (2) Issues with sample batches. For certain types of drug registration or application stage where the stringency of sample testing can be reduced, such as allowing the initial drug registration testing to be conducted with just one batch of samples and considering increasing the number of batches for testing if issues arise during initial testing, 55.6% of drug testing institutions do not support this approach, while 44.4% are in favor. Reasons: 1) A single batch of samples lacks representativeness and fails to demonstrate the maturity of manufacturing processes or the consistency of product quality, whereas three batches can showcase process stability; 2) The cost and time involved in testing one batch versus three are not significantly different. When issues are identified later, re-initiation of testing with additional batches will result in a waste of testing resources and reduce the efficiency; 3) For non-conforming samples for testing, not all three batches necessarily fail the testing at the same time, so reducing the number of batches makes it more challenging to identify potential issues.

Survey results of Chinese companies: (1) 88% of Chinese companies hold that for drug registration testing focusing on specification verification, if the remaining shelf life of samples is less than 180 days (two testing cycles), but the stability of the product to be registration is still under investigation, and the company declares that it will assume full responsibility, such samples may be accepted as appropriate; 85% of Chinese companies hold that during the review by CDE, if supplementary dossiers provided by a company need specification verification and the company declares that it will assume full responsibility and the CoA will only be used in response to the feedback from CDE, samples near the end of shelf life or expired samples from initial drug registration testing may be accepted as appropriate; 74% of Chinese companies hold that if there is a specified re-testing period for drug substances and the company provides a declaration that the drug substances remain eligible for re-testing beyond this period, they may also be accepted as appropriate. (2) Issues with sample batches. For certain types of drug registration or application stage where the stringency of sample testing can be reduced, such as allowing the initial drug registration testing to be conducted with just one batch of samples and considering increasing the number of batches for testing if issues arise during initial testing, 90% of Chinese companies support this approach. Reason: It is more scientifically sound. The samples for drug registration testing generally embody mature and stable manufacturing processes and scales, and application dossiers can also adequately demonstrate inter-batch quality consistency. Therefore, the number of batches can be reduced for initial testing as appropriate. Moreover, comparing the consistency of the testing data of the batch for initial testing submitted by drug testing institutions and that by companies can assist in judging the results of drug registration testing. In addition, companies state that subsequent post-marketing sampling and testing can continue to ensure the safety and efficacy of drugs. While achieving the testing purpose, this approach also improves the efficiency of testing, reduces the workload of testing institutions, shortens the testing time, and expedites the marketing of products. When a company is confident in its product, using a single batch of samples for testing and experimentation can save sampling and testing time without compromising the quality of drug registration testing.

Survey results of foreign companies: 91% of the companies undertake to bear the risks to use samples less than two testing cycles; regarding batch issues, 85% of the companies are willing to bear the associated risks under special circumstances, so that regulatory authorities can accept fewer than three batch samples for testing; regarding packaging issues, 93% of the companies expect that the packaging materials in direct contact with drugs be consistent with the materials to be registered in China, without the mandatory requirement for "complete market package".

[Causes of the issues]

- **Regarding the issues concerning sample batches, shelf life, and packaging in drug registration testing,** Chinese companies gave more feedback on the shelf-life issue during the survey, while foreign companies had more feedback on the feedback on the aforesaid three issues, likely due to their growing demand for simultaneous global submission and one-time submission of samples in multiple strengths. However, the current requirements make their expectation challenging to achieve in practice. To further investigate the causes of such issues, the project team conducted a further survey among foreign companies, as outlined below:

(1) Issues with sample batches for testing

In accordance with Article 34 of the *Working Procedures for Initiating Drug Registration Inspection and Testing (Interim)*, "Prior to and at the time of the acceptance of a drug registration application, the initiation of drug registration testing requires three batches of samples of traditional Chinese medicines and chemical drugs manufactured at a commercial scale, and in principle, three batches of samples of biological products continuously manufactured at a commercial scale, except in special circumstances.

Despite that companies strive to meet the aforementioned requirements, they indeed have several difficulties in providing samples for testing as follows:

a. Companies have finished the manufacturing of registration batches (manufactured with commercial production lines and processes, not yet at a commercial scale), but process validation has either not started or been completed, thus failing to provide samples at a commercial scale. In particular, for continuously-manufactured products, the registration batches are entirely manufactured using commercial-scale instruments. However, the duration of sample manufacturing is shorter, e.g., 1 to 2 hours, whereas commercial-scale manufacturing usually takes approximately 20 hours.

b. Registration batches of samples and the subsequent Phase 3 clinical samples manufactured by companies (manufactured with commercial production lines and processes, yet not at a commercial scale) may sometimes fall short of the required three batches, or the cycle to achieve three batches may be very long. Thus, the simultaneous provision of three batches of samples for drug registration testing is extremely challenging.

c. For multi-strength samples with the same concentration, equal proportions of drug substances and excipients, but different volumes, the difficulty for companies to provide three batches increases correspondingly. Moreover, in practice, for certain strengths applicable to small populations, the requirement for providing three batches of samples may not be met due to limited annual batches manufactured. Furthermore, variations in product quality are minimal despite different final dosages administrated, since the multi-strength samples have completely identical formulation processes and equal proportions of drug substances and excipients. Drug registration testing of three batches per strength also results in an indirect waste of resources for both regulatory authorities and companies.

In summary, under the current regulatory requirements, companies must wait for the completion of process performance validation before using samples from three process validation batches for drug registration testing, to meet China's regulatory requirements and control in-house manufacturing costs. In order to collect three batches of samples, companies must wait for a long time (several months at least), making it impossible for companies to achieve simultaneous global submission. Sometimes, to wait for multiple strengths of samples to be provided together to Chinese regulatory authorities for drug registration testing, the waiting time will be even longer, which also leads to the submission in the Chinese market being much later than that in the global market (even by several years). Companies are even forced to give up the registration of certain strengths, affecting patient access in clinical settings.

Similarly, for post-marketing changes, certain products have low market demand, limited annual manufacturing arrangement (e.g., pediatric drugs or drugs for rare diseases), or short shelf life, so it is difficult to collect three batches of samples for testing. If a bracketing approach is used for post-change process validation of multi-strength samples, lengthy manufacturing cycles of some products make it difficult to collect three post-change batches of samples per strength to support change applications. The difficulty in providing samples for post-marketing change testing may affect the supply of marketed products on the market.

(2) Issues with the shelf life of samples

In accordance with the requirements of the *Working Procedures for Initiating Drug Registration Inspection and Testing (Interim)*, "The remaining shelf life of the sample should be no less than 2 drug registration testing cycles. If the sample testing and specification verification are performed at the same time, it's 180 business days; if only the sample testing is performed, it's 120 business days".

Although companies strive to provide samples covering 2 drug registration testing cycles as required, the circumstance encountered by companies is more complicated in practice. For example, products have low market demand and limited annual manufacturing arrangement (e.g., pediatric drugs or drugs for rare diseases), so it is difficult to provide samples covering 2 drug registration testing cycles.

(3) Issues with sample packaging

In accordance with the requirements of the *Working Procedures for Initiating Drug Registration Inspection and Testing (Interim)*, "The samples should be of commercial manufacturing scale, and relevant information of the samples (e.g., the manufacturing sites and the packaging materials in direct contact with drugs) should be consistent with those provided when applying for marketing authorization".

However, in practice, it is sometimes impossible to provide samples for drug registration testing in accordance with the above requirements. For instance, the drug manufacturing sites, formulation processes, and packaging materials in direct contact with drugs are consistent with those of the product to be marketed, but the samples for testing only differ from the product to be marketed in terms of package size (e.g., the number of capsules or tablets per pack/carton, the number of vials per carton), the information on the MAH or secondary package manufacturer. The inconsistency in such information will not have a negative impact on product quality or the results of drug registration testing.

- **More feedback on issues with standard substances for drug registration testing is mainly because they are generally managed overseas based on the re-testing period.** For quantitative standard substances, the re-testing period is generally determined based on a company's in-house stability data and management requirements, such as once a year. Typically, re-qualification is performed one month prior to the expiry date of the shelf life of standard substances, generating the next version of the CoA. Consequently, it is currently impossible for the company to provide a CoA with a longer validity period. A company's short re-testing period is an effective means to control the quality of standard substances, but it also poses challenges to the submission for testing within the required period.

3.2 Testing Related to Inter-Provincial Contract Manufacturing of MAHs

[Current status, existing issues, and their causes]

Testing issues related to inter-provincial contract manufacturing of MAHs were raised during the interviews with Chinese companies and testing institutions. Under the current MAH system, an MAH and its contract manufacturer are sometimes located in different provinces. In this regard, the drug regulatory authority in the province where the MAH is located needs the collaboration in sampling from the drug regulatory authority in the province where the contract manufacturer is located. However, the delay caused by the coordination issue between the two drug regulatory authorities makes it difficult for the drug testing institutions to receive the samples for testing within the specified timeline, thus delaying the completion of drug registration testing and possibly affecting the overall review timeline for drug registration.

Chapter V

Reflections and Recommendations on Chinese Drug Registration Testing Management System

Drug registration testing is applicable to sample testing and specification verification carried out by drug testing institutions for the purpose of supporting the review of drug marketing authorization applications[ ]. Specification verification refers to laboratory assessment of the scientific basis of items included in the drug specifications submitted by the applicant, the feasibility of testing methods and the rationality of quality control criteria. Sample testing refers to laboratory testing of samples conducted in accordance with the drug specifications submitted by the applicant or approved by CDE. For those with their testing items and methods consistent with the testing items and methods used for drugs of the same variety listed in the National Drug Specifications, it is not required to conduct specification verification, and only sample testing is necessary[ ].

The project team has investigated the current issues in drug registration testing through a combined qualitative and quantitative approach. After comprehensive analysis, the issues are primarily on 2nd-round drug registration testing, drug registration testing for post-marketing changes of drugs, and other specifications for drug registration testing.

- 2nd-round drug registration testing

The problems faced by drug testing institutions and companies are slightly different. Feedback from testing institutions: Sometimes, notifications on 2nd-round drug registration testing are received before the initial drug testing is completed. However, the initial drug testing and 2nd-round drug registration testing involve different registration samples for testing, so re-testing is required, demanding separate review comments on each. This results in an unnecessary waste of both human and materials resources. Furthermore, non-standard and inaccurate writing of the submitted registration specifications is a primary cause for drug testing institutions' misunderstanding of the submitted specifications, hindering the smooth conduct of experimental verification. The problems faced by Chinese and overseas companies are quite similar. The survey feedback from overseas companies indicates that during the drug registration testing process, the time required for 2nd-round drug registration testing (from sample delivery to completion of testing) is excessively long. 48% of all parties surveyed report that it takes 6-9 months to complete the 2nd-round drug registration testing, which extends the approval time of new drugs, thus delaying benefits being delivered to patients at an early date.

[34] Announcement of the National Institutes for Food and Drug Control on Issuing the Specification for Working Procedures and Technical Requirements for Drug Registration Testing (Interim) (2020 Edition) and Relevant Issues [EB/OL](2020-07-01)[2023-11-16].https://www.nifdc.org.cn/nifdc/xxgk/zcfg/flfg/20200701134238784.html
[35] State Administration for Market Regulation, Provisions for Drug Registration [EB/OL](2020-1-22)[2023-11-16]. https://www.gov.cn/zhengce/zhengceku/2020-04/01/content 5498012.html

- Testing for post-marketing changes

In the survey, some drug testing institutions report that currently there are more drug registration testings for post-marketing changes, and a serious mismatch between the workload of specification verification and the manpower allocation of testing institutions. Meanwhile, several companies have reported that the current testing duration for post-marketing changes is longer. Under the Provisions for Drug Registration, the current timeline for initiating drug registration testing for supplementary applications concerning approval-related changes is 200 business days. This means that when supplementary applications involve testing, the review timeline will be extended to 200 business days, the same duration as the application for drug marketing authorization. This contradicts the idea of simplification for changes. Moreover, the current advance testing does not cover supplementary applications, significantly extending the timeline for testing required for post-marketing changes.

- Other specifications for drug registration testing

The issues are mainly related to the acceptance of samples and standard substances, as well as the cross-provincial contract manufacturing by MAH. The current criteria for sample and standard substance acceptance have made it challenging for companies to submit samples that comply with regulatory requirements within the timeline in certain situations. Under the MAH system, MAHs and contract manufacturers may not be located in the same province, so the drug regulatory authority of the place where the MAH of the drug under cross-provincial contract manufacturing is located needs to collaborate with the drug regulatory authority of the place where the contract manufacturer is located to conduct coordinated sampling. However, cross-provincial coordination can result in drug testing institutions failing to receive the testing samples within the specified timeline, thus delaying the completion of drug registration testing and potentially affecting the total review timeline for drug registration.

For this reason, the project team, after root-course analysis and discussion, has proposed relevant recommendations (as shown in Figure 1).

Figure 1: Summary of recommendations for optimizing drug registration testing

1. Strengthen Communication among All Parties Involved in Drug Registration Testing

Communication should be strengthened to avoid 2nd-round drug registration testing. Since July 2020, more than half (50.91%) of the foreign companies surveyed have been requested to undergo 2nd-round drug registration testing. When the 2nd-round drug registration testing is initiated, overseas companies cannot finalize or improve their analytical methods and validations or new limit confirmation and cannot supply drug registration testing samples and the corresponding standard substances that meet the requirements (3 batches/3 times in quantity/sufficient shelf life) in a short term, and overseas companies also have no way to amend the proposed specifications and methods based on the situations and/or feedback from the initial testing. As a result, the 2nd-round drug registration testing (from sample delivery to testing completion) takes too long, with 48% instances indicating that it takes 6-9 months to complete the 2nd-round drug registration testing. The aforementioned issue is not only faced by overseas companies. During qualitative interviews, some Chinese companies also mentioned that it took longer time to complete 2nd-round drug registration testing due to unclear process and sample preparation.

Therefore, avoiding the conduct of 2nd-round drug registration testing can accelerate the marketing process of new drugs, so that patients can benefit from new drugs earlier. In the survey on recommendations on “how to avoid initiating 2nd-round drug registration testing”, 82.8% Chinese companies and 100%overseas companies encountering 2nd-round drug registration testing believe that regulators shall communicate with companies promptly about problems encountered during the testing process. Therefore, to ensure the smooth conduct of drug registration testing and avoid 2nd-round drug registration testing, it is crucial to enhance communication among all parties concerned.

The testing institutions in the survey recommend that communication among multiple parties should be strengthened, the testing work that can be combined and completed during the initial testing should be completed as much as possible, and efforts be made to reduce the conduct of 2nd-round drug registration testing, while also optimize the procedure for 2nd-round drug registration testing and clearly define the items and requirements for 2nd-round drug registration testing, so as to shorten the testing timeline and save regulatory resources.

1.1 Establish Efficient Communication Mechanism

The primary purpose of drug registration testing is to facilitate specification verification. In light of the objectives of drug registration testing and the roles and capabilities of each party involved, the testing institution should evaluate the feasibility of the testing methods, and the review department shall focus on evaluating the scientificity of the items set in the drug specifications and the rationality of the quality control indicators. Due to the particularity of drug registration testing, it is necessary for testing institutions to communicate with companies and review departments in a timely and effective manner in order to truly establish a testing process required for review. The *Working Procedures for Initiating Drug Registration Inspection and Testing (Interim)* clearly defines the establishment of the coordination mechanism and regular communication mechanism by the CDE and NIFDC for review and testing. However, it does not specify the relevant responsibilities in the coordination process between CDE and the drug testing institutions. In the adjustments to the new drug registration testing model, it is urgent to address a series of communication and coordination issues between CDE and drug testing institutions. Therefore, when establishing procedures for communication and coordination between drug review divisions and drug testing institutions, it is necessary to further refine and implement the specific requirements for responsibilities as outlined in the *Provisions for Drug Registration* for both drug review institutions and drug testing institutions, enhance the procedure for coordination between drug review divisions and drug testing institutions, establish principles for addressing common issues, and ensure timely communication and resolution of problems, if any.

To establish an efficient mechanism for communication, it is recommended to create a communication system with the testing institutions at the core, with reference to CDE'S communication procedure documents[36]. The priority of communication should be classified according to the type of drug application, the content to be communicated and the drug registration testing initiation point, and the corresponding form (such as face to face/video/telephone/written) and the meeting minute recording requirements after reaching consensus should be recommended according to the meeting classification. At the same time, the testing institutions can record and summarize the communication issues on a quarterly basis and release common industry issues in the **Q&A** form for the industry's reference and implementation, so as to reduce unnecessary communication and improve communication efficiency. To further facilitate the establishment of a communication mechanism, the project team surveyed demands from CDE, drug testing institutions and the industry, and summarized the establishment of the communication mechanism from initiation point and content based on the results.

Regarding the initiation point for communication, the industry hopes that flexible communication methods should be established at various stages. However, considering the limited regulatory authority resources for feedback, the project team recommends that the procedure for communication between the two parties should be established at two time points with more feedback **during the formation of verification comments before the beginning of drug registration testing and after the completion of registration testing**. For example: appropriate communication should be made with the sponsor to grasp the key points of specification verification prior to the commencement of drug registration testing; operation problems encountered during experiments should be promptly communicated to the sponsor's relevant personnel; communication should be made with CDE when issuing the testing result to support the review process with drug registration testing results. If some special issues arise, three-party communication can be facilitated. If problems arise at any stage, the party identifying the problem can act as the initiator of communication. This recommendation is fully supported by 100% drug testing institutions and 97% of Chinese companies. The reason is that the individual identifying the problem is often more familiar with the details and background of the problem, and can promote the collation and solution of the problem more efficiently and clearly.

Regarding the content of communication, overseas companies urgently hope to communicate on the content of proposed specifications before testing, including **the rationality of proposed testing items and the setting of limits (96%), and the conversion of testing methods to be harmonized with Chinese Pharmacopoeia requirements (93%).** During the formation of the verification comments after the completion of drug registration testing, **discussions are held on arguable issues in the verification report (91%),** such as clarifying testing results, verification comments and the necessity of 2nd-round drug registration testing, and making communication on necessary testing items. It is expected that drug review departments, testing institutions and companies can issue relevant requirements to companies after reaching a consensus.

1.2 Establish Information Platform for Communication to Enhance Communication Efficiency

The building of an efficient communication requires information platform construction[37]. In qualitative interviews, the six drug testing institutions all mentioned the need for information construction through building the drug review and testing data sharing platform, or setting up a “window of communication” for testing institution at the website of the CDE so as to establish a smooth and efficient communication mechanism. For this purpose, the platform should contain functions such as data sharing, updates on detailed drug testing procedures, and exchange of information. The information exchange function is particularly important. During testing, if issues are found, testing institutions can communicate with companies and related personnel responsible for review at CDE through the exchange function of the information platform at any time,

[36] 国家药品监督管理局药品审评中心 . 国家药监局药审中心关于发布《药物研发与技术审评沟通交流管理办法》的通告 (2020 年第 48 号) [EB/OL](2020-12-11)[2023-11-16]
[37] 李源，蔺娟，史丽威等 . 新形势下我国药品注册检验启动与实施工作要求及挑战 [J]. 中国临床药理学杂志，2023，39(05)：757-760.DOI:10.13699/j. cnki.1001-6821.2023.05.031.

and retain all communication records to facilitate subsequent collation of common issues, regularly release Q&A documents, and unify opinions from all parties. Meanwhile, with the accumulation of a large amount of textual data and the continuous development of AI technology, AI can be used to answer low-level communication issues in the future, while higher-level communication can be conducted in the form of meetings, further promoting the optimized allocation of resources.

For the above recommendations, the project team has made appropriate modifications in the *Working Procedures and Technical Specifications for Drug Registration Testing (Interim)*. Please refer to the attachment for detailed information.

2. Avoid 2nd-Round Drug Registration Testing and Optimize the Process to Accelerate Drug Marketing

In addition to the aforementioned communication that is intended to reduce 2nd-round drug registration testing, Chinese companies that filled in the questionnaire: 1) 82.8% believe that sponsors should track the drug registration testing process, actively facilitate communication among various departments when issues arise, and try to resolve such issues within the initial testing period; 2) 77.6% assert that applicants should formulate scientific, reasonable, and clearly defined application standards based on the characteristics of processes, formulations and dosage forms, and check the consistency of the dossiers submitted to drug testing institutions with the dossiers submitted to the CDE; 3) 53.4% contend that sponsors should plan ahead, anticipate difficulties that may encounter, and prepare sufficient supplies for testing; 4) Half of the companies recommend that applicants should study, fully understand and master the Chinese Pharmacopoeia and the general format and writing guidelines of the drug specifications issued by CDE.

With respect to other problems arising from 2nd-round drug registration testing, the project team made further analysis and discovered that the reasons vary across different products and scenarios. Innovative drugs at the NDA stage may still in the exploratory research phase. With an increasingly intensified understanding of the testing methods, 2nd-round drug registration testing may occur due to revision of the limit of registration specification items during the review process; for imported drugs (Category 5.1 and Category 5.2) the 2nd-round drug registration testing is triggered primarily due to the different requirements of pharmacopoeia, relevant guidance documents and regulatory authorities of various countries for drug specifications, leading to different requirements for certain testing items, methods or limits. Additionally, there are other reasons. For example, the applicant’s deficiency in capability or failure to implement responsibilities properly; as some requirements are unclear, the applicant cannot control the specifications for testing[38], failing to meet the requirements for drug registration testing; also, for some products seeking advance drug registration testing, since testing and review are conducted simultaneously, it is more likely to encounter inconsistent comments in testing and review, thus triggering 2nd-round drug registration testing required in review after completing the testing or even before completing the testing.

2.1 Strengthen Business Training to Enhance Mutual Understanding Among All Parties Concerned

Adequate communication and business training can avoid the conduct of 2nd-round drug registration testing. During the formation of verification comments upon completion of testing, communication across three parties concerned can help clarify and clearly define testing results, verification comments, the necessity for 2nd-round drug registration testing and necessary testing items (100%). For information on establishing a communication platform, please refer to the communication section. The purpose of conducting business training is that Chinese companies sometimes use immature specifications in their application for registration, and overseas

[38] 蔺娟 , 乔利涛 , 李源等 . 现阶段药品注册检验启动工作要求及面临的挑战 [J]. 中国药事 ,2023,37(03):245-249. DOI:10.16153/j.1002-7777.2023.03.001.

companies may be not familiar with the laws and regulations of China, resulting in application specifications or dossiers failing to meet Chinese requirements. For the problems caused by the applicant itself, it is necessary to carry out relevant training regularly to improve the ability of the applicant, and enhance the mutual understanding between parties concerned in the training process.

2.2 Establish Mechanism for Risk-Based Initiation of 2nd-Round Drug Registration Testing

Recommendations for 2nd-round drug registration testing should be based on risk assessments, and the testing should be initiated only when the product faces significant risks in safety, efficacy, and quality control. For scenarios with no significant risks, such as no lack of testing items that affect product safety or efficacy, or adjustment of limit indicators or improper establishment of methods, regulatory authorities may, based on comprehensive risk assessment and company commitments, allow companies to apply in the form of supplementary applications after approval of new drugs (96.43%), in order to ensure better product supply. It is recommended that the regulatory authorities should sort out and summarize the current 2nd-round drug registration testing initiation situation, discuss it with relevant stakeholders, make classification based on risks, and form a relevant list. At the same time, it is necessary to periodically review the relevant data of 2nd-round drug registration testing and evaluate the rationality of 2nd-round drug registration testing, to control risks and rationally allocate relevant testing resources.

2.3 Optimize 2nd-Round Drug Registration Testing Related Procedure and Rationally Allocate Testing and Sample Resources

Establish related procedures for the 2nd-round drug registration testing and rationally allocate testing resources. Currently, there are no supporting documents regarding 2nd-round drug registration testing, and the requirements are the same as the initial testing, leading to prolonged testing cycles, thus delaying the registration and marketing of drugs. Some testing institutions have reported that when conducting the initial drug registration testing, applicants sometimes receive notice from CDE requesting supplementary information. In accordance with the current working procedures, the testing institutions can only enter the application and acceptance process for the testing requested by the notice of supplementary information after submitting the drug registration testing report and the specification verification comments of the initial drug registration testing to the CDE. For this purpose, it is important to establish relevant procedural documents. **In particular, it's necessary to specify how to flexibly set requirements for samples and standard substances (93.43%), testing cycles (75%), and how to list the testing items on *Notification on Testing***. Due to the difficulty for companies to provide samples that meet the requirements (3 batches/3 times the quantity for full testing items/sufficient shelf life) and corresponding standard substances in the short term. If the remaining shelf life of the retained samples from the initial testing can meet one testing cycle, the 2nd-round drug registration testing task can still be assigned to the drug testing institute of initial testing, and it should be allowed to use the retained samples to complete the 2nd-round drug registration testing [39]. Most 2nd-round drug registration testings involve one or part of the test items (not all test items), thus the testing items should be specified in the *Notification on Testing* to appropriately shorten the cycle of the 2nd-round drug registration testing.

[39] 薛晶，黄清泉，黄宝斌等 . 结合药品注册检验受理常见问题解读与之相关规章 [J]. 中国药事，2022，36(10)：1110-1116.DOI:10.16153/j.1002-7777.2022.10.003.

3. Improve Drug Registration Testing Mechanism for Post-marketing Changes

Efforts should be made to improve the drug registration testing mechanism for post-marketing changes and expedite the supplementary application review process. MAHs are further encouraged to apply new manufacturing technologies, methods, equipment, and scientific and technological achievements to constantly improve and refine the manufacturing process, continuously elevate the quality of drugs, and improve the safety, efficacy, and quality control of drugs[40]. Meanwhile, the initiation conditions for drug registration testing for post-marketing changes and the relevant documents should be clarified, and the testing resources should be rationally allocated.

3.1 Clarify Drug Registration Testing Initiation Conditions for Post-marketing Changes and Flexibly Conduct Advance Testing

Currently, application for advance testing is only allowed for initial marketing authorization application of drugs. For supplementary applications submitted for post-marketing changes, whether drug registration testing is needed should be determined and initiated by CDE. Therefore, advance drug registration testing does not apply to supplementary application 6. Therefore, the clearly defined initiation conditions for drug registration testing for post-marketing changes are the prerequisite for conducting advance testing in supplementary application. Moreover, the technical requirements for supplementary applications are more mature compared with that for marketing authorization applications, and are primarily for varieties that require enhanced product quality or expanded production capacity. If the initiation conditions are clearly defined, applicants will be able to independently evaluate whether to conduct testing, initiate early communications with testing institutions and review divisions, and improve quality and efficiency, thus to avoid medication interruptions in patients caused by the changes.

It is recommended to broaden the scope of advance testing. Furthermore, the regulatory authorities should refine the advance drug registration testing process (e.g., a one-off import channel), straighten out the connection between advance drug registration testing and the review, and coordinate the orderly conduct of the review and drug registration testing 4. For example: a communication platform should be established to avoid inconsistencies in comments between testing institutions and review divisions due to parallel processes, thereby triggering 2nd-round drug registration testing and leading to waste of testing resources; relevant one-off import channels should be established for imported drugs, etc.

3.2 Recommend to Clarify the Initiation Conditions for Drug Registration Testing for Post-marketing Changes and Relevant Documents

Clarifying the initiation conditions for drug registration testing for post-marketing changes can help companies make relevant assessments and plans to ensure patient access to drugs. In accordance with the current Provisions for Post-approval Changes of Drugs in China, “post-marketing changes of drugs shall not have adverse effects on the safety, efficacy, and quality control of drugs”. The purpose of initiating drug registration testing for post-marketing changes is to ensure the safety, efficacy, and quality control of drugs, which is one of important measures for post-marketing regulation based on the risk management principle. To this end, it is recommended to clarify the principles for initiating drug registration testing for post-marketing changes, discuss and formulate the procedural documents for initiating drug registration testing from a scientific perspective based on the risk of the changes, to enhance review efficiency and avoid unnecessary testing.

[40] 国家药品监督管理局 . 国家药监局关于发布《药品上市后变更管理办法 (试行)》的公告（2021 年 第 8 号）[EB/OL](2021-01-13) [2023-11-16] https://www.nmpa.gov.cn/xxgk/fgwj/xzhgfxwj/20210113142301136.html

In the survey result of the project team, of all drug testing institutions surveyed, exemption from drug registration testing is considered applicable by 44.4% for changes in manufacturing batch sizes; 27.8% for changes in the manufacturing sites of raw materials and excipients for low-risk varieties; 27.8% for changes in packaging materials and containers or changes in packaging materials and containers for oral solid dosage forms; 11.1% for changes in packaging specifications and changes in specifications for unchanged prescriptions; 5.6% for changes in the manufacturing sites for low-risk varieties; and 5.6% recommend that exemption from drug registration testing in supplementary application should be determined based on the variety-related risks or the company's production line and quality management system, and if it cannot be exempted, drug registration testing can be conducted; Of all Chinese companies surveyed, exemption from drug registration testing is considered applicable by 74.1% for the supplementary applications for changes in manufacturing batch sizes; 69% for changes in packaging materials and containers; 55.2% for supplementary application for changes in the manufacturing sites of raw materials and excipients; 27.6% for supplementary applications for changes in manufacturing sites; for varieties exempted from drug registration testing, 95% of the surveyed subjects believe that, following review and standardization of the text, the company's specification for shelf-life can be taken as the registration specification.

Overseas companies hope to be exempted from sample testing for the following changes: changes in shelf life (81%), addition of excipient suppliers of status I (78%), addition of starting material suppliers (76%), and changes only in drug substances, with no effect on the drug products (76%).

Therefore, under the principle that companies act as primary person responsible for drug quality, it is recommended to consider exempting drug registration testing for certain circumstances when all quality data of products before and after changes provided by companies are consistent and do not conflict with the superordinate laws, considering from perspectives of saving limited drug registration testing resources, shortening the review period for low-risk drugs, improving review and approval efficiency, and maintaining a balance between risk management and strict regulation, while preserving the CDE's authority to initiate drug registration testing and for-cause sampling testing in review of marketing authorization application . 1 batch.

3.2.1 Clarify the List for Drug Registration Testing Triggered by Post-marketing Changes

It is recommended that regulatory authorities should formulate relevant lists based on the existing situation of drug registration testing triggered by post-marketing changes and upon consensus across multiple parties concerned. The *Working Procedures for Initiating Drug Registration Inspection and Testing (Interim)* clearly states that "for the supplementary application for chemical drugs and biological products that require drug registration testing, drug products and drug substances that have not yet passed review and approval should in principle undergo drug registration testing. For the marketing authorization applications for biological products as well as supplementary applications requiring drug registration testing, drug products and drug substances are, in principle, subjected to drug registration testing concurrently. Supplementary applications without changes in drug substances are not required to undergo drug registration testing. [41]" However, for supplementary applications requiring drug registration testing, there are no explicitly defined requirements.

In the article authored by Li Yuan and other reviewers, it is noted that supplementary applications requiring testing include those situations that necessitate drug registration testing in the supplementary application for major changes as defined in the Technical Guideline for Studies on Post-approval CMC Changes to Chemical Drugs (Trial), the *Technical Guideline for Studies on Post-approval CMC Changes to Traditional Chinese Medicines (Trial), and the Technical Guideline for Studies on Post-approval CMC Changes to Biological Products (Trial)*. In terms of the consistency evaluation, except for the varieties seeking exemption from consistency evaluation,

[41] 国家药品监督管理局药品审评中心 . 国家药监局药审中心关于发布《药品注册核查检验启动工作程序 (试行)》的通告 (2021 年第 54 号) [EB/OL](2021-11-22)[2023-11-16]

other varieties, in principle, all need to go through drug registration testing. Taking the major changes in manufacturing processes as defined in the *Technical Guideline for Studies on Post-approval CMC Changes to Chemical Drugs (Trial*) as an example, the Guideline stipulates the study and validation work required includes the "comparative studies on quality before and after changes, testing of three consecutive batches of samples manufactured after changes, and studies on the stability of the three batches of samples." Same as stability studies, testing of samples is the study-related work that companies need to undertake on their own for this change, not the basis required by regulatory authorities to conduct drug registration testing. Therefore, it is recommended to refine the guidelines for initiating drug registration testing for supplementary application and issue to the guidelines to the industry.

The initiation of both drug registration testing and registration inspection must be based on a comprehensive assessment of the risks, resources and efficiency, rather than be applied to all "major changes" in a one-size-fits-all manner. To ensure the proper use of testing resources, it is recommended to perform hierarchical management for different situations. For example, for changes in specifications requiring drug testing institution to conduct method transfer and confirmation for the new specification, registration testing should be conducted upon approval of the change; for changes in excipients, packaging materials, and manufacturing sites that are assessed as major changes based on the risk level, if the company has completed self-testing and stability studies, and such changes do not involve testing method transfer and evaluation, it is recommended that the review conducted based on the company's study data and results and drug registration testing be initiated proportionally based on the risk; after approval of the change, it is recommended to achieve overall assessment of product quality through strengthening commercial testing and sampling testing for import.

In conclusion, the project team recommends that CDE should clarify the principles for initiating drug registration testing for post-marketing changes in the subsequent revision of the *Working Procedures for Initiating Drug Registration Inspection and Testing (Interim)*, or release it to the industry in a Q&A format. For CMC changes in prescriptions, processes, drug substances, excipients and packaging materials, etc. that do not change the approved specification and/or release specification, or do not result in changes in critical quality attributes that cause approved specifications and/or release specification and in-process control specification not detectable and controllable, the drug registration testing should not be initiated during the review of the supplementary application for such changes.

3.2.2 Long-Term Plan for the Establishment of a Risk-Based Mechanism for Initiation of Drug Registration Testing Using Real-World Data

In the latest *Provisions for Drug Registration*, the principle of risk-based management is followed and guidance concerning the establishment of a scientific management system for drug research and development as well as review is provided, to ultimately achieve the goal of ensuring the safety, efficacy and accessibility of drugs for the public. For this reason, the risk-based mechanism for initiating drug registration testing is one of the actions to implement the Provisions. Besides, in 2021, CDE released the *Working Procedures for Initiating Drug Registration Inspection and Testing*, and in Article 4, it explicitly states that "the Center for Drug Evaluation, NMPA (hereinafter referred to as the CDE) should determine whether to initiate drug registration inspection and testing based on risk."

To this end, it is recommended that relevant departments establish a database for drug registration inspection and testing, make classification based on changes, periodically analyze companies or products with deviations, determine risk factors in a combined quantitative (e.g., ineligibility rate) and qualitative (discussion by various experts) forms, and conduct risk assessment.

3.2.3 Specify Conditions and Requirements for Initiating Testing in *Notification on Testing*

After the conditions for initiating testing is clearly defined, it is recommended that the *Notification on Testing* for the post-marketing changes should explicitly specify the conditions and requirements for initiating drug registration testing, to facilitate the reserve of testing samples by companies and the smooth initiation of the related testing by the testing institution. Meanwhile, this also aims to avoid ambiguity in the testing requirements that may result in the waste of testing resources. The CDE should formulate and issue normative documents, specifying the review conditions, types of samples, number of batches, and the specific items for testing or specification verification. At the same time, under the principle of drug registration testing based on review needs and risk, efforts should be made to reasonably reduce unnecessary testing items and contents. For example, when the proposed change does not involve new testing methods and additional new risk factors, there is no need to conduct specification verification; it should be clarified under which condition a single testing item or full testing item should be performed. For example, it can be written as "Based on the review needs, the drug registration testing items for this product are full testing items/XX items for specification proposed by the applicant, with the testing content being sample testing/specification verification".

4. Optimize Specification for Drug Registration Testing Procedure

To further expedite the drug registration testing process to ensure patient medication, the project team reviewed the details relating to the specifications for drug registration testing, and found that the testing issues related to samples and MAH cross-provincial contract manufacturing were more prominent. The project team has proposed relevant recommendations and made modifications in the *Working Procedures and Technical Specifications for Drug Registration Testing (Interim)*. For more details, please refer to the attachment.

4.1 Issues Regarding Samples and Standard Substances

For the drug registration testing issues related to sample batch, shelf life and packaging, issues related to shelf life are most commonly reported by Chinese companies in the survey. The above three issues are all commonly reported by overseas companies, mainly because their demand to achieve simultaneous global submission and one-off submission for multi-strength samples is getting increasingly strong, but in actual operation, it is difficult to achieve such goal in consideration of the current requirements. To address this, the project team conducted further survey on overseas companies to identify the causes of the issue.

There are many feedbacks on issues related to standard substances used in registration, mainly because overseas management is mainly based on the re-testing period. For quantitative standard substances, the re-testing period is generally determined based on a company's in-house stability data and management requirements, such as once a year. Typically, re-qualification is performed one month prior to the expiry date of the shelf life of standard substances, generating the next version of the CoA. Consequently, it is currently impossible for the company to provide a CoA with a longer validity period. The short company retesting period is a good quality control method for standard substances. Based on the characteristics of different varieties, some companies carry out a shorter period of re-testing of standard substances, which presents difficulties for submitting samples for testing according to the required shelf life.

4.1.1 Recommend to Formulate Acceptance Requirements for Samples Tailored to Different Situations

Efforts should be made to formulate acceptance criteria for samples tailored to different situations to reduce unnecessary waste of time. The marketing of drugs in China should be accelerated to bring benefit to patients sooner. Referring to the feedback from preliminary survey, the project team made the following recommendations through comprehensive consideration:

(1) Issues regarding batches of samples submitted for testing

Drug batches for drug registration testing should be provided reasonably based on risks, such as representative commercial scale batches. Currently, according to Article 54 of the *Provisions for Drug Registration*, "The applicant is permitted to submit a drug registration testing application to NIFDC or the drug regulatory authorities of the provinces, autonomous regions, or municipalities directly under the Central Government after completing CMC related studies that support the marketing of drugs, establishing specifications, and finishing commercial-scale manufacturing process validation." However, for Category 1 innovative chemical drugs, Europe and the United States allow commercial-scale process validation to be completed after the approval of their marketing applications. For this reason, overseas companies need to wait at least several months to collect samples that meet Chinese requirements, which will affect the overall progress of R&D and registration. It is hoped to retain some flexibility for drug registration testing samples, such as the use of representative commercial-scale batches of samples for drug registration testing, to promote the simultaneous R&D and registration of innovative products.

For companies that face challenges in providing three batches of proposed application samples for drug registration testing, it's recommended to consider reducing or exempting sample batches for drug registration testing. For example, a company provides a letter of undertaking, and under the premise of the company's undertaking to bear the risk, the regulator can flexibly accept fewer than 3 batches of samples, less than 3 times the quantity of samples required for full testing items and representative commercial-scale batches of samples6. For different situations, the company undertaking should vary accordingly. For instance, in case of accepting fewer than 3 batches of samples, the agreement to accepting fewer than 3 batches of samples for drug registration testing or commercial testing should be based on the premise of the company's undertaking to provide data comparison of 3 consecutive commercial-scale batches (such as key data about content, impurities, dissolution); in case of accepting representative commercial-scale batches, the agreement to accepting representative commercial-scale batches for drug registration testing should be based on the premise that the company signs a letter of undertaking stating that samples for registration are manufactured on a commercial-scale production line with the commercial process, and agrees to provide data comparison of registration batch and 3 consecutive commercial-scale batches (such as key data about content, impurities, dissolution).

(2) Issues regarding shelf life

On the premise that the company undertakes to bear the risk and the qualified person signs a letter of undertaking 2 (undertaking to provide the product CoA that covers two testing cycles before the expiration date), it is recommended that the regulatory authority can accept samples with the remaining shelf life meeting one testing cycle (90 days), but not enough for two testing cycles (180 days).

(3) Testing of samples of large or small strength

For products of equal proportions with multiple strengths, it is recommended that the regulatory authority accept the use of the parenthesis method (e.g., large or small strength) or the number of process validation batches as the basis for sample testing batches, provided that the company provides a reasonable explanation and ensures product quality.

(4) Testing and packaging issues regarding samples of post-marketing innovative drugs

If the packaging material in direct contact with products is consistent with the material intended for registration in China, and the samples submitted for testing only differ from products to be marketed in terms of packaging specifications (e.g., the number of capsules/tablets per pack/box, the number of injections per box, etc.), MAH or information about secondary packaging site, it is recommended that the regulatory authority may accept "incomplete commercially available packaging" provided that the company undertakes to bear risks and the qualified person signs the letter of undertaking 2, despite the said inconsistency.

(5) Drugs for rare diseases with low yield

Considering the small batch size of the product, it is recommended to make specific analysis according to the specific situation of the product, and minimize the quantity and batches for testing as needed, so that more products can be made available to Chinese patients.

4.1.2 Recommend to Set Flexible Acceptance Requirements for Standard Substances

For standard substances with a shelf life less than 9 months, it is recommended that regulatory authorities can accept the standard substances and their current CoAs, provided the company undertakes to bear risks or signs a letter of undertaking (e.g., ensuring the submission of qualification report for re-testing before the standard substance expires).

4.2 Testing Issues in MAH Cross-Provincial Contract Manufacturing

During interviews with Chinese companies and testing institutions, many of them provided feedback on the testing issues regarding MAH cross-provincial contract manufacturing. Under the current MAH system, MAHs and contract manufacturers may not be located in the same province, so the drug regulatory authority of the place where the MAH of the drug under cross-provincial contract manufacturing is located needs to collaborate with the drug regulatory authority of the place where the contract manufacturer is located to conduct coordinated sampling. However, cross-provincial coordination can result in drug testing institutions failing to receive the testing samples within the specified timeline, thus delaying the completion of drug registration testing and potentially affecting the total review timeline for drug registration.

4.2.1 Allow Applicants to Choose Conducting Drug Registration Testing in Drug Testing Institutions within the Jurisdiction of MAH or Contract Manufacturer

The project team conducted a survey on the support for applicants to choose to perform drug registration testing at drug testing institution located in either the MAH's or the contract manufacturer's jurisdiction. 67% testing institutions and 88% Chinese companies expressed their support for the applicant's choice. To efficiently address this issue, when the MAH and the contract manufacturer are located in different provinces, it is recommended that applicants, with the *Notification on Testing* for drug registration, directly apply for sampling to the drug regulatory authorities of the provinces, autonomous regions, or municipalities directly under the Central Government where the contract manufacturer is located. This can effectively avoid the problem that samples cannot be submitted and tested within the prescribed timeline due to cross-provincial coordination of sampling matters between the two drug regulatory authorities.

4.2.2 Clarify the Drug Registration Testing Procedures for Cross-Provincial Contract Manufacturing

Upon receiving Notification on Testing for registration, the MAH must first consult the provincial regulatory authority concerning the process via telephone. Taking Henan Medical Product Administration as an example, after multiple rounds of phone consultations, the specific procedure is confirmed as follows. The MAH should first submit an application for drug registration testing sampling to the Henan Medical Product Administration (Note: MAH that is not manufacturer may not be clear about the specific content included in the application letter). Upon receiving the application letter from the MAH, Henan Medical Product Administration will then send a Letter of Contract Sampling to the provincial regulatory authority where the contract manufacturer is located. The timeline for this process is also unspecified. As a result, the manufacturer cannot predict the overall arrangement. It is recommended that relevant authorities summarize and clarify the drug registration testing procedures for cross-provincial contract manufacturing.

Project Guidance Team

Zhang Wei	President of China Society for Drug Regulation
Xue Bin	Executive Director of China Society for Drug Regulation and Chairman of Professional Committee on International Exchange and Cooperation in Drug Regulation

Project Responsible Scientists and Experts

Yu Li	Assistant to the former Director of Beijing Institute for Drug Control
Ma Yunan	Former Head of Division I of Center for Drug Evaluation, National Medical Products Administration
Zhang Qiming	Institute for Chemical Drug Control of National Institutes for Food and Drug Control
Zhou Lichun	Assistant to the former Director of Beijing Institute for Drug Control

Project Team Members

Sara Wang	Vice President of Science & Regulatory Affairs, RDPAC
Judy Yu	Director of Science & Regulatory Affairs, RDPAC
Wang Tianyang	Regulations and Project Specialist, Science & Regulatory Affairs, RDPAC
Irene Deng	Head of Regulatory Affairs, Sanofi
Gao Rong	Head of Research and Development, Novartis
Liu Jing	Senior Director of Regulatory Affairs, Novo Nordisk
Qin Jinyu	Senior Director of Pfizer
Wang Ruiqi	Head of China Projects, Pharmaceutical Sciences, Pfizer
Lian Jianwei	Senior Director of CMC Registration, Lilly China Drug Development and Medical Affairs Center
Wu Zhengyu	Director of Regulatory Affairs, Novo Nordisk (China) Pharmaceuticals Co., Ltd.
Lu Jingyan	Deputy Manager of Regulatory Affairs, Sanofi (China) Investment Co., Ltd.
Wang Xu	Deputy Director of Regulatory Affairs, Novo Nordisk (China) Pharmaceuticals Co., Ltd.
Xu Zheng	Senior Manager of Regulatory Affairs, Medical & Regulatory Affairs and Quality Assurance, Novo Nordisk China
Wang Ruping	Assistant Manager of Regulatory Affairs Department, Eisai China Inc.
Chen Yao	Head of Regulatory Affairs, Novartis Greater China
Zhang Zhang	Director of Regulatory Affairs, China Novartis Institutes for Biomedical Research Co., Ltd.
Tang Bailing	Director of Regulatory Affairs, Johnson & Johnson Innovative Medicine R&D Center
Xu Dan	Deputy Director of Regulatory Affairs, Johnson & Johnson Innovative Medicine R&D Center
Li Limin	Deputy Director of Regulatory Affairs, Johnson & Johnson Innovative Medicine R&D Center
Hou Rong	Deputy Director of Regulatory Affairs, AbbVie Pharmaceutical Trading (Shanghai) Co., Ltd.
Huang Lin	Director of Regulatory Affairs, Bayer Healthcare Company Limited
Wang Guannan	Senior Manager of Regulatory Affairs, Bayer Healthcare Company Limited
Zhang Tianjuan	Deputy Manager of Regulatory Affairs, Eisai China Inc.