Fostering China Pharmaceutical Innovation System

Series Report 4: Promoting Simultaneous R&D, Registration and Review of Innovative Drugs

China Pharmaceutical Innovation and Research Development Association (PhIRDA)
R&D-Based Pharmaceutical Association Committee (RDPAC), China Association of Enterprises with Foreign Investment

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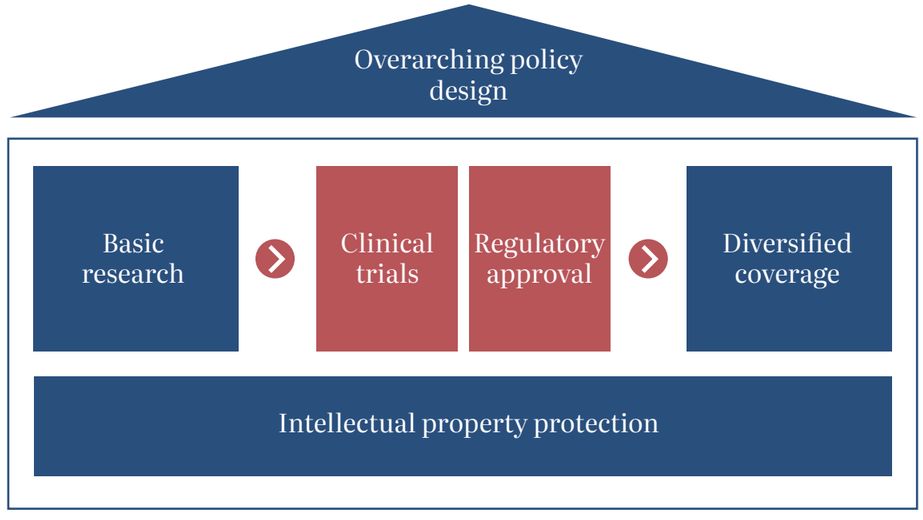
Preface

Fostering China Pharmaceutical Innovation System is a series of reports, of which Report 1: 2015-2020 Review and Future Outlook outlined the framework of the pharmaceutical innovation system for the period of 2021 to 2025, Report 2: Activating the Source of Innovation: Investing in the Basic Research focused on sources of sustainable development of the pharmaceutical innovation system and Report 3: Multi-layer Medical Security System to Improve People's Health and Drive High-quality Industry Development paid attention to China's medical security system and the payment system for innovative drugs. This report, Report 4: Promoting Simultaneous R&D, Registration, and Review of Innovative Drugs, focuses on clinical research and regulatory approval in light of China's ongoing reform of the drug review and approval system, which was on fast track over the past five years (Figure 1).

Figure 1: "Clinical research" and "Regulatory approval" as the core of the pharmaceutical innovation system from 2021 to 2025



The purpose of realizing simultaneous R&D, registration and review is to promote the alignment of translational research and clinical development of innovative drugs in China with that globally. To this end, the China Food and Drug Administration (CFDA) joined The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) in 2017 and was successfully elected as an ICH Management Committee (MC) member in 2018, with the National Medical Products Administration (NMPA) (the successor to the CFDA) being re-elected as ICH MC member in 2021. China's active involvement in the ICH has seen globally accepted technical requirements for drug development and registration being embraced and becoming a driving force for reform and innovation within the Chinese drug review system. To date, utilizing 'Chinese efficiency', China has fully implemented more than 70% of all ICH guidelines, and as such, is well down the road of internationalization, thereby creating favorable conditions for China to achieve simultaneous R&D with other countries in the world, which in turn provides Chinese patients with timely access to the latest innovative drugs, and helps local Chinese pharmaceutical companies to advance innovation.

Putting more effort into promoting simultaneous R&D, registration and review is meaningful from three perspectives. Firstly, it will enable Chinese patients to have earlier access to global innovative drugs under the guiding principle of 'putting people at the core'; secondly, it will encourage greater alignment of China's pharmaceutical innovation system with those of other countries, thereby improving mutual recognition and realizing integration into the global innovation system; and thirdly, it will help improve China's pharmaceutical innovation system, especially its overall R&D and review capacity. In summary, such effort ensures sustainable development of pharmaceutical innovation in China and strengthens China's role and influence in this realm globally.

This report contains an in-depth analysis of the current deep-seated challenges facing simultaneous R&D, registration and review, with a focus on registration and regulatory science, the efficiency and regulation of clinical research, and clinical research capacity-building. Through analysis of the current situation and case studies, the report provides well-targeted and forward-looking recommendations, ten in all, on how to promote simultaneous R&D, registration, and review as follow.

Three ways to break through current bottlenecks

1. Develop rational application requirements relating to human genetic resources and optimize the application process to improve efficiency.
2. Set more scientific requirements for the enrollment of Chinese subjects and enhance mutual recognition of global data.
3. Standardize and synchronize standard operating procedures across clinical institutions and ensure high-efficient implementation thereof.

Five foci to form a sound system

1. Streamline the review processes and encourage clinical value-oriented review.
2. Set more scientific requirements for dossiers submitted for review and approval with reference to global standards.
3. Promote the implementation of marketing authorization holder mechanism in line with global standards.
4. Establish clinical study platforms and dedicated clinical study teams to help institutions clarify their roles and accumulate management experience in exploratory clinical trials.
5. Optimize the incentive mechanism for, and resources invested in, clinical studies.

Two guarantees to drive continuous improvement

1. Guarantee talent, including capacity and capability building of regulatory teams and training of professional talent by means of formal and informal education.

2. Guarantee systems, including improving the regulatory system to make it more scientific, transparent, risk aware and predictable, and promoting the construction of a digital platform for clinical research.

We would like to express our sincere gratitude and appreciation to the external experts and member companies of PhIRDA and RDPAC for their valuable advice and strong support during the preparation of this report.

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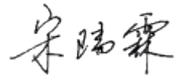

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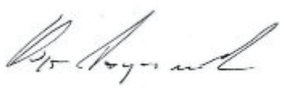

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Note: The descriptions, analyses and recommendations in this report are based on the information available at the time of preparing the report. Given the dynamic changes in policies and rapid development of the industry, the contents of this report may not always be up to date.

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Chapter 1
Importance of promoting simultaneous R&D, registration and review

Over the past five years, China's admission to the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and the introduction of several policies reforming the drug review and approval system have laid the foundation for promoting the simultaneous R&D, registration, review and marketing of new drugs. In this historical context, more scientific regulatory requirements and a more efficient clinical study process are required to further shorten the time lag between the marketing of new drugs in China and elsewhere in the world, to enhance patient benefits, facilitate the upgrading of the innovation system and promote the sustainable development of the industry. At the same time, the whole process of new drug R&D, registration and review requires the oversight of several government authorities, including the National Medical Products Administration (NMPA), the Ministry of Science and Technology (MOST), the National Health Commission (NHC), the China National Intellectual Property Administration (CNIPA), the National Healthcare Security Administration (NHSA) and the General Administration of Customs (GAC), etc. Full collaboration and cooperation among government authorities, and between government authorities and companies and researchers, is essential if simultaneous R&D, registration and review is to be achieved.

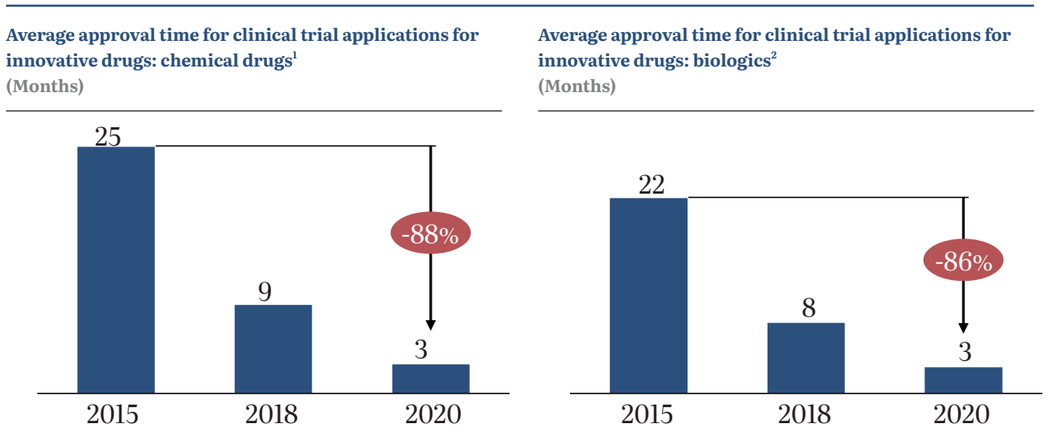
Background: Reform of the review and approval system has driven the accelerated marketing of new drugs, enabling the simultaneous global marketing of innovative drugs

Since 2015, China has issued a series of important documents on review and approval reform to point the way for accelerating the reform of drug regulatory legislation. The approval time for clinical trials was once a link that seriously restricted the speed of approvals of new drugs. In 2018, the 60 working days implied for clinical trial application (CTA) were remarkable advances, significantly improving the efficiency of clinical trials. In 2019, the Standing Committee of the National People's Congress considered and adopted the newly revised Drug Administration Law to solidify the achievements of the reform of the drug review and approval system from a legal perspective. Four accelerated approval pathways for the registration and marketing of new drugs are clearly stipulated in the latest edition of the Drug Registration Regulation published in 2020, including breakthrough therapy, conditional approval, priority review and approval, and special approval.

The former China Food and Drug Administration (CFDA), now the National Medical Products Administration (NMPA), joined the ICH in 2017 and was elected as an ICH Management Committee (MC) member in 2018, being re-elected as ICH MC member in 2021. This development has led to China's standards for drug registration becoming more scientific, technical requirements for drug registration being progressively harmonized with international requirements, and optimal conditions for China's simultaneous R&D being created, all of which play an important role in establishing a foundation for China to participate in global simultaneous R&D, registration and review.

In summary, the review efficiency of the NMPA has improved significantly over the past five years. Since 2016, China has seen a year-on-year rise in the number of drug registration applications, including a 51.7% increase in 2018 alone. Since 2019, the drug review backlog has been addressed, and the number of review assignments completed has increased by 30%. By 2020, the overall on-time completion rate of the review of drug registration applications was 94.5%, and it has been over 95% since July 2020. In 2020, the Center for Drug Evaluation (CDE) accepted 1,618 clinical trial applications involving an implied license, and the on-time review completion rate was 99.9%, while from January to April 2021, the on-time review completion rate was 100% with the average review time having been reduced from 16 months in 2015 to its current level of 50 days. The significant improvement in the approval time for clinical study applications and marketing authorization applications (MAA) for innovative drugs in China (Figure 2) has brought about a significant increase in the number of innovative drugs (including Category 1 innovative drugs and overseas branded drugs) approved in China in recent years, approaching the level seen in the United States, the European Union and Japan (Figure 3).

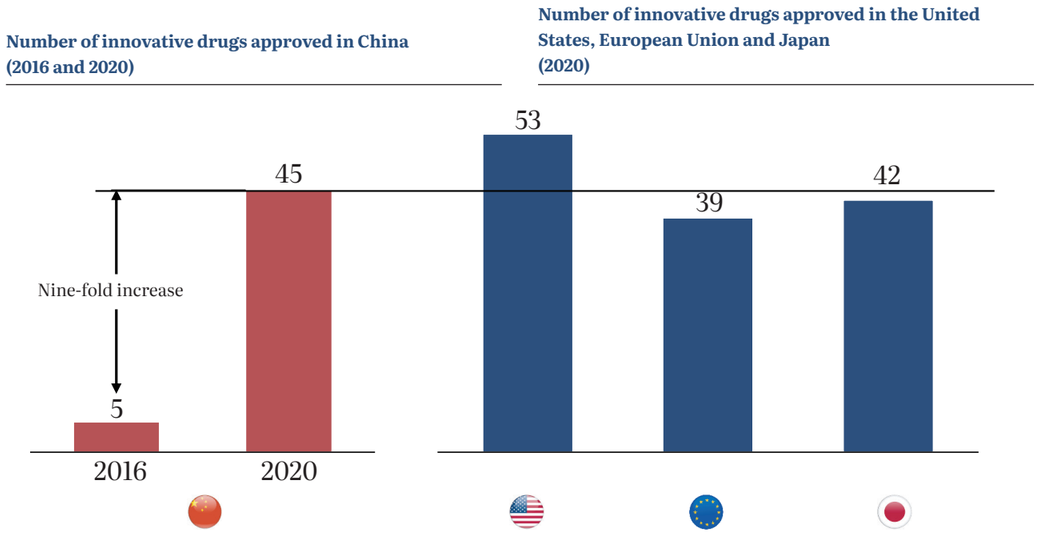
Figure 2: Significantly accelerated review and approval of innovative drugs



1. Includes category 1.1 innovative drugs and category 5.1 branded drugs.
2. Includes category innovative therapeutic biological products and category 3 branded therapeutic biological products.

Source: GBI

Figure 3: Approval of innovative drugs1 in China (2016 and 2020)



1. USA: FDA-certified New Molecule Entity (NME); EU: EMA-designated new drugs containing any new active substances; Japan: PMDA-approved new drugs containing any new active ingredients; China: (in terms of registration classification) category 1.1 and 5.1 chemical drugs, as well as category 1 and 3 biological products, excluding traditional Chinese medicine and any branded drug approved for the first time before 2020 or whose re-registration occurred in 2020 as well as any branded drug approved after any of its generic drugs had been marketed and any new indication for the same product that has been added in China,

Sources: GBI, NMPA 2020 Drug Review Annual Report, FDA, EMA and PMDA

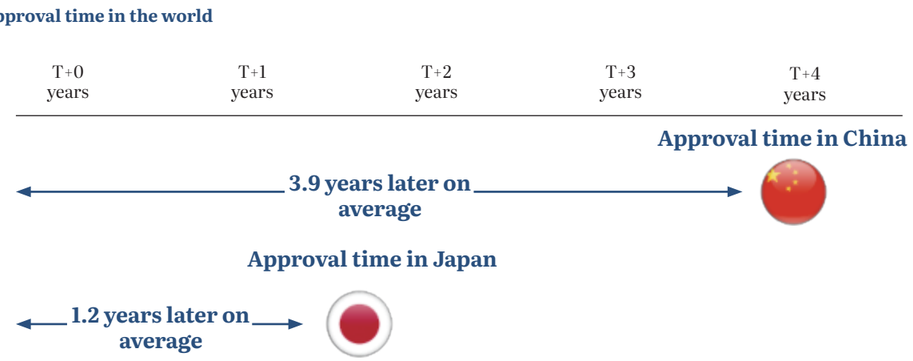
Current Gap: 'Time Lag' Between R&D, Registration and Review in China and the World

The 'blended measures' that have been implemented to reform the drug review and approval system have greatly shortened the approval time for new drugs and enabled the simultaneous registration and marketing of new drugs in China and overseas. However, gaps remain. With respect to the nearly 30 overseas manufactured branded drugs approved for the first time in China in 2020 (excluding re-registration and where generic drugs were available in China before the approval of the branded drug, and any new indication having been added for the same product), the approval time in China was on average 3.9 years after approval had been granted in other global markets (median of the 30 products). In contrast, an analysis of branded drugs from multinational pharmaceutical companies approved for marketing in Japan in 2020 showed that the time lag between approval in Japan and the first approval in other global markets was only 1.2 years on average (Figure 4). The lag in approval time in China is due to the fact that the acceleration brought about by China's review and approval system reform has not yet been fully manifested as of 2020. On the other hand, China has not yet fully joined in global simultaneous R&D, resulting in the late submission of new drug applications in China. Furthermore, 19.7% of global multi-center clinical trials conducted in 2018 included Japan, while only 9.4% included China (Figure 5).

The alignment of the regulatory system in China with international standards, which are global synchronization-oriented, and the overall improvement of clinical study capabilities are essential to the globalization of China's local innovation. For multinational pharmaceutical companies, China's participation in global simultaneous R&D is key to achieving simultaneous submission and approval of applications in China. Looking back to industry practice over the past few years, **China's participation in global simultaneous R&D and registration has achieved results, though it is still faced with many challenges.**

A survey conducted by RDPAC in 2020 showed that between January 2017 and October 2020, only 8.5% of its member companies' new drug applications (NDA) (17 projects in total) were simultaneously submitted (simultaneous submission here means that the NDA submission in China occurred before the first approval in global markets), most of which involved expansion of product indication or new combination drugs, and few of which involved simultaneous submission of applications for the first indication of an innovative drug. Multinational companies usually have to start the process four to five years in advance if they want to achieve simultaneous global submission of applications for innovative drugs, so for products with an NDA submitted simultaneously before 2020, it would have meant that China needed to be taken into consideration for global R&D and registration in or before 2015. Due to the long time taken for drug registration and a large backlog of registration applications before the start of China's review and approval reform in 2015, a company needed to be quite forward-looking if it were to include China into simultaneous global R&D and registration. However, there is reason to believe that the proportion of products involved in a simultaneous application submission process will continue to increase in the future.

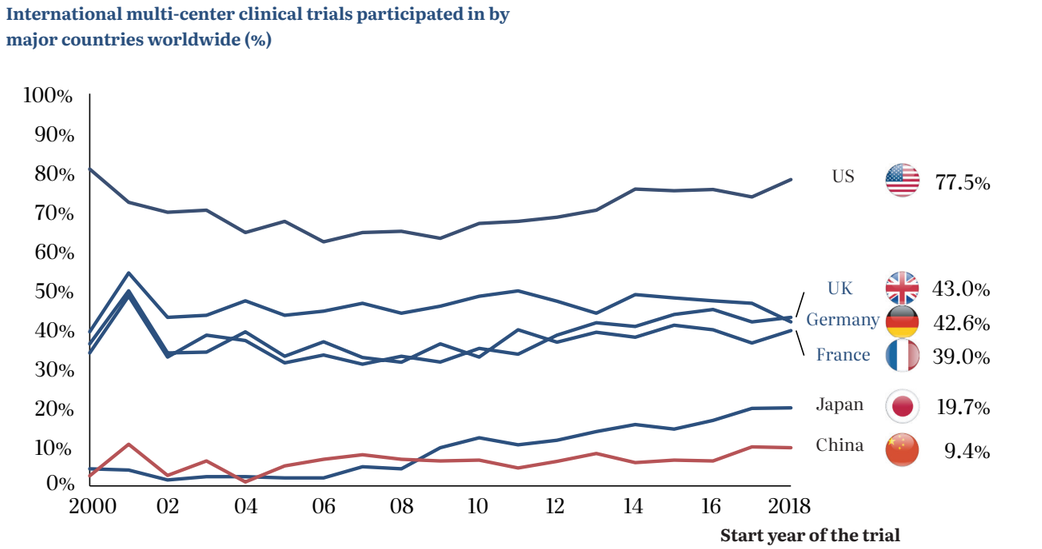
Figure 4: Average time lag between approval of innovative drugs in China and Japan in 2020 and the first approval in global markets 1



1. New drugs approved in China and Japan include only those products that had already been marketed in other markets worldwide; for drugs with multiple indications, the time when the product was given marketing approval for the first indication applies; average time lag is the median for all products.

Sources: GBI; PMDA

Figure 5: China's rate of participation in global multi-center clinical trials, 2000-2018



Source: Policy News No. 58, November 2019, Analysis of Participating Countries in International Multi-center Trials in Japan

Importance of achieving simultaneous R&D, registration and review

Shortening the existing time lag and achieving simultaneous R&D, registration and review are of great significance when it comes to accelerating the marketing of innovative drugs in China and overseas for the benefit of patients worldwide, the alignment of China's pharmaceutical innovation system with international standards and its mutual recognition and upgrading, and promoting the sustainable development of the industry.

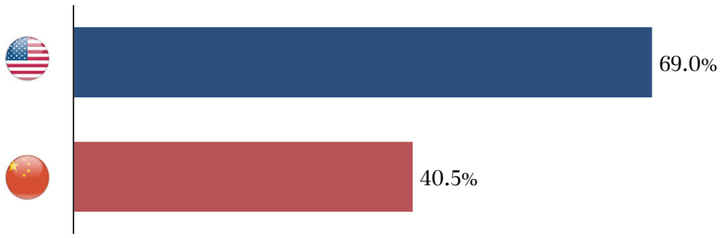
First, achieving simultaneous R&D, registration and review will help accelerate the marketing of innovative drugs in China and overseas for the benefit of patients worldwide. The large number of patients in China (i.e. a clinical resource) is a major advantage when it comes to helping to improve the efficiency of global R&D. The implementation of global simultaneous clinical studies will help accelerate the R&D and registration of innovative products in China and allow Chinese patients to simultaneously benefit from global innovation as early as possible. Thanks to a series of reforms of the regulatory system and upgrading of the R&D system over the past five years, significant progress has been made in the speed of approvals and the number of innovative drugs approved in China, improving the accessibility of innovative drugs to Chinese patients. However, there are still huge unmet clinical needs in China. Using malignant tumors as an example, although the five-year survival rate of Chinese patients has increased from 30.9% a decade ago to the current rate of 40.5%, there is

still much room for improvement compared with the near 70% survival rate in the US (Figure 6). Simultaneous R&D, registration and review will help make innovative drugs available to Chinese patients earlier, which, when combined with proper clinical application and upgrading of payment security for innovative drugs, will ultimately improve drug accessibility and benefit patients. At the same time, China's local innovation achievements can benefit a wider range of global patients and promote the building of a global community of health for all by going beyond China's borders as soon as possible (Figure 7).

Second, achieving simultaneous R&D, registration and review will help improve the capabilities of China's pharmaceutical innovation system to further integrate into the global innovation system. Simultaneous R&D, registration and review encompass higher requirements for the scientificity of regulatory policies, the soundness of systems, review capabilities and transparency, and the reasonableness of key processes and links in clinical R&D. The advancement of related work will help to provide a solid foundation for China's overall pharmaceutical R&D system, including promoting China's alignment with international standards, optimizing regulatory approval, and enhancing clinical study capabilities. Including China in early stages of development and achieving simultaneous submission and marketing of new drugs in China will help drive China towards playing a key role in the global R&D system.

Figure 6: Five-year survival rate of patients with malignant tumors

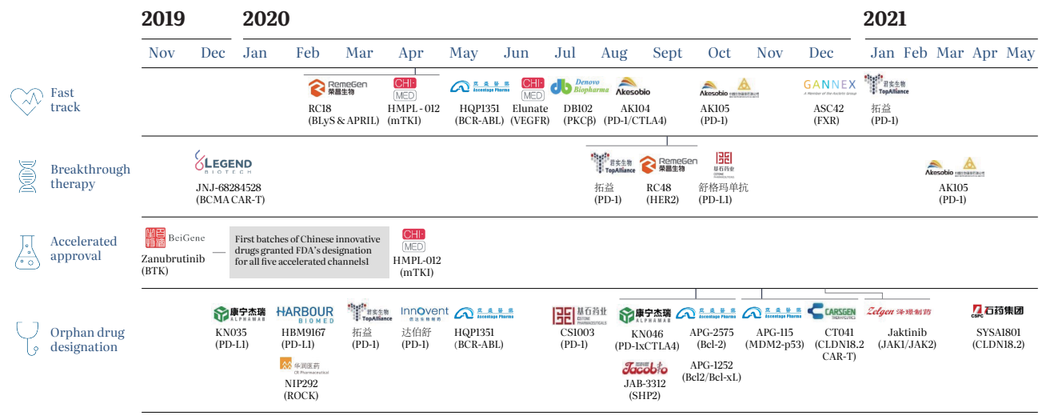
5-year survival rate of patients with malignant tumors



Source: Cancer Statistics Review, 1975-2016 - SEER Statistics; Zeng H, Chen W, Zheng R, et al. Changing cancer survival in China during 2003-15: a pooled analysis of 17 population-based cancer registries[J]. *The Lancet Global Health*, 2018, 6(5): e555-e567.

Figure 7: Internationalization progress of China's local innovative products

Examples of Chinese innovative products granted accelerated channel designation by the USFDA



1. For different indications; 2019: accelerated approval, priority review and breakthrough therapy; 2018, fast track; 2016, orphan drug designation

Source: News release; US FDA; company website

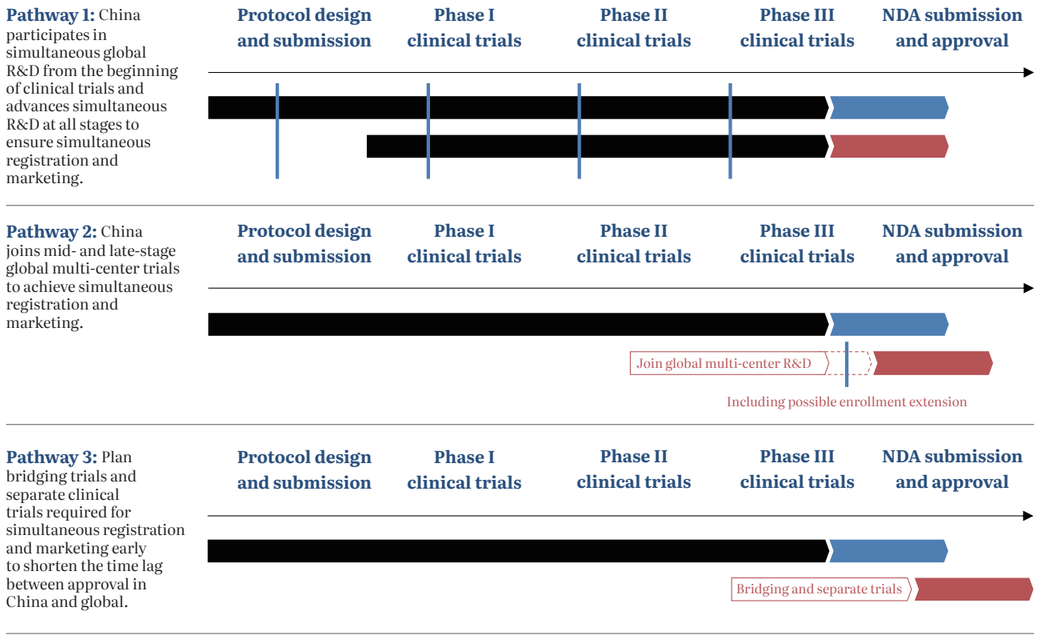
Finally, achieving simultaneous R&D, registration and review helps enhance the overall R&D capability and promotes the sustainable development of the innovative drug sector. Considering the high-investment and high-risk nature of the innovative drugsector, simultaneous R&D, registration and review will be helpful for China's local innovative drug companies to share their innovation achievements with the world more quickly, thereby establishing a virtuous cycle of investment and return to underpin the sustainable development of the industry. From a multinational pharmaceutical company's perspective, better integration of China into global R&D eliminates the need to conduct separate clinical studies for registration in China and allows for more efficient investment of R&D resources.

Key dimensions of vigorously promoting simultaneous R&D, registration and review

For China, there are currently three potential pathways to achieve simultaneous global R&D, registration and review with respect to innovative drugs (Figure 8).

Pathway 1: Based on the concepts of ICH E17, innovative drug developers include China in the early stages of clinical trials, inform the appropriate Chinese regulatory agencies in a timely manner about key issues and links in the R&D process for the new drug, and achieve simultaneous registration and marketing in China by synchronizing all stages of clinical studies.

Figure 8: Three potential pathways for China to pursue simultaneous R&D, registration and review



Pathway 2: Based on the principles of the ICH E17 Guideline, innovative drug developers include China in mid- and late-stage confirmatory clinical trials of a drug's global R&D to ensure that sufficient data are available (including, if necessary, extending the enrollment period in China) to support simultaneous registration and marketing in China.

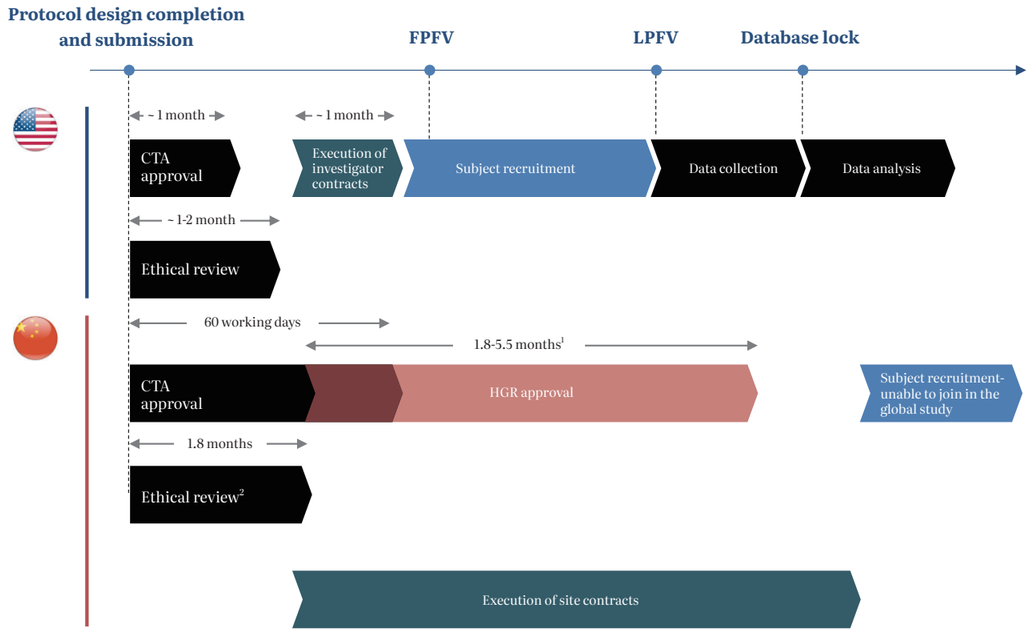
Pathway 3: If China is unable to participate in international multi-center clinical trials, the bridging trials and separate clinical trials required for simultaneous registration and marketing in China should be planned as early as possible. It should be noted that the separate trials would result in increased R&D costs for pharmaceutical companies and a prolonged R&D cycle.

Based on a review of the three potential pathways above, **improving the scientificity of registration supervision and the efficiency of clinical studies are the keys to promoting global simultaneous R&D, registration and review.** For China, achieving simultaneous global R&D, registration and review requires the full cooperation of various regulatory authorities, companies and researchers at all key points of the process, with any delays potentially impacting negatively on the overall R&D and registration process. Currently, compared with the US which is in the first echelon of global pharmaceutical R&D, China has a significantly extended timeline for clinical trial start-ups, and further improvements to the overall process are required.

With respect to participating in simultaneous global R&D from the commencement of early clinical trials (pathway 1), China often misses the opportunity to participate because there is almost no recruitment time window due to the long time required before being able to start a trial (Figure 9). Furthermore, with respect to global confirmatory clinical trials (pathway 2), the recruitment time window in China is usually shorter with greater uncertainty compared with other participating countries, causing sponsors to have concerns about clinical trial timelines being met, which has to some extent been the reason behind China's failure to fully join in simultaneous global R&D (Figure 10). **More scientific regulatory requirements and a more efficient clinical study process will help to harmonize and synchronize Chinese and global R&D in terms of timelines.**

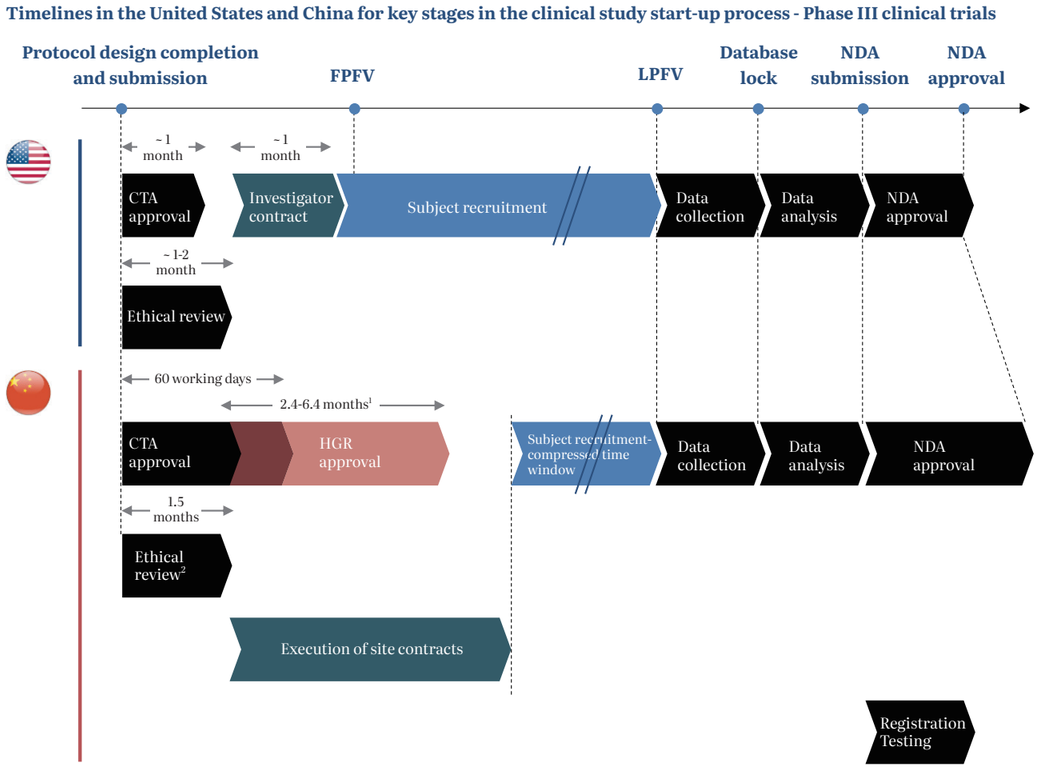
Figure 9: Comparison of the timelines of key links of early clinical trials between the US and China

Timelines in the United States and China for key stages in the clinical study start-up process - Phase I and Phase II clinical trials



1. Based on the results of the Survey of Clinical Operations of RDPAC member companies in 2020, 25th percentile: ~1.8 months; median: ~4.1 months; 75th percentile: ~5.5 months.
2. Assuming the ethical review is conducted in parallel with the submission of the clinical application.

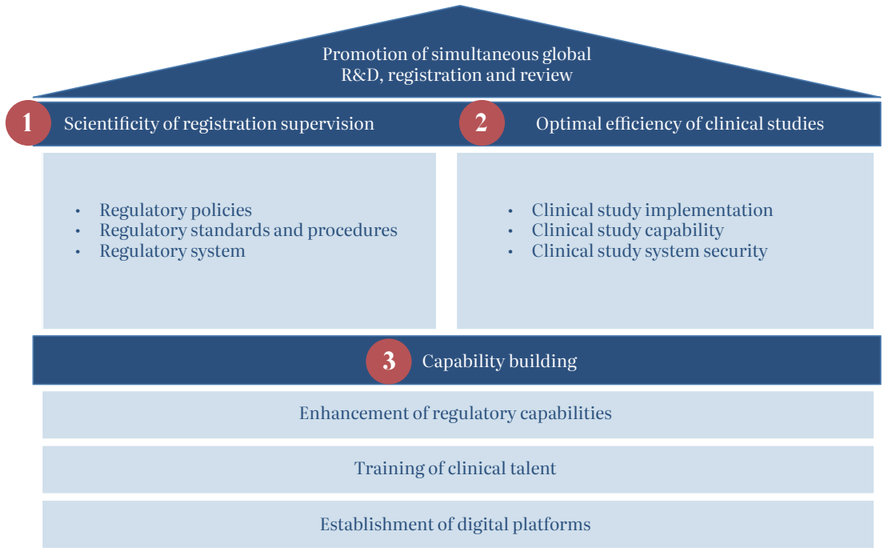
Figure 10: Comparison of timelines of key links of clinical trials for registration between the US and China



1. Based on the results of the Survey of Clinical Operations of RDPAC member companies in 2020, 25th percentile: ~2.4 months; median: ~3.7 months; 75th percentile: ~6.4 months.
2. Assuming the ethical review is conducted in parallel with the clinical application, with the timelines for data collection, data analysis, and NDA review and approval consistent with those in the US.

The scientificity of registration supervision is reflected in three aspects: **regulatory policies, regulatory standards and procedures, and the overall regulatory system.** On the premise of ensuring scientificity, global clinical data must be made full use of during the drug registration process in China with a sufficient recruitment time window for international multi-center clinical trials conducted in China and registration applications being submitted simultaneously after the trial data lock. The **efficiency of clinical studies** can be optimized from three aspects: **clinical study implementation, clinical study capabilities and clinical study system security,** all of which place require the efficient recruitment and enrollment of Chinese clinical trial subjects and high-quality trial data. In addition, enhancement of regulatory capabilities, training of clinical talent, and establishment of digital platforms are also prerequisites for achieving simultaneous global R&D, registration and review (Figure 11).

Figure 11: Key prerequisites for achieving simultaneous global R&D, registration and review



Chapter 2
Scientificity of registration supervision: Status quo and current challenges

The scientificity of registration is currently facing challenges on three fronts - scientificity of regulatory policies, scientificity of regulatory standards and procedures, and scientificity of the regulatory system.

Scientificity of regulatory policies

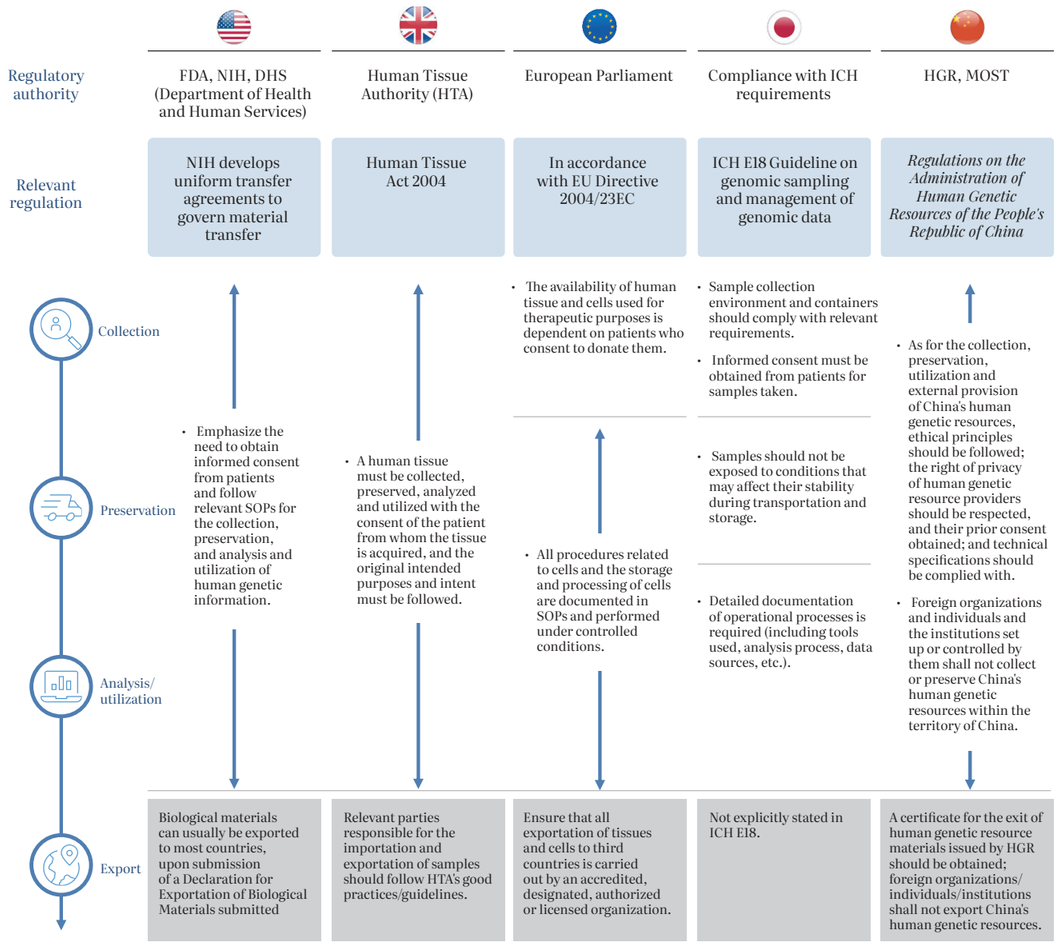
The pain points with respect to the scientificity of regulatory policies are the **scientificity and transparency of the Human Genetic Resource (HGR) administration and approval** and the **gap between the design and the actual implementation of the Marketing Authorization Holder (MAH) system**.

1. Scientificity and transparency of HGR approval

Clinical studies in China must be conducted in strict compliance with the regulatory requirements pertaining to Good Clinical Practice (GCP) and are subject to parallel regulation by the Human Genetic Resource Administration (HGR). In recent years, under strong supervision, administration, education and guidance from HGR, China's pharmaceutical R&D industry has paid increasing attention to the protection and reasonable utilization of human genetic resources (HGR), as reflected by an increased level of awareness within the pharmaceutical industry as a whole and the concomitant establishment of internal processes and systems within individual companies. Considering the ongoing globalization of China's pharmaceutical innovation and the fact that local innovators receive foreign investment, HGR management is of particular relevance to multinational and local pharmaceutical companies. Compared with developed countries and regions, administrative approval of HGR has become the major impediment to the speed with which clinical studies can be implemented in China. Therefore, China may miss the subject recruitment window of global early clinical studies, with the subject recruitment window of mid- and late-stage clinical studies also being greatly reduced.

In terms of regulatory requirements, ICH guidelines emphasize the importance of establishing a system of informed patient consent and the implementation of standard processes. At the same time, while ICH guidelines for sample export controls are relatively lax, China maintains strict requirements for the regulation of genetic resources, particularly with respect to sample export controls (Figure 12). In addition, a high bar has been set for IP sharing requirements in the current regulation, though those requirements are somewhat unclear, especially with respect to management scope, data backup and filing. Furthermore, a HGR pre-approval mechanism during the clinical trial start-up stage is still lacking. In terms of regulatory oversight, the scientificity and transparency of HGR approval affects the overall R&D timeline.

Figure 12: Human genetic resource (HGR) regulation in China and major developed economies



Sources: FDA, UK HTA, EMA, PMDA, NMPA

The main current challenges with respect to HGR approval are:

Management process: Compared with developed countries, administrative approval of HGR has become the main impediment to the speed with which the start-up stage of clinical studies can be realized in China. The current cumbersome approval process makes it difficult for China to participate in a timely manner in the subject recruitment

window of global early clinical studies, whilst at the same time compressing the subject recruitment window for mid- to late-stage global clinical studies.

Data: The current management scope for data backup and filing under HGR's guidelines is unclear, and furthermore, requirements are cumbersome and the review process takes too long.

Sample export: The review and approval process for clinical studies requiring exportation of biological samples is stringent, with any delay or withdrawal of approval greatly affecting China's opportunities to participate in simultaneous global R&D, especially in early studies, as the drug candidates under study are still in the early methodological exploration stage. Uncertainty at this stage in an early study is more complicating than it would be in mid- and late-stage clinical trials, as the judgment of testing results may affect the efficacy of treatment because of methodological deviations among different laboratories. Also, due to sample export restrictions, companies may have to exclude some exploratory testing indicators, which would compromise the completeness of patient data. So, in summary, the stringent controls around export of HGR affects China's ability to participate in global early clinical studies and reduces the value of Chinese patient data.

Intellectual property: Currently, a high bar has been set with respect to intellectual property sharing, though there is a lack of clarity with cooperating partners interpreting intellectual property allocation differently and thereby limiting consensus.

Researcher-initiated studies and real-world studies: For researcher-initiated clinical studies, the sponsor should be a site of a Chinese entity, with the pharmaceutical company, as the funding provider, assuming no role in the study and with no right to influence the study results or study data in any way. However, the funding provider should have reasonable access to study data and such data should be subject to reasonable HGR management.

2. Gap between the design and the actual implementation of the MAH system

The manufacturing license is independent of the marketing authorization (MA) under the MAH system, which enables more efficient and flexible market resource allocation and thereby encourages innovation. Based on the outcomes of the pilot implementation of the MAH system, the system was formally established in China in 2019 by means of the Drug Administration Law of the People's Republic of China (2019 Revised Version). The current MAH system in China clearly specifies the requirements to qualify as a MAH, the relationships with manufacturing and sales, and the situation where the MAH is an overseas company. Compared with the designs of the MAH systems in the US, the EU and Japan, the design of the Chinese system takes into account the situation in China and provides the possibility of fully realizing the system dividends in the long term under the main framework of the Drug Administration Law. At this stage, however, the full implementation of the MAH system has some challenges to overcome, namely: obstacles in the administrative pathway implemented for cross-border MAHs, insufficient promotion of the capability combination among the MAHs of conglomerates' subsidiaries, and unclear provisions with respect to segmented, multi-site and CMO manufacturing in the manufacturing license.

Obstacles in the administrative pathway implemented for cross-border MAHs[1]

Although the Drug Administration Law does not restrict companies in China from acting as MAHs for drugs manufactured overseas, nor does it restrict foreign companies from acting as MAHs for drugs manufactured in China, the actual implementation pathway of the two cross-border situations - manufacturing license in China, Marketing Authorizsation (hereinafter as MA) outside China and manufacturing license outside China, MA in China - has not been fully opened up.

Manufacturing license in China and MA outside China: For a multinational pharmaceutical company supplying products to multiple countries, its group headquarters of that company cannot be the MAH of each country where the products are marketed due to the restrictions imposed by the regulatory framework of individual countries, nor can it set up manufacturing site(s) in every country in the world. So, an overseas company cannot be the MAH of imported products in China at this stage. Also, some overseas companies own packaging companies that package imported products in China, but currently, such companies cannot be MAHs in China. This situation, to a certain extent, deprives foreign companies of the right to market drugs manufactured by themselves, which affects their commercialization decisions when it comes to the Chinese market, and thus potentially affects the accessibility of drugs to Chinese patients.

Manufacturing license outside China, MA in China: For a Chinese company, if it wants to become a MAH in China, it is required to obtain a manufacturing license and have its manufacturing site(s) in China, which may result in Chinese companies being unable to fully realize the optimal allocation of resources for manufacturing, thereby negatively impacting on their global competitiveness. Given the ongoing rapid development of China's pharmaceutical industry, more and more Chinese companies have acquired or are considering acquiring innovative drugs and/or companies overseas. However, due to a cross-border MAHs being unavailable, even after acquiring innovative drugs overseas, Chinese companies cannot act as MAHs in China and cannot obtain the MA of the acquired products from a legal perspective. So, they are forced to act as the MAH's agent to indirectly 'service' the products for which they should have the MA. Alternatively, the company could become the MAH in China by transferring the manufacturing of the acquired products to China, but the requirements and procedures for such a transfer are quite complex, which may greatly delay the marketing of innovative drugs in China or may even result in the transfer of manufacturing failing, ultimately affecting the accessibility of drugs to Chinese patients.

Unclear provisions on segmented, multi-site and CMO manufacturing in the manufacturing license

Segmented, multi-site and CMO manufacturing are essential for the efficient allocation

[1] Long-term Opportunities of MAH System in China (Part 1)

of manufacturing resources, and in this regard, there is still room for improvement in the current regulatory system. In the case of biological products, for example, firstly, there are differences in the segmentation requirements for the manufacturing in China and that outside China. For biological products manufactured in China, the products and their active pharmaceutical ingredients (API) are required to be manufactured at the same site in China; in contrast, biological products and their APIs that are manufactured outside China can be manufactured at different sites in different countries by means of segmented manufacturing. Secondly, the regulatory strategies for multi-site and CMO manufacturing still require clarification. Specifically, based on the current regulatory requirements in China, although there is no clear regulatory restriction, biological products manufactured in and outside China can generally have only one manufacturing site for one process; the steps and pathways at the implementation level for the CMO manufacturing of biological products in China are unclear; and it is also unclear whether APIs of biological products can be reviewed through the joint review of preparations and their APIs, excipients and packaging materials (DMF) as per APIs used in chemical drugs.

Scientificity of regulatory standards and procedures

1. Full implementation of ICH E17 still to be promoted

In the era of globalization of drug R&D, it is quite challenging to conduct a global drug R&D program for several reasons. For example, data from the same multi-regional clinical trial (MRCT) often has to be submitted to multiple regulatory authorities, and different countries and regions begin to accept data from a multi-regional clinical trial as primary evidence to support approval for marketing, and unify regulatory perspectives through the development and implementation of a series of ICH guidelines to create conditions for simultaneous global R&D.

As mentioned above in this paper, there is still room for improvement in the proportion of simultaneous submissions in China, and the time for clinical trial start-up in China is one of the main factors restricting China's participation in simultaneous global R&D. Considering the overall short trial recruitment time in China, meeting the requirement for the number of subjects to be enrolled in China in a competitive global enrollment system is proving difficult from the perspectives of global trial planning and implementation. In order to encourage simultaneous R&D, the industry is urgently calling for a more comprehensive alignment of China’s regulatory system with the international system.

The main operational challenges currently potentially precluding the inclusion of China in global innovative drug R&D initiated by multinational pharmaceutical companies are:

- The slow clinical trial start-up time in China compared with that in other countries, and the required proportion of Chinese patients lead to potential delays in global R&D timelines. Therefore, multinational pharmaceutical companies do not prioritize the inclusion of China into simultaneous global R&D when developing global R&D strategies.
- For some drugs under study that are already undergoing mid- to late-stage global clinical trials, the drug regulatory authority requires the conduct of a separate Phase I study in China and may require that the Phase I study precedes Phase III, further depriving China of the opportunity to join in pivotal simultaneous global Phase III clinical studies.

The NMPA requires that when data from international multi-center drug clinical trials are used to support drug registration applications in China, the sample size of Chinese subjects be sufficient for evaluating and making inferences about the safety and effectiveness of the investigational drug in Chinese patients and meet statistical and related regulatory requirements. In the implementation of clinical studies, this requirement is often reflected in the requirements for the enrollment of Chinese subjects. China needs to further implement the requirements of the ICH E17 guideline for multi-regional clinical trials and make scientific arrangements for the requirements for the enrollment of Chinese subjects based on a comprehensive analysis of multiple factors.

2. Review process to be further improved to support simultaneous R&D

The main issues related to the review process that are currently affecting companies' inclusion of China into global innovative drug R&D are:

- The process requirements for registration testing in China are different from those in other ICH member countries, and in practice, the overall time limit for obtaining MA is affected due to issues surrounding samples, method verification, implementation of the Chinese Pharmacopoeia, the requirement for the relevant substances in raw materials to be tested in the preparations, and the procedure and process for standard re-review. Although the newly revised Provisions for Drug Registration allows proposals for drug registration testing, applicants can only make such proposals to the relevant authority after having completed CMC studies to support the marketing of the drug, to determine specifications, and to verify commercial-scale manufacturing processes, all of which will affect the practical application of the proposed registration testing.
- During on-site verification of participating sites, questions beyond the scope of on-site verification will be raised with immediate responses being required, which subsequently affects the progress of verification. Therefore, it is necessary to further clarify the scope and requirements of on-site verification by taking scientificity and practical application into consideration.
- There is no feedback process with respect to suggestions and requests made by the CDE during the clinical trial notification process.
- The resumption of suspended clinical trials requires the resubmission of supplementary information, disrupting the ability to conduct studies simultaneously in China.

3. Requirements for registration application dossiers to be further optimized and ICH guidelines to be further implemented

The additional technical material and supporting documents required by China take a long time to prepare and are complicated, and are inconsistent with international practice, thereby affecting the speed with which clinical trial and MA applications can be submitted.

Clinical trial applications

- There are many requirements for administrative documents and drug information-related materials in Module 1 (Regional Administrative Information).
- Materials in Module 2 (Overviews and Summaries of Study-related Content) are required to be prepared separately for China at the stage of clinical trial application submissions.
- The requirements for submission of batch manufacturing records at the stage of clinical trial application submission require discussion.

During clinical studies

- There are many data requirements for the Development Safety Update Report (DSUR) during the R&D process in China.
- Marketing authorization application
- The requirements for the submission of regional CMC data (M1 and M3) remain to be discussed, including manufacturing inspection procedures.

In addition, compliance with ICH guidelines needs to be further strengthened, especially the implementation of the Q-series (quality) guidelines, and the Chinese Pharmacopoeia needs to be further harmonized with ICH requirements.

4. Four accelerated channels for registration to support innovation need to be supported by detailed rules

It is specified in the Drug Administration Law and the Provisions for Drug Registration that a system for the accelerated approval of registration and marketing of drugs should be established to support clinical value-oriented drug innovation. Currently, China has established four accelerated channels, i.e. breakthrough therapy, conditional approval, priority review and approval, and special approval (Figure 13), and both regulatory authorities and the industry have found room for improvement while gaining corresponding experience in practice.

Figure 13: Accelerated channels for the marketing of new drugs in China and in major developed economies

	Priority review	Accelerated review	Fast track	Breakthrough therapy	Orphan drug	Other channels
	Reduced approval time for drugs with the potential to significantly improve medical care level.	Drugs with outstanding clinical value can be accelerated to be marketed with 'surrogate endpoints' and clinical results can be supplemented later.	Drugs have the potential to meet unmet medical needs.	Innovative drugs for which preliminary clinical evidence suggests that they may be significantly superior to existing treatment options.	Drug for rare diseases	
US	**Priority review** Drugs that have achieved significant improvement in safety or effectiveness. Approval time reduced from 10 months to less than 6 months.	**Accelerated approval** Drugs developed for serious and fatal diseases that are more effective than existing treatment options and for which there are unmet needs.	**Fast track** New drugs for severe diseases that are more effective than existing drugs. Accelerated drug R&D and approval (e.g. increased communication with FDA and allows for CDER to review applications in advance).	**Breakthrough therapy** For pioneering new therapeutic drugs Increased FDA guidance based on Fast Track to promote effective drug development.	**Orphan drug** For drugs for diseases with a patient population of up to 200,000 Access to preferential treatment such as financial assistance, tax breaks, agreement consultation.	**Emergence Use Authorization** Authorized for use in public health emergencies to defend against chemical, biological, radiological, and nuclear threats, including infectious diseases.
EU	**Accelerated assessment** For new drugs that are expected to play a greater role in public health. Get feedback from CHPM within 150 days.	**Accelerated approval** For medicinal products developed for severe diseases, urgently needed for public health, rare diseases.		**PRIME** Potential novel therapies showing positive results in early clinical settings, or new drugs targeting unmet patient needs.	**Orphan** Drugs for rare diseases with an incidence of less than 0.05% for which no alternative treatment exists. Access to multiple preferential policies (normal review time).	**Exceptional Circumstances** Drugs for which clinical data collection is difficult, or for which data collection is restricted due to ethical reasons. Allow marketing with insufficient data, requirements for additional information and limited scope of application.
JP	**Priority review** For drugs for severe and rare diseases Approval time reduced from 12 months to less than 9 months.	**Expedited review** Drugs for which public applications are submitted, pre-assessed by the regulatory authority concerned and which are automatically included on the list of drugs subject for expedited review. No applications from individual applicants will be accepted.			**Drugs for rare diseases** Policies such as financial assistance, priority review, tax breaks, etc. for drugs for diseases with a patient population of up to 50,000 in Japan.	**Pre-review designation system** Required to meet the following conditions: 1. The drug should be of an epoch-making nature; 2. The disease should be severe; 3. The drug should have a high level of efficacy; 4. The drug has been developed in Japan before other countries, for which there is willingness to submit an application, and with access to a variety of preferential policies.
CN	**Priority review and approval** Drugs with obvious clinical value, such as undersupplied drugs, innovative drugs, pediatric drugs, innovative vaccines, etc. The review time limit is 130 days, with 70 days applying to drugs for rare diseases with an urgent clinical need.	**Conditional approval for marketing** Drugs for severe diseases or urgently needed drugs for which data from clinical trials demonstrates effectiveness and of which the clinical value can be predicted. Vaccines for public health emergencies or other vaccines that the NHC determines to be urgently needed and whose benefits outweigh the risks upon assessment.		**Breakthrough therapy** Innovative drugs or modified new drugs for the prevention and treatment of diseases that are seriously life-threatening or seriously affect the quality of life and for which there is no effective means of prevention or treatment, which have a clear clinical advantage over existing treatments as demonstrated by sufficient evidence. Priority is given in terms of allocation of resources and processing.		**Special approval** Drugs required for public health emergencies for which the NMPA orders accelerated drug registration and approval, and other work.

Sources: FDA, EMA, PMDA and NMPA

Using 'breakthrough therapy' as an example, applications for this accelerated pathway should be for innovative drugs or modified new drugs for the prevention and treatment of diseases that are seriously life-threatening or seriously affect the quality of life and for which there is no effective means of prevention or treatment, and which have a clear clinical advantage over existing treatments as demonstrated by sufficient evidence. Once the breakthrough therapy designation has been granted, the development of the drug will be greatly facilitated by means of comprehensive technical support and guidance from the regulatory authorities throughout the review, a significant reduction in the review time limit, and smooth inclusion into the priority review and approval channel at the stage of MAA submission. However, the timing of breakthrough therapy designation, which must be during clinical trials, is quite restrictive (usually no later than the conduct of Phase III clinical trials), which may result in some drugs that meet the aforementioned scope of application, but which are already in Phase III clinical trials, missing the time window for being designated as a breakthrough therapy designation. This may also preclude them from any of the accelerated channels because they fail to meet the scope of 'undersupplied drugs with urgent clinical need, innovative drugs and modified new drugs for the prevention and treatment of diseases such as major infectious diseases and rare diseases; specific pediatric drugs or vaccines', as specified in the priority review and approval procedure. In addition, Chinese patient data is required to be provided when applications are submitted for breakthrough therapy designation for some drugs, though whether the support of global clinical data alone would be sufficient should be scientifically considered. Another point for discussion is the reasonableness of a situation whereby if a new drug has been approved in a country after submission of an application for breakthrough therapy, should such an application be able to be rejected.

Regarding the 'priority review and approval procedure', it should be noted that an application for priority review designation must be submitted during the communication before a MA application has been submitted and be confirmed before an application is submitted for inclusion in the priority review and approval pathway at the time of MAA submission, if subsequent policy benefits are to be enjoyed. At this stage, communication for priority review has become the most critical limiting factor with respect to speed of MAA submissions (via the priority review pathway), diluting the favorable conditions provided by priority review policies that are intended to accelerate submissions.

At the same time, it should also be noted that the detailed rules for the rolling submission process for any of the accelerated pathways remain unclear. For example, rolling submissions require separate applications each time an application is submitted, and approval requirements may differ each time. It has been noted that any consensus reached with respect to allowing rolling submissions during MAA pre-submission meetings with applicants tends to be recorded differently by different reviewers, some of whom record the agreed upon material requirements clearly while others fail to do so, which subsequently affects the applicant's submission. Also, the authority responsible for accepting applications fails to coordinate and reach agreement with the reviewing authority, manifesting in issues such as the lack of uniform requirements for the specific submission process and materials.

It should be recognized that the introduction of regulatory review policies in China in recent years has been 'time reduced', which has largely stimulated and facilitated innovative drug R&D. However, more attention needed to be paid to the considerations of foreign regulatory authorities when designing the various pathways. For example, the US FDA includes terminal acceleration (priority review); accelerated entry into clinical trials, transition from series model to parallel model, rolling submissions, compact between steps; and recognition of intermediate or surrogate endpoints based on an understanding of the disease mechanism (classification of biomarkers) to support innovative design of clinical trials. Due to different national conditions and industry development stages, as for the four accelerated approval pathways established in China, although the experience of the US is unable to replicated completely, it still needs to be recognized that due to limited review resources, in the clinical value-oriented review process optimization, the detailed rules of the four accelerated review and approval pathways are not clear, and there is still much room for the dividends of the policy changes to be realized.

Scientificity of the regulatory system

With the ongoing improvement in the quality, efficiency and innovativeness of the pharmaceutical industry, a sounder drug regulatory system and stronger regulatory capabilities are needed to support the rapid and healthy development of the industry so that it can better meet patient needs. To this end, in April 2021, *Implementing Opinions of the General Office of the State Council on Comprehensively Strengthening the Capacity Building of Drug Supervision* (Document No.16) was issued. Document No.16 requires the reform of the review and approval system to be deepened, regulatory innovation to be promoted continuously, and a scientifically sound, efficient and authoritative drug regulatory system operating on the principle of 'People Foremost and Life First, to be established. This regulatory initiative involves improving the system of laws and regulations, implementing the *Drug Administration Law of the People's Republic of China* and the *Vaccine Administration Law of the People's Republic of China* along with supporting regulatory guidelines and standards, improving the inspection and law enforcement system, improving the emergency management system, and promoting digital management of the whole life cycle of a drug. There is a realization that it is necessary to align global standards, to fully participate in international regulatory harmonization mechanisms, to actively participate in the development of international rules, and to enhance the internationalization of regulation. It has also been deemed necessary, if China is to make the leap from a pharmaceutical power to a pharmaceutical powerhouse, it needs to overhaul its regulatory system to ensure that it is science-based, complies with appropriate legal requirements, and is harmonized with global standards, i.e. it is modernized.[2]

In recent years, the NMPA has continuously promoted the reform of the review and approval system, with past reforms that have proven to be effective having been incorporated into legal documents to provide a stronger legal guarantee for public health. In 2020, the new version of the *Provisions for Drug Registration* and a series of supporting normative documents were promulgated, underpinning the

[2] *Implementing Opinions of the General Office of the State Council on Comprehensively Strengthening the Capacity Building of Drug Supervision*

gradual establishment of a science-based, transparent, appropriately risk-controlled and predictable regulatory system, which is playing a positive role in stimulating pharmaceutical innovation and providing such innovation with a strong legal foundation.

1. Continuing to promote the transition to risk-based regulation

Over the past five years, the basis of China's drug regulation has gradually shifted from a generic drug review and approval model to an innovative drug management model, the goal being to encourage innovation at the same time as achieving a balance between imitation and innovation. This goal is being worked towards as evidenced by the many reforms to the legal and regulatory frameworks that have occurred one after the other. At present, the reform process has entered a 'deep-water zone' whereby through detailed regulatory action, it is in the process of transforming its underlying concept to that of risk management-based regulation. This process requires the capabilities of existing personnel of regulatory authorities to be continuously improved and the joint effort of regulatory authorities at all levels. There is still a need to accumulate relevant experience with respect to the trade-offs between risks and benefits so that a sound foundation can be built to enable the dividends of the reforms to be fully realized.

2. Continuously improving the regulatory system so that it is science-based, flexible, transparent and predictable

During this current process of comprehensive reform, and given long-term development needs and the overall situation, the sustainable development of a high-quality drug regulatory system is a long-term strategic goal. A more scientific mechanism for the efficient and overarching management of all stages in the regulatory process, such as drafting, review, publishing, soliciting of opinion and revision of policies, is needed.

Ensuring the scientificity of regulatory documents: The industry is often faced with the situation whereby the time afforded for the soliciting of opinions on regulatory documents is insufficient, and the transition period is either lacking or insufficient. Such a situation poses a great challenge as industry is often faced with insufficient time to adjust operations in order to meet the new requirements (regulations, guidelines, etc.). So, the establishment of a more reasonable mechanism for soliciting opinions on regulatory reforms would enhance the overall predictability of the regulatory system and thereby contribute to the overall goal of the sustainable development of a high-quality regulatory system.

Improving the flexibility of the revision of policies and regulations: It is necessary to establish a regular, dynamic revision mechanism. For example, the time interval between the *Provisions for Drug Registration* introduced in 2020 and the previous version was 13 years, with some technical guidelines still needing to be revised.

Improving the transparency of review and approval regulation: At present, the communication process, methods and information transparency at all stages of the drug review and approval process warrant improvement. For example, the Pre-Clinical Trial Application (CTA) communication meeting has become one of the steps that has been restricting the speed of the whole registration application process, with the information being conveyed by the regulatory authority to applicants at times being inadequate and untimely. So, methods of information exchange need to be optimized to facilitate communication between the regulatory authority and applicants.

Ensuring the predictability of policy and regulation development: It is recommended that regulatory authorities publicize plans for policy, regulation and guideline development. The process of rapid reform that is underway requires a large number of regulations and documents to ensure the implementation of various reform measures, and regulatory authorities at all levels and companies need time to digest and absorb these changes so that they can be effectively and efficiently implemented.

3. Ensuring the orderly and sustainable development of innovation

China's pharmaceutical innovation is still at a stage of accelerated development. With the introduction of policies to encourage innovation, some fields have seen the development of many products without significant differences between them leading to a widespread phenomenon of homogenization of products. This phenomenon has not only spread thin valuable clinical resources, but it has also hindered the advancement of clinical R&D capabilities. Innovation requires painstaking effort, and pharmaceutical innovation should be clinical value-oriented, with patient benefits as the mission, to address unmet medical needs. So, when it comes to pharmaceutical innovation, clearer rules are needed to guide orderly development, and there is an urgent need for long-term security policies that can guide R&D practices (e.g. clinical value-oriented technology requirements), so that regulatory systems can effectively facilitate innovative drug R&D.

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Chapter 3
Scientificity of registration supervision: future prospects

In the future, there will be a need to further optimize regulatory processes and requirements for product registration, to ensure effective and efficient implementation and to enhance supervision, the aim being to further facilitate simultaneous global R&D, registration and review.

Scientificity of regulatory policies

1. Improve the reasonableness of requirements for HGR applications, optimizing processes, and improve efficiency

Optimization of the administrative approval process and requirements for HGR will help further promote China's participation in simultaneous global R&D. So, it is recommended that a HGR management system that is based on science and reasonable risk control be established, along with an effective multi-party (inter-ministry, inter-agency and within industry) communication and dialogue mechanism, to improve the transparency of regulatory policies and the predictability of approval time frames. It is also recommended that the *Regulations on the Administration of Human Genetic Resources of the People's Republic of China* incorporate detailed rules with respect to HGR, specific recommendations being:

Management process: In order to accelerate the promotion of pharmaceutical R&D in China and achieve the goal of China's participation in simultaneous global R&D, registration and review as soon as possible, the HGR needs to adopt a management model that facilitates the streamlining of administrative processes, delegates power, improves regulation, and upgrades services. Such changes will enable companies to bring innovative drugs to patients in China and worldwide more quickly.

Data material: Considering the diversity of data collected in clinical studies, HGR could define and implement stratified management of data of different risk levels. For example, information that does not involve Chinese patients' genes or genomes could be afforded a lower risk management level lower. HGR could also simplify the requirements for data backup and filing and enhance the operability of data management to better reflect the Government's management principles of efficiency and convenience for people.

Sample export: In order to encourage and promote the participation of China in global early clinical studies, and to obtain complete and equivalent Chinese patient treatment data and experience in global new drug R&D, HGR could consider relaxing the export approval requirements for samples from early clinical studies conducted in China. It could do so by considering other countries' requirements for sample export, with such an approach being conducive to the advancement and modernization of China's governance of HGR.

Intellectual property: With the comprehensive promotion of national security management and reasonable utilization of resources in mind, HGR could consider allowing cooperating parties to negotiate and define the contractual terms regarding their intellectual property allocation and data ownership in accordance with the principles of fairness and impartiality, and in compliance with the requirements of China's existing laws and regulations.

Investigator-initiated and real-world studies: With respect to investigator-initiated studies and real-world studies, it is necessary to implement hierarchical data management based on the different risk levels of various types of data acquired by companies during such studies.

2. Establish a flexible MAH system to fully realize the dividends thereof

It is necessary to fully open up the implementation pathway in the case of cross-border MAHs (manufacturing license in China, MA overseas; manufacturing license overseas, MA in China), to ensure adequate synergy among the MAHs of subsidiaries (e.g. pharmacovigilance), and to specify the provisions for segmented, multi-site and CMO manufacturing, etc. in the manufacturing license.

In the case of vaccines, for example, the traditional vaccine manufacturing model is that a vaccine's MAH has to undertake all the work from vaccine R&D to plant construction, process verification, vaccine registration to subsequent manufacturing and quality management, and continuous process and quality improvement. The Contract Development and Manufacturing Organization (CDMO) model has been used for China's domestically manufactured COVID-19 vaccines, i.e. the MAH entrusts some or all of their manufacturing to CDMOs in order to expand capacity. Since the outbreak of COVID-19, Chinese vaccine companies have carried out whole-process cooperation with many countries. The orderly and controlled use of the CDMO model has enabled vaccine capacity to be rapidly increased and has been conducive to improving the level of vaccine manufacturing and quality management in China and to aligning vaccine R&D and manufacturing in China with international standards. It has also been conducive to increasing the volume of vaccine available, helping to ameliorate domestic and global supply shortages to the benefit of people worldwide. Internationally, vaccine CDMOs have provided more than half of the capacity of the COVID-19 vaccines approved for emergency use overseas, making an important contribution to the control of the pandemic.

In the future, if Chinese companies are to become bigger and stronger, they will need to expand into overseas markets, appropriately arrange their product pipelines and create supply chains across the country or even globally. Such global expansion may result in the following: (1) establishing R&D centers within and outside China; (2) establishing single or multiple manufacturing sites within and outside China for phased manufacturing, or conducting mutual backup of the same process across multiple manufacturing sites, or carrying out CMO manufacturing; (3) expanding product lines and production lines through overseas acquisition, etc.; (4) carrying

out manufacturing and R&D outside China, with a Chinese company as the MAH responsible for the marketing and sale of products in China and full lifecycle management of the drugs; (5) having a Chinese company as the MAH responsible for the marketing and sale of products outside China and the full lifecycle management of the drugs (the manufacturing and R&D may be within China or outside China). [3]

As the pharmaceutical industry goes down the path of conglomeration and globalization, both Chinese and overseas companies will inevitably face competitive pressure as they navigate opportunities and challenges in the market such as global resource allocation, provision of products for global markets and providing benefits for patients globally. In terms of regulation, the formation and capability enhancement of overseas inspection teams should be accelerated to ensure proper regulation while the MAH system addresses the issue of cross-border MAHs. Cross-border MAHs is an inevitable trend if the long-term development of China's pharmaceutical industry is to be sustained and Chinese patients are to receive a stable supply of drugs from both Chinese and foreign companies. Therefore, China needs be more flexible in its implementation of the MAH system, within the limits of the law, to address potential challenges and to fully reap the benefits of the system.

Scientificity of regulatory standards and procedures

1. Strengthen the concept of scientific decision-making and promote further implementation of ICH E17, etc.

In the ICH series of guidelines, ICH E5 recommends a framework for evaluating the impact of ethnic factors, i.e. factors relating to the genetic and physiologic (intrinsic) and the cultural and environmental (extrinsic) characteristics of a population, upon the efficacy and safety of a medicine at a particular dosage and dose regimen to facilitate the medicine's registration in the ICH member countries. It provides guidance with respect to regulatory and development strategies that will permit adequate evaluation of the influence of ethnic factors while minimizing duplication of clinical studies and supplying medicines expeditiously to patients. Also of importance is ICH E17, which addresses some R&D program issues as well as those issues that are specific to the planning and design of confirmatory MRCTs, and which describes general principles for the planning and design of MRCTs with the aim of increasing the acceptability of MRCTs in regulatory submissions globally.

Therefore, it is suggested that early research and ethnic sensitivity analysis should be considered complete for drugs already under research globally, with the evidence generated by clinical trials in other regions being examined to determine whether early studies in China can be foregone or need to be supplemented. In addition, it is recommended that a reasonable population pooling strategy, based on ICH Guideline E17, be adopted, along with establishing a regionally consistent evaluation based on an East Asian population with an appropriate number of Chinese patients as the primary study population. And, in certain programs where China is unable to enroll the number of Chinese patients required by the NMPA during the global enrollment period due to objective reasons, the NMPA could consider allowing the applicant to complete the enrollment of Chinese patients during global Phase III trials using an extension strategy (i.e. China continues to recruit patients after the end of the global enrollment period until the required number has been included).

[3] Long-term Opportunities of MAH System in China (Part 1)

2. Continue to deepen reforms and optimize the review and approval process

Currently, drug review and approval reform has entered a deep-water zone, with regulatory processes needing to be optimized in a more detailed and precise manner. It is recommended that communication be further optimized as follows:

- For the section entitled 'Comments', which should be completed by the CDE in the Clinical Trial Notification, it is recommended that applicants be provided with more adequate communication channels to ensure that they can fully understand and implement the regulatory recommendations therein. It is also necessary to optimize the resumption process for certain suspended clinical trials, making it unnecessary to submit supplementary material so as to improve the efficiency of simultaneous global studies in China.

- It is necessary to optimize the registration testing process as well as the technical requirements thereof, basing them on science and meeting the requirements of relevant ICH guidelines to achieve alignment with international standards. The verification process and technical requirements thereof also need to be optimized ensuring that the scope and requirements of on-site verification are science-based and take practical application into consideration. Such measures will facilitate China's regulatory procedures becoming more scientific, transparent and predictable.

3. Improve the reasonableness of data material requirements for approval to better align with international standards

The long preparation time and complex requirements for additional technical data and supporting documents required by China, and the demanding requirements for sample batches for drug quality inspection that are inconsistent with international best practice, have greatly restricted the speed of clinical trial application and MAA submissions. It is thus recommended that administrative documents and drug information-related materials in Module 1 be optimized to avoid excessive repetition, and that the materials in Module 2 be exempted during clinical trials to improve the efficiency of submission of clinical trial applications in China. Furthermore, DSUR information requirements during clinical trials should be reduced. The purpose and significance of the submission of regional materials in the CMC data(M1 and M3), such as manufacturing inspection procedures and batch manufacturing records, need to be discussed. Also, it is necessary to further clarify certain material requirements and submission rules to avoid unnecessarily delaying the application process. In addition, compliance with ICH guidelines should be further strengthened, especially the implementation of the Q (quality) series of guidelines, along with further harmonizing the Chinese Pharmacopoeia with ICH requirements.

4. Fully leverage the four accelerated channels to encourage clinical value-oriented new drug R&D

The four accelerated channels that have been implemented in China are of great significance to the fostering of new drug R&D and marketing. As the channels have only been implemented for a short period of time, there may be some teething problems, as is to be expected during this process of gradual improvement.

At this stage of development of the pathways, regulatory authorities and industry should work together to ensure that the pathways are 'good' and 'fast'. 'Good' requires a greater focus on the clinical value of drugs, meeting clinical needs, developing drugs from scratch from existence to excellence, and drugs being able to withstand the test of time. 'Fast' means accelerated marketing, shortened R&D time, reduced review time etc. It is necessary to further improve the accelerated review and approval system, such as dynamically adjusting the scope of applications to better align with the development of, and changes in, clinical needs. It is also necessary to issue, as soon as possible, the detailed rules for rolling submissions for each of the four accelerated channels to clarify the approval process for such submissions, the content and format requirements for submission materials, and the acceptance process for rolling submissions of both reviewing and accepting authorities.

For products that are granted breakthrough therapy designation, the US FDA provides targeted policies and biased resource allocation and engages in frequent and effective communication with experienced regulatory personnel and companies as needed. China could also consider establishing such a mechanism to ensure CDE's efficient support of the review process for drugs included in the channel and to encourage clinical value-oriented new drug R&D.

Priority review is currently required to be applied for during pre-NDA communication prior to NDA submission, with applicants having to wait for the minutes of the pre-NDA meeting to confirm the decision. This process impacts on the NDA submission and dilutes the intent of policies designed to accelerate the review process. Therefore, it is recommended that for simultaneous global R&D programs, applicants be able to confirm eligibility for priority review in advance rather than having to wait until pre-NDA communication. This would enhance the timeliness of the process and be in accordance with China's regulatory strategy for encouraging innovation.

Scientificity of the regulatory system

1. Transform to a risk-based concept and concomitantly improve management capabilities

It is recommended that the transformation to a risk-based management concept and the corresponding improvement of management capabilities be gradually implemented to optimize management effectiveness with reference being made to the experience of regulatory authorities overseas. It is necessary to adhere to the reform and opening-up policy, to actively participate in global drug regulation bilateral and multilateral cooperation mechanisms, to actively participate in the study and development of international specifications and standards, to participate in tailored cooperation and exchange with respect to drug review and approval processes, and to steadily promote the translation and implementation of ICH technical guidelines with a view to promoting regulatory trust and mutual recognition.

It is also necessary to vigorously promote scientific research in the field of drug regulation, to deepen cooperation and collaboration with colleges and universities, and national, local and non-government research institutions, and to accelerate the translation of study results and the application of new tools, methods and standards for the review and approval of innovative drugs.

2. Improve the scientificity, transparency and predictability of the regulatory system

It is recommended that further improvements be made to the overall management of laws, regulations and standards pertaining to the pharmaceutical industry. With respect to the compilation mechanism for specifications and guidelines, the regular review mechanism, the development and management of regulations, rules and administrative normative documents, and the transparency of legislative work all require enhancement. Furthermore, the timetable for the formulation and revision of regulations and guidelines, and the content thereof, should be publicized regularly to facilitate communication and interaction with the industry.

It is also necessary to promote the establishment of efficient and smooth management processes, and decision-making pathways for review and approval. It is further necessary to establish effective communication, timely response to demand, equitable dispute resolution and regular opinion collection mechanisms. Good Review Practice (GRP) should be developed and implemented to ensure the quality of work and to improve the efficiency of the approval process.

3. Guide the orderly development of innovation

A patient-centric approach should guide drug R&D with the concepts of meeting clinical needs and being clinical value-oriented at the core. The establishment and implementation of such an approach will facilitate the development of an innovation ecosystem. Subsequently, with the ecosystem subject to continuous improvement, more early-stage R&D of new drugs will take place in China, and China will become better integrated into the global innovation system and enhance its potential to become a hub for pharmaceutical innovation and R&D. China's participation in simultaneous global R&D and registration of new drugs will translate into globally available innovative drugs being introduced to the Chinese market in a timely manner and to the benefit of Chinese patients. On the other hand, China's participation will also enable the domestic industry to go global with its innovative products being offered to patients worldwide.

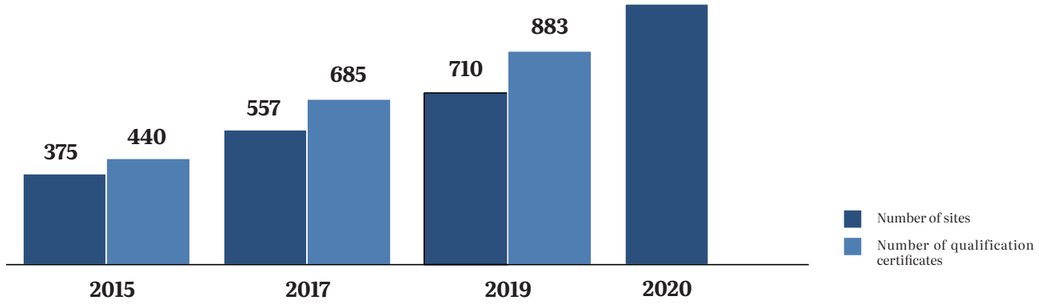
Chapter 4
Clinical research efficiency: Status quo and current challenges

Overall status quo of clinical trial sites in China

Driven by various policies to encourage pharmaceutical innovation, the number of clinical trials in China has been rising rapidly. In 2019, the number of drug clinical trials in China exceeded 1,600, a more than 20-fold increase from less than a decade ago. **The number of clinical trial sites in China has also increased steadily over recent years,** growing from less than 400 in 2015 to more than 1,000 in 2020, mirroring to some extent the increased number of clinical trials (Figure 14).

Figure 14: Number of clinical trial sites in China has increased steadily in recent years

Number of qualified clinical trial sites and number of qualification certificates in China, 2015-2020



The filing system was officially implemented as of the end of 2019, so the number of qualification certificates has not been recorded for year 2020.

Source: Data search on the website of the Center for Drug Evaluation, NMPA

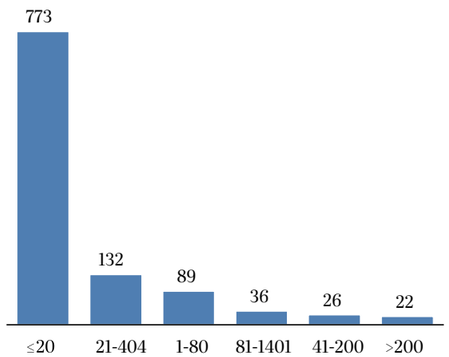
Despite the steady increase in the number of clinical trial sites in recent years, the accumulated experience of most Chinese sites remains generally inadequate. Among the 1,078 sites undertaking clinical trials in 2019-2020, less than 30% of them had undertaken more than 20 clinical studies within the previous two years. Furthermore, Chinese clinical trial sites are relatively inexperienced in undertaking international MCCT, with only 6% having undertaken more than 20 international MCCT within the previous two years (Figure 15). Sponsors are also inevitably attracted to leading clinical trial sites when choosing a site, with little willingness to consider other sites. With the rising status of the Chinese innovative drug market in the world, the demand for international MCCT will undoubtedly continue to grow in the future; so,

improving the efficiency of clinical studies will help underpin China's participation in simultaneous global R&D.

Figure 15: Experience of most clinical trial sites in China to be improved

Number of sites undertaking clinical trials

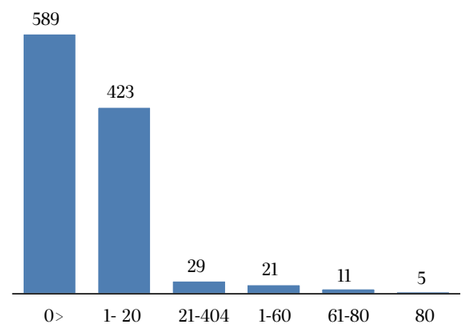
2019-2020, total number of sites = 1,078



<30% of the sites had undertaken more than 20 clinical studies in the previous two years.

Number of sites undertaking international multi-center clinical trials

2019-2020, total number of sites = 1,078



Only about 6% of the sites had undertaken more than 20 international multi-center clinical trials in the previous two years.

Source: Data search on the website of the website of the Center for Drug Evaluation, NMPA

Key challenges for enhancing the efficiency of clinical studies

The quality and efficiency of clinical studies centers around two important dimensions - implementation of clinical study protocols and clinical study capabilities. Key pain points in the implementation of a clinical study protocol include accelerated start-up of clinical trials being restricted by processes related to clinical trial sites and sponsors, and regional and centralized ethical review mechanisms that have room for improvement. **Key pain points in terms of clinical study capabilities** include the need to upgrade the capabilities of clinical trial sites and researchers with respect to overall clinical study management and risk response, the need to strengthen site set-up to ensure clinical studies are conducted appropriately (including construction of study platforms, study wards, and dedicated clinical study teams), the lack of management experience and capabilities with respect to early exploratory clinical trials, the need to enhance sponsors' clinical study concepts and capabilities, and the need to improve the overall capability of third-party service providers including in the areas of supervision and management.

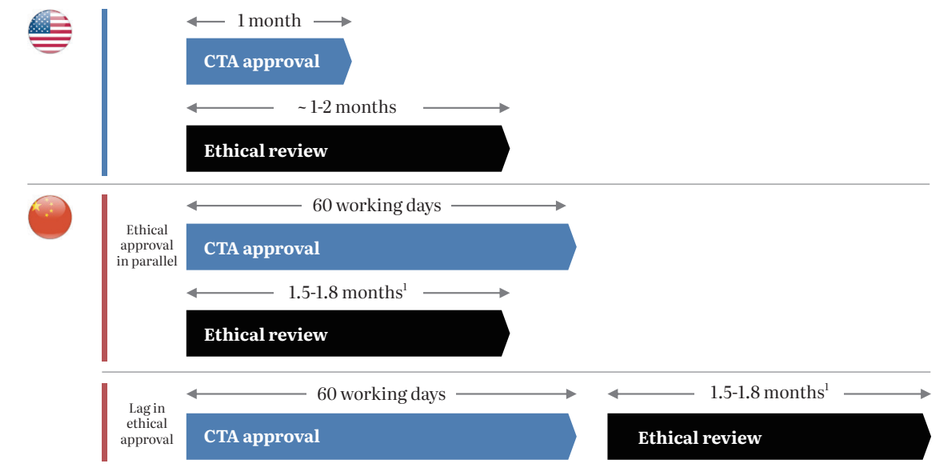
1. Challenges facing the implementation of clinical study protocols

The accelerated start-up of clinical trials is restricted by the processes of the institutions at which the studies are hosted and those of the study sponsors. At present, the start-up of clinical trials in China takes a long time, with the main pain points

being **cumbersome on-site management processes, insufficient harmonization of inter-site processes, and inefficiencies within sponsor processes. Cumbersome on-site management processes:** On-site project setup, the process of gaining ethical approval and the contract signing process all tend to limit the speed with which clinical trials can be implemented. In some cases, there are site contracts that involve issues not directly related to the sites (e.g. issues pertaining to intellectual property and trial data), resulting in an unnecessary degree of complexity and consequently timeline delays. **Insufficient harmonization of inter-site processes:** Differences in processes and information requirements for clinical study start-up protocols among sites lead to a high level of uncertainty among sponsors preparing for trial start-up and forces them to carry out customized preparation for individual sites, thereby compromising the overall efficiency of the start-up process and dampening the speed with which they can be launched. **Inefficiencies within sponsor processes:** In addition to factors related to the clinical trial sites, sponsors' processes also need improvement. At present, their internal processes and communication mechanisms in relation to the start-up of clinical trials are generally not efficient enough, which often impacts negatively on the timelines specified in trial contracts.

Need to improve regional and centralized ethical review mechanisms: The specific measures on 'improving the Ethics Committee-related mechanism' and 'increasing the efficiency of ethical review' as outlined in the Opinions on Deepening the Reform of the Review and Approval System and Encouraging the Innovation of Drugs and Medical Devices issued by the General Office of the CPC Central Committee and the General Office of the State Council in 2017 have not yet been implemented leading to several issues as follow. **Lag in ethical approval process:** Some sites only conduct an ethical review and grant approval after a clinical trial application has been approved, and most of the participating sites can only conduct their own ethical reviews and grant approvals following the ethical approval being granted by the leading site failing to achieve sufficient parallelism (Figure 16). **Insufficient collaboration on ethical approval:** There is a general lack of recognition by sites of centralized ethical approval or regional ethical approval, resulting in unnecessary duplication of ethical approval processes among different sites. **Lack of appraisal of the ethical approval process:** The lack of appraisal of the efficiency of the ethical approval process affects the motivation of the approving authority.

Figure 16: Comparison of ethical review timelines in China and the US



1. Based on the results of the Survey on Clinical Operation of RDPAC Member Companies in 2020, it is calculated on the basis that one month = 4 weeks. The median for Phase I and bioequivalence trials is 1.5 months, while the median for Phase II and III clinical trials is 1.8 months.

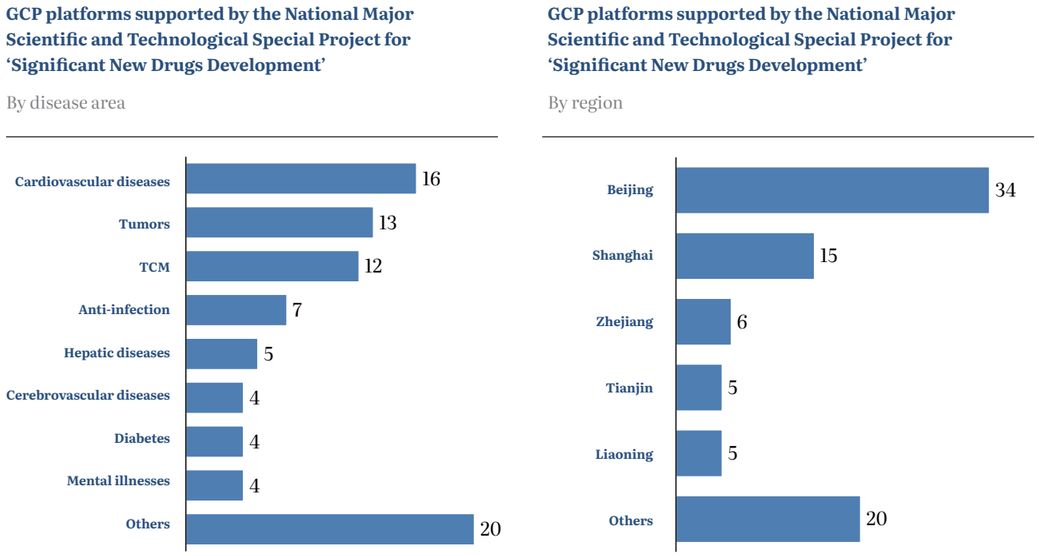
2. Challenges for clinical study capabilities

The overall level of clinical trial management carried out both by clinical trial sites and by investigators needs to be upgraded. Sites and investigators still tend to focus more on the absolute number of subjects enrolled rather than conducting clinical studies from the perspective of scientific expectations for clinical trial results. Furthermore, the concept of enrolling subjects in accordance with enrollment criteria should be more firmly established and its implementation monitored, and guidance provided as required. Investigators need to strengthen their compliance with study protocols and GCP principles for subject and documentation management, as currently it is common for front-line study personnel to continue to use routine diagnosis and treatment practices and medical records in the management of clinical studies. In addition, there are great differences among the sites, with some sites having complex management links that lead to slow study start-up or even failure to conduct study start-up, while others lack quality control in relation to the operation of clinical studies. Chinese clinical trial sites and investigators need to manage trials according to the spirit of ICH E6 R3, rather than solely and strictly following regulation.

The set-up of clinical trial sites to ensure clinical studies are conducted in compliance with relevant standards needs to be strengthened. With the support of the National Major Scientific and Technological Special Project for 'Significant New Drugs Development', China's GCP platforms have made significant phased improvements in the construction of ethics committees, information technology management systems and clinical evaluation laboratories in recent years (Figure 17). However, there is room for improvement in terms of the level of protocol design and the quality of clinical

study data, which can be impacted by deficiencies at clinical trial sites, and in terms of investigators and sponsors, personnel capabilities and quality control during the conduct of trials.

Figure 17: Support of GCP platforms by disease and by region



Source: 13th Five-Year Strategic Report on the National Major Scientific and Technological Special Project for 'Significant New Drugs Development'

At this time, Chinese clinical trial sites generally lack dedicated clinical study teams and are faced with challenges in securing appropriate levels of investment in time and resources. As for investigators, the time available for clinical trials is limited due to the heavy clinical workload undertaken by clinicians acting as clinical investigators. In addition, most hospitals lack dedicated teams of clinical study nurses and clinical trial assistants, and have not been able to establish competent internal teams. Some sites and investigators use clinical trial site management services provided by third parties, which has resulted in unclear supervision and management responsibilities and an overreliance on third-party clinical research coordinators (CRC). The 'Significant New Drugs Development' project and the establishment of a GCP platform have substantially enhanced the hardware facilities for clinical studies in China, while the formation of professional clinical study teams with appropriate soft skills will be the focus of site capability enhancement.

Management experience and capabilities with respect to early exploratory clinical trials are insufficient. Participation in early exploratory studies facilitates China's integration into global innovation by means of simultaneous global R&D, and at the same time, enhances China's clinical study capabilities and systems. The short cycle of early studies and the frequent need to conduct exploratory studies on biomarkers, which are affected by the approval time for, and regulation of, HGR in China, means that fewer global trials of first-in-class drugs and first-in-human trials can be undertaken in China as its clinical trial sites and investigators are currently generally inexperienced in exploratory clinical trials. In addition, the scientific management and execution of studies still has room for improvement (e.g. the scientific definition and handling of adverse events during studies).

Sponsors' clinical study concepts and capabilities need to be enhanced. As beneficiaries of the review and approval reforms, sponsors should strengthen their implementation of the reforms and fully consider the needs of Chinese patients at the various stages of the clinical study. In terms of clinical study design, the unmet needs of Chinese patients and targeted clinical trials need to be fully considered and the revision process for clinical study protocols needs to be optimized to reduce the impact on the overall timeline. China's role in global R&D should not only be considered from the perspective of contributing to the number of subjects enrolled, but also from the perspective of the role it can play in exploratory discovery and the design of global R&D. In terms of the implementation of clinical studies, firstly, sponsors need to improve the quality and efficiency of their clinical study management system and to optimize internal coordination, protocol revision processes and timelines within sponsors. Secondly, the strict implementation of enrollment criteria and the rigor of clinical follow-up testing need to be improved. Finally, cooperation with clinical trial sites and the supervision of third-party service providers in clinical operations need to be strengthened.

The overall capability of third-party service providers and their level of trial supervision and management need be improved. Contract Research Organizations (CROs) play an important role in clinical studies, there is a wide variation in capabilities among the CROs and even within an individual CRO. Fierce competition for R&D talent has resulted in increased staff turnover leading to challenges in ensuring the quality of studies. In addition, the immature supervision and management systems of CROs increase risks related to the quality of clinical study data.

Chapter 5
Effectiveness of Clinical Research: Future Outlook

Looking into the future, it will be necessary to further optimize the implementation process of clinical research, improve clinical research capabilities, and build guarantees into the system to incentivize clinical research and the necessary investment in resources.

Implementation of clinical research

1. Optimize intra-institutional processes and inter-agency synergies in the implementation of clinical research

Regarding the internal processes of clinical research institutions, sponsors could be encouraged to sign master agreements with institutions, so as to reduce the number of departments participating in the review. In terms of institution teams, the efficiency of communication with sponsors and CROs could be improved by establishing and strengthening internal teams of clinical trial assistants. In those instances where a sponsor has multiple projects at the one institution, regular progress meetings could be held to find solutions to common challenges that may arise. In addition, the time limit for contract approval needs to be defined to shorten timelines and to provide more reassurance that expectations will be met.

A standardized process among clinical research institutions would contribute significantly to the overall acceleration of clinical research projects. Such standardization of processes could be promoted through government departments such as the Health Commission, with the implementation thereof being included as a key performance indicator with respect to the regular evaluation of institutions.

2. Promote the simplification of ethical review and approval processes and improve the efficiency and level of regional and centralized ethical reviews

In terms of the ethical review and approval process, it is necessary to further implement and promote the synchronization of ethical review and approval processes and clinical study applications, to standardize, in a top-down manner, the materials and processes required to be used by the ethics committees at all hospitals for the review and approval of clinica study applications, and to implement indicators for measuring the efficiency of ethical review and approval at the hospital level (e.g. feedback time and frequency of ethics committee meetings).

In terms of ethical review and approval synergy, the establishment of a centralized ethical approval and accreditation system should be promoted, including the establishment of regional ethics committees and recognition of such committees by clinical trial institutions. In addition, mutual recognition among different institutions within the same system (e.g. hospitals in the Peking University Health Science Center and Chinese Academy of Medical Sciences systems) needs to be encouraged. After having passed the ethical review and approval process at the lead institution level, other clinical research institutions should give priority to endorsing the lead institution's approval or at least simplify the approval process to avoid repeated reviews. It is suggested that leading medical institutions could assume the responsibility of centralized ethical approval, while local secondary hospitals could consider delegating the relevant responsibilities to regional or central units. In addition, consideration could be given to establishing an appeals channel, with regional or centralized ethics review committees assuming the role of arbitrator.

In terms of the assessment of ethical review and approval processes, certification standards should be developed against which the quality and capability of ethical review and approval processes could be evaluated.

Clinical research capabilities

1. Promote the establishment of a clinical research institution platform

A professional clinical research platform could provide technical support for all aspects of clinical research including design, implementation, quality control, and data management and analysis to ensure, and to improve, the quality of clinical research. Currently, there is an extreme lack of research platforms for carrying out clinical trials in China, so it is an imperative to establish public technology platforms that can effectively support clinical research. On the one hand, a clinical research institution platform would enable clinical investigators to ask for support from related disciplines as required and provide comprehensive and systematic technical support for large-scale MCCT. On the other hand, a clinical research institution platform could also support and develop related disciplines, as it is conducive to bringing professionals together who can then bring their respective strengths into play and participate in academic discussions, thereby promoting continuous improvement in theoretical and technical levels and allowing for experience to be accumulated on a larger scale and play a demonstration role. Additionally, a clinical research institution platform, as a unique source of expertise, could play an irreplaceable role in the regulation and quality control of clinical research. A clinical research institution platform could also assist in the management of personnel, finance and materials to ensure effective implementation of clinical research outcomes. Finally, a clinical research institution platform could also facilitate a relationship with the pharmaceutical industry, enabling clinical research of innovative products to be organized and undertaken and thereby further promote innovation and development within the industry.

At the same time, first- and second-tier urban hospitals with rich experience in clinical research could be encouraged to take the lead in forging clinical research alliances with hospitals lacking experience in clinical research and those in the lower-tier cities. Such an initiative would not only help to expand the potential subject population, but

would also enhance the clinical research capability of a wider range of institutions.

2. Promote the formation of full-time clinical research teams

To promote the formation of full-time clinical research teams, effort should be made on two fronts – develop career pathways and establish a performance assessment system that is compatible with the nature of the work undertaken.

In terms of career pathways, it is necessary to provide opportunities for full-time doctors and nurses devoted to research by means of evaluation of professional titles, continuing education, certification of qualifications, and opening up channels for promotion.

In terms of a performance assessment system, the design of such a system must take into account the nature of the work undertaken by personnel participating in clinical research.

3. Promote clear positioning of institutions and accumulate experience in the management of exploratory clinical trials

Considering the many and varied demands of exploratory clinical research, research institutions should identify areas in which they will take the lead in making breakthroughs and solving problems. They should then clearly determine the capacity required in their area of specialty and concomitantly develop objectives and plans to achieve their goal (e.g. the leading research institutions could focus a greater percentage of resources on projects with a higher degree of innovation).

System guarantees for clinical research

1. Clinical research incentive mechanisms

Hospital level: Optimize the assessment system and raise the level of importance of clinical research. Optimize the assessment system: Despite being included in the current accreditation standards for tertiary general hospitals and current hospital performance appraisal systems, performance indicators related to clinical research are not weighted highly and as such have had limited contribution to the ranking of hospital departments. Consequently, hospitals are not sufficiently motivated to conduct clinical trials. Raise the level of importance: Although the level of importance attached by clinicians to clinical research is increasing year by year, hospital management is not yet fully onboard as they are more focused on undertaking national projects and on numbers of published research papers. Undertaking new drug development has not yet been raised nationally to a level equivalent to that of the National Natural Science Foundation.

At the physician level: Reform physician title evaluation and performance appraisal systems, and encourage physicians to conduct and participate in clinical research. In terms of professional title evaluation: One issue of concern is that in considering promotion opportunities for physicians, little importance has been placed on clinical research. Furthermore, a system for evaluating the professional titles of physicians engaged full-time in clinical research has not yet been implemented. This situation is further complicated by the fact that the right to evaluate professional titles varies across the regions, lying in the hands of different organisations including health commissions, hospitals and universities. Therefore, the standardization of evaluation systems across the regions should be promoted along with the actual situation of clinical research being fully considered. In terms of performance appraisal: Clinical research could be included as an indicator in the performance appraisal systems for hospital departments and individuals, by for example sub-categorizing the indicator for patient care into clinical research patients and general patients.

Current policies on accreditation standards for tertiary general hospitals

Current policies

The evaluation criteria in the *Accreditation Standards for Tertiary General Hospitals (2020 Edition)* are divided into three parts, 101 sections and 342 articles, with 448 clauses pertaining to scoring standards of which four relate to clinical research, i.e. less than 1%.

- Part 1 addresses pre-requirements and consists of three sections and 25 pre-requirements for review, which are not directly related to clinical research.
- Part 2 addresses the capacity for medical service, data quality and safety monitoring and consists of 74 sections that outline 240 monitoring indicators, with two indicators related to clinical research as follow:

  Chapter I. Resource allocation and operational data indicators

  V. Research indicators

  (1) Number of new technologies clinically transformed

  (2) Number of clinically relevant national patents obtained
- Part 3 addresses on-site inspection. There is a total of 24 sections and 183 articles, including two articles related to clinical research.

  Chapter 3. Hospital management

  VIII. Scientific research and teaching, and library management

  (176) There are systems and measures to encourage all staff to participate in scientific research and promote the transformation of scientific research achievements into clinical applications, and appropriate funds, conditions, facilities and personnel support are also provided.

(177) The conduct of clinical trials for drugs and medical devices as well as investigator-initiated clinical research shall comply with *Good Clinical Practice for Drugs, Good Clinical Practice for Medical Devices* and other relevant provisions.

Proposed amendments

- Refine the requirements for the evaluation criteria of scientific research indicators related to clinical research. For example, in addition to the quantitative indicator of new technologies transformed clinically, add quality indicators that measure the actual clinical value brought about by such transformation. Also, add an indicator that measures the influence of patents to complement the quantitative indicator of national patents related to clinical research.
- Refine the system and measures to encourage all staff to participate in scientific research. For example, provide specific guidance and suggestions with respect to funds, conditions, facilities and personnel support required to promote the transformation of scientific research achievements into clinical application.
- Increase the number of evaluation criteria related to clinical research. For example, add content related to clinical research management and continuous improvement into V. Quality assurance and continuous improvement of diagnosis and treatment in Chapter 2 (Clinical service quality and safety management).
- Add follow-up monitoring indicators for the completion of clinical research. For example, clinical trials undertaken and completed/per 100 open beds could be added into the resource allocation and operational data indicators.

Current policies on performance evaluation of hospitals

Current policies

Based on the *Opinions on Strengthening the Performance Evaluation of Tertiary Public Hospitals* issued by the General Office of the State Council in 2019, the current performance appraisal system for hospitals covers four aspects: (a) medical quality; (b) operational efficiency; (c) continuous development; and (d) satisfaction evaluation, totaling 55 articles, of which two involve clinical research.

(11) Discipline construction

- 50. Funding for scientific research projects per 100 health technicians
- 51. Amount of transformation of scientific research achievements per 100 health technicians

Proposed amendments

- Add indicators relevant to the number and level of clinical trials completed. For example, the indicator of 'the completion of clinical trials in hospitals' under 'continuous development' should be added, and the inclusion of specific indicators such as 'the number of clinical trials/average number of in-service physicians or beds', or 'high-level scientific research achievements and construction of key clinical disciplines in hospitals' under 'discipline construction' could be considered, as could the inclusion of 'the number of international multi-center clinical trials participated in'.
- Add indicators related to clinical research efficiency. For example, add an indicator of 'cost efficiency of clinical trials' under 'operational efficiency'.

2. Investment in clinical research resources

Currently, the mainstream funding sources for the development of medical research in China include the National Natural Science Foundation of China (NSFC), the National Science and Technology Major Project, the National Key R&D Special Project, and the Base and Talent Special Project; however, the support available for clinical research within those funding options is limited at present. Among the health sciences department projects approved by the NSFC in 2019, only 94 were clinical medical research-related, accounting for less than 1.0% of the total funding in this area. The total amount of funds allocated by the NSFC in 2019 was 47.331 million Yuan, accounting for 0.2% of the NSFC's total budget that year, with the average project grant being 500,000 Yuan. So, the gap between the level of available funding and the cost of clinical research is of significant magnitude.

Consideration should be given to increasing the proportion of funds allocated by medical research funding bodies to clinical medical research, and to promoting the establishment of special research programs or research funds for clinical trials by the Health Commission, MOST, medical institutions and institutions of higher learning to encourage and support clinicians in their clinical medical research endeavors.

Chapter 6
Regulatory and clinical capacity building: Current status and future outlook

Enhancement of regulatory capabilities

Strong regulatory capacity provides the foundation for the rapid and healthy development of the pharmaceutical industry, and as such, regulatory capacity must be continually strengthened as required by the *Implementing Opinions of the General Office of the State Council on Comprehensively Strengthening the Capacity Building of Drug Supervision* (Document No.16). It is not only necessary to strengthen the coordination of regulation, including cross-regional and cross-level drug regulation, but also to strengthen regulatory technical capacity in a number of areas including review, inspection and standard management, and to accelerate research into, and the application of, new regulatory tools, methodology and standards. Furthermore, it is recommended that national drug supervision training bases should be established that provide training in research and practical application with a view to improving the quantity and quality of core regulatory talent, and to narrow the gap in regulatory capacity among different regions.

In the process of promoting simultaneous global R&D, registration and review of drugs, the key issue currently at the regulatory level is the capacity development of reviewers. There is a need to build teams that are capable of adapting to an environment of rapid development of innovative drugs and increasing demand for clinical treatment, otherwise the lack of such capacity building may evolve into a bottleneck. The efficient conduct of the review and approval process brings with it **increased demand for the development of regulatory personnel (both in terms of numbers and professional ability), inter-departmental coordination, and international exchanges focused on modernizing regulatory practice and other aspects.** Therefore, it is necessary to introduce policies to encourage talent recruitment, individual development plans for regulatory staff and continuing education and training plans for professionals (reviewers and inspectors).

1. Formation of regulatory teams

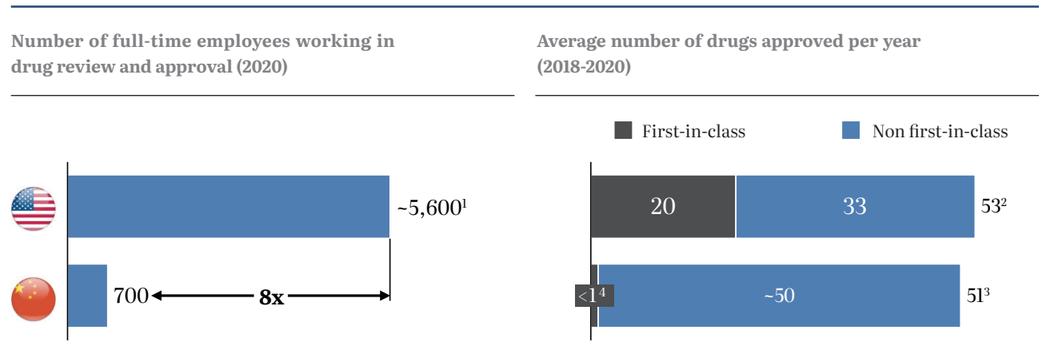
Size of regulatory personnel

Although the number of personnel in the Center for Drug Evaluation (CDE) has increased considerably over the past five years, there is a scarcity of experienced reviewers and the growing demand for application reviews is unable to be met. The scarcity of experienced reviewers is attributable to several factors including retirement at the mandated retirement age, transfers and resignations. There is a particular shortage of biological and clinical review experts. In addition, the workload of other departments (e.g. coordination, quality and compliance, and drafting of registration certificates) has also increased, exacerbating the shortage of reviewers.

Based on the full-time equivalent workload of the review team in the US (Figure 18), the NMPA requires a team of 3,000 reviewers, though currently there are only about 700. Therefore, an all-out effort is required to strengthen the allocation of human resources, to reasonably divide administrative power among the central administration, the regional sub-centers of the central administration and the provincial administrations, to accelerate the recruitment of experienced talent, to implement policies to attract, retain and develop talent, and to implement continuous improvement initiatives with respect to ability and experience of reviewers and the efficiency and quality of reviews. In addition, given the current staff shortage, the review and approval authorities could consider flexible staffing mechanisms, which for example could allow for the interchange of talent between the regulatory authorities and industry, using the experience of other countries to avoid any potential conflicts of interest.

In the future, it will be necessary to further optimize the implementation process of clinical research, to improve clinical research capability, and to build in system guarantees for the strengthening of clinical research by improving incentive mechanisms both for undertaking, and for investing in, clinical research.

Figure 18: Comparison of the size of regulatory review teams and their throughput in China and the United States



1. The number of US drug review and approval staff only includes the personnel from the Center for Drug Evaluation and Research (CDER). Over and beyond the CDER, the US Food and Drug Administration (FDA) has a total of 18,062 employees working in more than 10 departments including the Center for Biologics Evaluation and Research (CBER) (1,191 employees) and the Office of Regulatory Affairs (4,997 employees).
2. Includes only new molecular entities and new therapeutic biological products, and excludes vaccines, blood products and other biologics approved by CBER.
3. Chemical drugs include Category 1.1 innovative drugs and Category 5.1 original drugs, while biological drugs include Category 1 innovative therapeutic biologics and Category 3 original therapeutic biologics.
4. Excludes first-in-class innovative drugs that have been approved in the US prior to their launch in China.

Sources: CDE, FDA, GBI

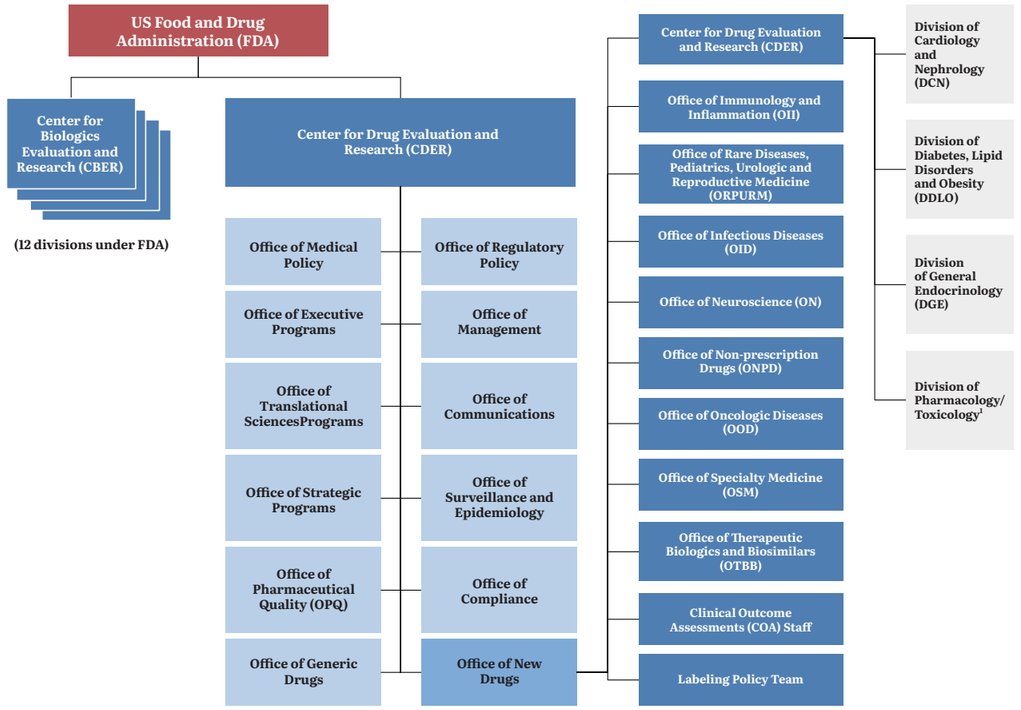
The reform of the review and approval system has greatly accelerated the pace of new drug registration and approval, with associated workload in areas such as testing, verification, supplementary applications, pharmacovigilance and post-marketing regulation concomitantly increasing with the growing number of new drug applications and product launches. It should be remembered that regulatory personnel not only include CDE personnel who review and approve new drugs at the CDE, but also the regulatory personnel employed by the NMPA and provincial drug administrations, the inspectors of the Center for Drug Reevaluation, testers at the various testing centers, the regulators of pharmacovigilance, and their colleagues in supporting functions such as project management, quality, compliance and administration. It is necessary to comprehensively sort out the needs of personnel assigned to investigational new drugs (IND) and new drug applications (NDA), as well as supplementary applications, pharmacovigilance and marketing regulation across the entire life cycle of new drugs post-marketing, and to meticulously coordinate planning for the recruitment and deployment of regulatory personnel.

Regulatory expertise

With the rapid development of the industry, the knowledge base of regulatory staff in China has been unable to keep pace with new scientific methodologies and breakthroughs in technology, so enterprises with dual applications in China and the US often choose to submit applications in the US before submission in China. With respect to new technologies, although regulators have issued guiding principles one after another, they need a deeper understanding of the technology in question to better control risks. So, to enhance overall knowledge in relation to the latest trends in technology, the reviewing agencies should take full advantage of opportunities to share global experience and resources by means of bilateral or multilateral international cooperation agreements, actively exploring joint review pathways, and sharing regulatory scientific achievements. At the end of the day the goal is to expedite the launch of new drugs on the market so that the unmet clinical treatment needs of patients are satisfied and China no longer lags developed countries in this respect.

The drug review and approval agencies in developed countries and regions are at a more mature stage of development compared to those in China, and they tend to have established specialized offices. Taking the US FDA as an example (Figure 19), it has established the CBER and CDER, the latter having 13 specialized divisions including the Office of New Drugs, the Office of Generic Drugs and the Office of Pharmaceutical Quality. The Office of New Drugs is further subdivided into 11 offices and 28 departments by disease area and function.

Figure 19: Organizational chart of the US Food and Drug Administration (FDA)



1. Division of Pharmacology/Toxicology is designated for Cardiology, Hematology, Endocrinology and Nephrology CHEN)
Source: FDA

Sustainable development of the regulatory workforce

It must be recognized that capability training of the regulatory workforce is a long-term and gradual process, which requires institutional guarantees, the provision of career pathways and an stepping-up platform for systematic ability. In the ongoing process of building a suitably skilled regulatory workforce, there is an urgent need to enhance expertise in the different disease areas. At present, there is a lack of appropriately trained reviewers able to take up posts directly, which is impacting negatively on the overall improvement of regulatory capacity and the building of a regulatory workforce over the long-term. From an overall perspective, the demand for reviewers exceeds supply, so more intensive training is needed to ensure a supply of appropriately qualified reviewers.

At present, the tough penalty provisions incorporated into China's drug regulations lead regulatory personnel to strictly interpret the regulation in question and deters them from showing any reasonable level of flexibility while still adhering to the scientificity of regulatory review. There is also room for optimizing the treatment of reviewers, which would be conducive to reducing the attrition rate within the

regulatory workforce. In addition, currently, the regulatory workforce in China tends to be drawn from a single pool of regulatory talent, so diversification of the talent pool should be promoted through cooperation among regulatory authorities, academia and sponsors.

2. Inter-departmental coordination on drug review and approval

The *Implementation Outline for the Construction of Law-based Government (2021-2025)*, as issued by the State Council in August 2021, clearly states the need to improve how government institutions function, as well as promoting the need for the efficient functioning of those institutions by means of optimization and coordination. Multiple government institutions, including MOST, CIIP, NHC, NHSA and GAC, are required to participate in the management of the development, registration, review and marketing of new drugs, as are a large number of clinical trial institutions, ethics committees and offices of drug clinical trial institutions. So, the regulatory process would be enhanced by greater coordination and cooperation among the various stakeholders. For example, poor linkages between stakeholders have been impeding China's ability to participate in simultaneous global R&D, review and registration, especially with respect to early clinical trials, with the opportunity to join the latter being missed due to unscientific and/or uncoordinated technical requirements and procedure settings.

The NMPA, the principal regulatory agency for drugs, and its affiliated organizations such as CDE, National Institutes for Food and Drug Control (NIFDC), CDR, Chinese Pharmacopoeia Commission and the provincial drug regulatory agencies are all involved the process of drug review and approval, each being responsible for specific aspects of regulatory oversight. However, under this current setup, cross-agency communication, coordination and linkages between central and local authorities, transparency of transmission of information, and allocation of responsibilities and rights have yet to be optimized, and efficiency dividends are yet to be fully realized. At present, there is insufficient communication among agencies during the review and approval process, with agencies often providing feedback separately or in contradiction of that from other agencies. So, improvement in the level of coordination and cooperation among agencies should be a priority so that sponsors are provided with comprehensive and consistent feedback. The expertise of project managers also needs to be enhanced to ensure adequate understanding of an applicant's questions and appropriate feedback is given.

It is recommended that the various agencies form a relatively consistent understanding and recognition of what simultaneous global R&D, registration and marketing of new drugs entails, implement an appropriate division of regulatory powers as soon as possible, and strengthen collaborative guidance with respect to cross-regional and cross-level drug regulation. NMPA could take the lead in simplifying and unifying the process to minimize the cost for industry of having to meet differing requirements among agencies. Joint working mechanisms should be implemented across departments and agencies to enhance regulatory efficiency and to synergize government regulatory resources.

3. International exchange capacity to regulate modernization practices

The US FDA is committed to regulatory concept and mechanism innovation to optimize review and approval processes and to stimulate innovative drug research. It has accordingly initiated a series of mechanisms to accelerate the review and approval of new drugs, including a rapid review channel, priority review rights and ground-breaking certification. Over the past three years, the FDA has successively launched several new initiatives to further promote the globalization process and enhance the efficiency of new drug review and approval (e.g. Project Orbis which promotes cross-regional cooperation among regulators, and real-time review of innovative cancer drugs), which could act as an important reference point for deepening the reform of pharmaceutical innovation in China. Chinese regulators need to better understand the review and approval policies of their American and European counterparts if they are to adapt and implement the core principles locally, and thereafter realize the internationalization of China's review and approval process.

Project Orbis is designed to promote cross-regional simultaneous marketing of new drugs through communication and sharing of information among regulators in various countries: In line with the trend towards globalization of new drug development, multi-center clinical trials are becoming more and more common in clinical research along with multi-location registration and marketing. However, it is still difficult to achieve the simultaneous global launch of new drugs due to varying jurisdictional policies and processes for review and approval of drugs, with there often being a gap of one year or more in regional launches. So, to accelerate the synchronization of drug review and approval, and to promote global accessibility of innovative drugs, the FDA launched Project Orbis in May 2019, which aims to build a communication channel between regulators in various countries to advance joint applications and expedite the approval of new drugs across regions. Project Orbis particularly targets drugs with major impact and clinical value. After an applicant selects a country in which to submit an application, the FDA, as project coordinator, organizes regular meetings with regulators from various countries to discuss the processes involved in the review and share information about the application. Each country remains independent in its decision making, but can control the source of information through information sharing to improve the quality and efficiency of the review. Within one year of Project Orbis having been launched, 60 applications were accepted and 38 applications for marketing had been approved. The time lags between the FDA and other countries with respect to dossier submission and marketing approval were 0.6 months and 1.1 months, respectively, greatly advancing the goal of simultaneous global drug development. To date, regulators from Australia, Brazil, Canada, Singapore, Switzerland and the United Kingdom have joined the initiative.

Real-time review of innovative cancer drugs accelerating drug review and approval through early review of key data and early communication: The approval of new drugs is often time-consuming, typically taking six to 10 months

even under fast-track review. To further enhance the speed of approval for new drugs, in 2018, the FDA proposed a real-time review mechanism designed to accelerate the review and approval of new drugs and designed to do so without compromising the quality of the review. The mechanism would protect the integrity of the review by approving key data in clinical trials in advance and communicating with applicants on data quality, data analysis and other issues as early as possible. Drugs considered for the real-time review mechanism are usually innovative drugs with concise trial design, easy-to-analyze trial endpoints, and which offer the promise of significant improvement to existing therapies. Applicants can submit an application for real-time review up to within three weeks of data lock, and, with the consent of the FDA, can have their first meeting with the FDA four to six weeks later to discuss details such as the review timeline, and are able to submit key trial data as initial dossiers in the ninth week. The FDA generally holds the second meeting around week 16 to communicate with applicants on any issues in the initial dossiers and to solicit additional material as required. Applicants then formally submit complete dossiers in week 20. Compared with the traditional review and approval process, the FDA being able to review and approve some core data at the outset and to provide feedback before the submission of formal dossiers by applicants, greatly expedites the formal review and approval process. KISQALI® is the first drug marketed through real-time approval, with it only having taken three weeks from submission of the formal dossier to approval.

Training of clinical talent

1. Education

There is a relative lack of training for clinical research talent in the Chinese tertiary education system, although there have been some breakthroughs in curricula, including the establishment of new disciplines (e.g. clinical research methodology) and the introduction of new courses (e.g. the clinical research project management course offered by the Peking University Health Science Center for the first time in the 2020 spring semester). So, it is recommended that the number of courses be expanded and that they be made available across a wider range of universities and colleges.

Clinical research is a scientific theory and methodology specifically used in the conduct of clinical research and is a relatively new discipline formed out of the integration of disciplines involved in clinical research practice. In 2015, Peking University recruited the first postgraduate students for its Clinical Research Methodology program, which is regarded as a secondary discipline under the primary discipline of clinical medicine. Currently, the program follows six main research directions, namely: 1) ethical practice of clinical research; 2) project development and design of clinical research; 3) data technology and application in clinical research; 4) statistical design and analysis of clinical research data; 5) clinical research project management and quality control; and 6) regulations pertaining to clinical research on new drugs and medical devices.

The Clinical Research Project Management course has been offered by the Peking University Clinical Research Institute (PUCR) since 2020, with it being a compulsory course for postgraduate students who major in clinical research methodology (clinical research project management and quality control. The course is also offered as an elective for masters and doctoral students studying in fields allied to clinical research. Furthermore, the course is also open to professionals working in related industries in the wider society. The course was established to help students to acquire a basic theoretical knowledge of clinical research methodology and the practical skills required with respect to clinical research project management and quality control, and to understand the laws, regulations and ethical requirements with which clinical research needs to comply in China. Furthermore, the course is intended to help students to implement and manage their own postgraduate projects, and to help them understand the differences between project managing clinical studies initiated by sponsors and those initiated by investigators, with a view to encouraging them to consider their future career direction and development in advance.

In talking about expanding training options for the development of clinical research talent, the provision of courses for clinical research nurses should also be considered. Internationally, a more independent scope of work with a clear job description has been developed for clinical research nurses. The International Association of Clinical Research Nurses was established in the United States in 2010 to provide a worldwide platform for exchanges on the development of clinical research nursing. As a member of a clinical research team, clinical research nurses are responsible for the nursing of patients and healthy subjects participating in clinical trials. They play an important role from two aspects: 1) Nursing is indispensable during clinical trials: Clinical trials involve clinical diagnosis and treatment as per standard medical treatment, and as such, trial subjects are subject to formal medical practices and require appropriately qualified nurses to perform tasks such as administration, giving of injections and the drawing of blood. (2) Full-time clinical research nurses have unique advantages in terms of the coordination and management of clinical trials: At present, there is a huge shortage of clinical research coordinators (CRC) in China exacerbated by a high turnover rate within the field and a varying level of skills. Therefore, given these constraints, it has proven crucial to have professional clinical research nurses who can coordinate clinical trials independently without having to rely too much on CRCs. At the same time, clinical research nurses are familiar with the operations of their own hospital departments and as such they can assist in optimizing the coordination and management of clinical trials. In addition to developing appropriate college curricula, the development of career pathways and performance appraisal systems for clinical research nurses also need to be fully supported, including providing opportunities for evaluation of professional titles, continuing education, certification of qualifications, opening up channels for promotion, and ensuring that performance appraisal for clinical research nurses is strongly linked to their clinical research-related tasks.

2. Vocational education

In addition to theory, new drug development is also an empirical science and as such it requires systematic and ongoing on-the-job training; so, the importance of adult education and socialized learning cannot be ignored. To comprehensively promote

vocational education, the skills and knowledge of regulators, academia, sponsors (pharmaceutical companies) and CROs, under the leadership of industry associations, could be pooled with the aim being to cultivate clinical research talent at nursing colleges or vocational schools through integrating medium- and high-end vocational education and qualification accreditation with practical application (i.e. assisting with actual clinical trials). Alternatively, professional development courses, delivered by experienced clinical research professionals, could be offered to regulatory and clinical trial personnel, with course completion being considered when candidates are assessed for promotional opportunities.

Clinical research, an interdisciplinary applied science requiring multidisciplinary cooperation, requires talent with independent thinking and learning skills to be drawn from a wide variety of professional backgrounds. At present, clinical research talent in China is mainly drawn from the fields of medicine, pharmacy and public health, each with a relatively narrow professional focus. However, going forward, Chinese clinical research talent needs to be drawn from a much wider range of backgrounds, emulating overseas experience. Talent in other fields need to better understand the science of clinical research in the hope that more of them will be attracted to join clinical research teams.

Digital management and platform construction

The building of a digital tool platform could promote the quality and efficiency of clinical research in several ways. There is no doubt that the COVID-19 pandemic has affected the progress of clinical research trials worldwide, but it has also served to further stimulate and accelerate the uptake of existing digital technologies by those conducting clinical trials. For example, in early 2020 the Chinese Government responded quickly to the situation by formally encouraging sponsors and CROs to adopt ground-breaking amendments made to the Good Clinical Practice (GCP) guidelines by the CDE, which encouraged the use of remote monitoring and other methods in order for clinical trials to continue uninterrupted. Given the ongoing impact of the pandemic, the digitization of clinical research has been accelerated with the data being generated helping to provide insight into how the efficiency of clinical trials can be improved and trial costs reduced, both of which are important propositions for the industry.

A digital platform for clinical research needs to facilitate the development and implementation of clinical research projects and their associated institutional filing requirements, strengthen data tracking throughout the clinical research process, provide for comprehensive digital supervision and management of clinical data, and provide an evaluation system across a range of indicators to promote continuous improvement.

A digital platform could also be used to unlock the potential of technology to assist in the selection of clinical sites, subject enrollment, management of decentralized clinical sites, remote monitoring and a range of other dimensions, ultimately enhancing the efficiency, minimizing the risk, and optimizing clinical research outcomes.

In addition, a digital platform should also consider connectivity with other systems with respect to data which is required to improve the efficiency of data collection (e.g. collecting basic patient medical data from the hospital system, rather than repeated collection during clinical trials).

Promotion of the digital management of a drug's whole life cycle and improvement in the level of 'Internet plus drug regulation' are clearly stipulated in the *Implementing Opinions of the General Office of the State Council on Comprehensively Strengthening the Capacity Building of Drug Supervision* (Document No.16). Specifically, the Document No.16 outlines the need to establish and improve the electronic common technical document system for drug registration and electronic application information system for medical device registration to promote the digitization and networking of review and approval and license management, to promote the construction of a network monitoring system, to strengthen the application of big data in the regulation of drugs, medical devices and cosmetics, to improve data collection, association and integration, risk judgment and information sharing throughout a product's life cycle from laboratory to end-user, to strengthen the construction and application of an archive of varieties of drugs, medical devices and cosmetics, to strengthen the use of data by government departments, industry organizations, enterprises and third-party platforms, to study and explore key common technologies and applications based on big data, and to promote the digitization of regulation and industry.

Chapter 7
Conclusions

Currently, China's pharmaceutical innovation is entering into a higher level of development. As part of the global response to the COVID-19 pandemic, Chinese vaccines have been recognized by many countries with two of them having been included in the World Health Organization (WHO) Emergency Use Listing (EUL). Inclusion in the EUL not only demonstrates China's pharmaceutical innovation capacity, but it has provided China with the opportunity to put internationally recognized technical standards into practice, thereby helping the country to accumulate invaluable experience as it strives towards the gradual implementation of scientific, internationalized and modern drug regulations. The further promotion of simultaneous global R&D, registration and review in China will facilitate patients being able to benefit from innovative drugs in a timelier manner, greatly assist China to participate in simultaneous global R&D, enhance the level and capabilities of China's drug R&D, and better integrate the Chinese pharmaceutical industry into global innovation ecosystem. Furthermore, through constantly improving its regulatory system in line with international standards, improving its R&D capabilities and adapting to the globalization trend in new drug R&D, China has risen to the second echelon of global pharmaceutical innovation and is on the path to becoming a pharmaceutical powerhouse as it continues to build on its strengths.

The promotion of simultaneous global R&D, registration and review is a complex project requiring the close cooperation of national governments, enterprises and investigators. For example, the realization of simultaneous global R&D in the first instance requires optimizing requirements and processes of application for the use of genetic resources, and significantly improving regulatory and clinical capabilities at every point in the process to ensure timeliness. For those projects choosing to follow simultaneous global R&D, registration and review pathways, enterprises need to include China at an early stage. Both Pathway 1 (joining early clinical trials to ensure simultaneous registration and marketing by realizing simultaneous R&D at various stages) and Pathway 2 (joining mid- and late-stage global multi-center clinical trials to achieve simultaneous registration and marketing) require the active participation of a range of parties including domestic and foreign regulators, innovative pharmaceutical enterprises, and Chinese investigators, to promote mutual recognition of international data and the further implementation of ICH standards. In those instances where the first two pathways cannot be realized for various reasons, Chinese bridging trials and separate clinical trials (Pathway 3) would be required, and which would depend upon communication with regulators being improved to give sponsors the opportunity to forward plan. In addition, all stakeholders could actively explore feasible alternative pathways with regulators to increase China's rate of participation in simultaneous global R&D, registration and review.

This report outlines ten recommendations in total for promoting simultaneous global R&D, registration and review, including **three that address current bottlenecks, five that outline the key tools needed to ensure a sound system, and two that address capacity guarantees for the promotion of continuous improvement.**

Three ways to break through current bottlenecks

Improve the rationality of application requirements for human genetic resources (HGR) and optimize process efficiency

Establish a sound and science-based HGR management system encompassing a reasonable level of risk, set up an effective multi-party (cross-ministry and industry) communication and dialogue mechanism, improve the transparency of regulatory policies and the predictability of review and approval timelines, and introduce targeted rules for the implementation of the *Regulations on Management of Human Genetic Resources*.

Improve the scientificity of requirements for subject enrollment in China and enhance mutual recognition of international data

Use a more scientific, accurate and systematic approach to determine subject enrollment requirements in China that takes into account the difficulties faced when recruiting for clinical R&D projects, the science behind cross-ethnic differences, and the statistical rationale. Also, increase the openness of clinical trial data for Northeast Asia to ensure the scientificity and reliability thereof.

Promote uniform standardization and synergy of clinical institution processes and ensure relevant high-efficient implementation

Standardize the project approval, ethical review and approval, and contract signing processes at clinical research institutions, and shorten the time it takes to initiate clinical trials through comprehensive overall planning and streamlining of processes. The National Health Commission and other regulatory agencies could promote the standardization of clinical research institution processes and quality control by incorporating key clinical research implementation indicators into institutional evaluation.

Optimize the ethical review and approval process (e.g. the further implementation and promotion of simultaneous ethics approval and clinical applications, and the standardization of materials and processes required for review and approval by hospital ethics committees), promote the establishment of regional ethics committees and recognition thereof by clinical trial institutions, and enhance the formulation of certification standards with respect to the quality of ethical review and approval.

At the same time, sponsors should also ensure efficient internal processes and communication in relation to the initiation of clinical research.

Five foci to form a sound system

Optimize review-related processes and encourage clinical value-oriented reviews

Optimize the process for accelerated review applications (e.g. applications for priority review could be submitted in advance or at the time of marketing application), clarify the criteria for defining clinical value, and encourage the development and implementation of review incentive mechanisms for original innovative drugs (e.g. breakthrough therapeutics).

Improve the reasonableness of dossier requirements for review and approval, and further align with international standards

Align dossier requirements with international standards to reduce the need to submit unnecessary China-specific documents.

Promote the comprehensive implementation of the marketing authorization holder (MAH) system in line with international standards

Open up pathways for the implementation of the MAH system in cross-border situations, ensure the full coordination of the MAH capacity of enterprise subsidiaries (e.g. pharmacovigilance), and clarify the regulations for segmentation, multi-site, and CMO production in manufacturing licenses.

Promote the building of platforms in clinical research institutions and the formation of full-time clinical research teams, clarify the positioning of institutions, and accumulate experience in the management of exploratory clinical trials

A professional clinical research platform should be built to effectively support clinical investigators and associated relevant disciplines. Promote the formation of full-time clinical research teams, open up career pathways and establish a fit for purpose assessment system. It is also recommended that based on clear positioning among research institutions, that they identify the areas in which they will take the lead in making breakthroughs and solving problems, and then develop corresponding objectives and plans, so as to continuously and efficiently accumulate experience in the management of exploratory clinical trials.

Improve incentive mechanisms and investment in resources for clinical research

Optimize the clinical research assessment system of hospitals, raise the profile of clinical research, reform the methods used to evaluate doctors' professional titles and assess their performance, and encourage them to conduct and participate in clinical research. Guarantee investment in clinical research through increasing the proportion of medical scientific research funds allocated to clinical research and promote the establishment of special clinical research programs or scientific research funds.

Two guarantees to drive continuous improvement

Talent assurance

Strengthen the formation of regulatory teams, ensure the allocation of a reasonable number of regulatory personnel, optimize the employment conditions of reviewers, and enrich the sources of regulatory talent. Build an education and training system that combines research, training and practical experience, improve the quality of core regulatory talent, and narrow the gap between regions in terms of regulatory expertise. Accelerate the establishment of cross-border regulatory teams to enhance participation in simultaneous global R&D and regulation.

Encourage regulatory teams to show reasonable flexibility at the same time as adhering to the principles of science-based regulatory review. Enhance direct communication with regulators in developed markets to facilitate a better understanding of the reasons and considerations behind review policies and to ensure local adaptation and continued modernization of regulatory implementation.

Continuously expand tertiary education curricula for clinical research talent (e.g. clinical research nurses) and expand course offerings to more universities and colleges countrywide. Under the leadership of industry associations, promote vocational education across the board and consider integrating multiple capabilities (e.g. regulators, academia, pharmaceutical sponsors, CROs and third-party providers) involved throughout the lifecycle of clinical trials to develop clinical research expertise.

System assurance

Improve the scientificity, transparency and predictability of the regulatory system. Gradually complete the transformation to a risk management-based concept and improve management capacity thereof, optimize management efficiency; actively and fully participate in bilateral and multilateral cooperation mechanisms for global drug regulation, play an active role in the study and development of international norms and standards; vigorously promote scientific research on drug regulation and deepen cooperation and coordination among academia, national, local and private research institutions. Coordinate and manage legislative programs that facilitate the integrated management of regulations and standards and improves the transparency of legislative work.

Promote the development of a digital platform for clinical research and explore opportunities to apply new technologies during clinical research. Promote the digitization of regulation and the industry so as to cover the whole product lifecycle.