Fostering China Pharmaceutical Innovation System

Report 1: 2015-2020 Review and Future Outlook

China Pharmaceutical Innovation and Research Development Association (PhIRDA)

R&D-based Pharmaceutical Association Committee (RDPAC)

March, 2021

Preface

The world is undergoing major changes unseen in a century, new wave of scientific & technological revolution and industrial transformation are developing in depth, and China is entering a new stage of development during the "14th Five-Year Plan" period. Innovation is placed at top of the five new development concepts and the country has clearly made strengthening strategic scientific and technological capabilities a priority in 2021. “Innovation-driven development" will become China's core strategy in the next five years and mid-long term. In the context of prevention and control of COVID-19 global pandemic, the important role of pharmaceutical innovation in disease control and restoring the economy has become more apparent. The pharmaceutical innovation capability is an indispensable element of demonstrating the country's overall capabilities.

2015-2020 is a five-year period with extraordinary development of China’s pharmaceutical innovation ecosystem. The “Major New pharmaceutical innovation" project launched in 2008 demonstrated the government’s determination to transform China into a global leader in pharmaceutical innovation, encouraging a large group of talents to devote to pharmaceutical innovation, and the results achieved are remarkable; government support also triggered private capital investment. “Opinions of the State Council on Reform of the System of Evaluation, Review and Approval of Drugs and Medical Devices” in 2015 and “Opinions on Deepening the Reform of the Review and Approval System and Encouraging the Innovation of Drugs and Medical Devices” in 2017 by the Central Office and the General Office of the State Council (hereinafter referred to as the “Two Documents”) laid out the overall design of the ecosystem, and pointed out the direction for transformation of mindset and mechanism: transforming the role of the government, integration with international standards, encouraging the participation of ecosystem stakeholders, strengthening collaboration in governance, and emphasizing the importance of intellectual property rights. The introduction and implementation of policies such as the reform of the drug regulatory and medical insurance system is an effective practice of the “Two Documents” principles and has improved the policy environment of the pharmaceutical innovation ecosystem. China’s pharmaceutical innovation ecosystem has been established, and the booming pharmaceutical innovation industry in China will continue to integrate with the global pharmaceutical innovation value chain.

Development of vaccines and effective treatments have become the key for COVID-19 prevention & control and economy restart. China’s successful development of COVID-19 vaccines has already helped in many countries. The world is looking at China’s rapidly rising pharmaceutical innovation capabilities and potential contributions to global public health from a new perspective. This will certainly further help China’s pharmaceutical innovation, promoting scientific and technological cooperation, integrating into the global innovation network.

China’s guiding principles for the development of science and technology have evolved from 2016 to 2020 to cover four key elements, now emphasizing “people’s lives and health” together with “the frontiers of world science and technology”, “the main economic battlefield” and “the major needs by the country”. In the next 5 to 10 years, disease burden of cancer and chronic diseases are expected to increase, while the COVID-19 pandemic reminds us that the long-term threat from infectious diseases still exists. Therefore, improving the prevention and treatment of cancer, chronic diseases and infectious diseases will help achieve “Health China 2030” should be the focus of the pharmaceutical innovation industry.

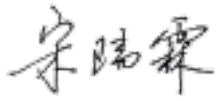
It is critical to maintain the momentum building on achievements in the past five years, and achieve higher-quality development through deeper reform, and further international cooperation: from “catching up” as a tier 3 market in pharmaceutical innovation, to rising to a tier 2 market, and marching towards becoming a tier 1 market.

At the beginning of 2021, the two drug industry associations launched the effort to develop a series of reports to conduct in-depth research on how to continue to promote the China pharmaceutical innovation ecosystem. This report is the first of the series, and it focuses on reviewing the development of China pharmaceutical innovation ecosystem in the past five years, including systematically reviewing the progress of ecosystem, and comprehensive assessment of the output of China pharmaceutical innovation and global competitiveness. The follow-up reports will elaborate on the direction and specific recommendations for the improvement of China pharmaceutical innovation ecosystem in the next five years.

This report has been guided by experts of the advisory committee and sincere appreciation of valuable suggestions is hereby extended to them.

China Pharmaceutical Innovation and Research Development Association

President: Jinsheng Ren　　Executive President: Ruilin Song



R&D-based Pharmaceutical Association Committee

President Asgar Rangoonwala　　Managing Director Wei Kang

Advisory Committee

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Chapter 1

Strategic Importance of Fostering China Pharmaceutical Innovation Ecosystem

Promoting pharmaceutical innovation is part of China's national innovation-driven development strategy, and plays critical role in transforming and upgrading the pharmaceutical industry achieving the ambitious "Healthy China 2030" goal, deepening healthcare reform and benefiting the patients. In 2008, China started "Major New Drug Development Program" and has since invested tens of billions RMB to support pharmaceutical innovation; in 2012, biopharmaceutical industry was listed as one of the seven strategic industries of China. However, there still had been a series of challenges in the development of pharmaceutical innovation in China until 2015: capability gaps throughout the value chain, few innovative drugs in the market and access challenges post launch, limited market returns; contribution to global innovative drug pipeline was about 4%[1], putting China as a tier 3 market for pharmaceutical innovation.

From a global perspective, with breakthroughs in basic research of life sciences, development and innovation in pharmaceutical industry has become a critical domain. From 2011 to 2015, the only tier 1 country in pharmaceutical innovation United States, and UK, Japan as well as other tier 2 countries introduced overarching design from a national perspective to guide accelerated development of pharmaceutical innovation so as to evolve regulatory and policy environment along with advancement of science and technology.

As far as pharmaceutical innovation was concerned, China faced historical opportunities and intensifying global competition in 2015 while having a relatively weak foundation. The situation was complicated and the task was arduous. However, drug development has a long cycle (on average, it takes ten years for a new medicine to complete the journey from R&D to market), associated with high risk (only less than 8% success rate from phase I to approval[2]), and very costly (with risk adjustment, it costs on average about 2.6Bn USD to develop a new drug[3]). Promoting pharmaceutical innovation requires not only government's support to provide investment or introduce specific policies, but also clear top-level design from a national perspective. In addition, scientific concepts, improved policy and mechanism, and strong support from stakeholders are needed throughout the value chain (basic research, clinical research, regulatory, and payment). It is imperative to establish an ecosystem for China's pharmaceutical innovation.

While five years are not enough for an innovative drug to complete the full cycle from R&D to launch; from 2015 to 2020, China built a relatively complete ecosystem for pharmaceutical innovation. It is an ecosystem where policy, capital and capability are reinforcing each other in a virtuous cycle; the innovators are emerging and market returns attract continuous investment; there are a great variety of participants including local and MNC pharmacos, biotechs, investors, academics, and regulators, and they widely cooperate and closely communicate to jointly drive development of the system. In 2020, China ranked the top among tier 2 countries for contribution to global pharmaceutical innovation, accounting for 14% of global innovative drug pipeline assets, only second to the US.

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[1] 2016 RDPAC Report "Fostering a Sustainable Ecosystem for pharmaceutical innovation in China"

[2] BIO, Clinical Development Success Rates and Contributing Factors 2011-2020

[3] Tufts Center for the Study of Drug Development, Innovation in the pharmaceutical industry: New estimates of R&D costs, J Health Econ. 2016 May;47:20-33

Chapter 2

Policy Environment Improved

Overarching ecosystem design

Opinions of the State Council on Reforming the Review and Approval System for Drugs and Medical Devices in 2015 and The *Opinions on Deepening the Reform of the Review and Approval System and Encouraging 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 ("Document of the Two Offices") are major milestones for promoting the pharmaceutical innovation industry. The documents clearly point out the overarching strategy, give all-round considerations of the support needed by various steps of pharmaceutical innovation, and ensure cross-ministerial collaboration and consistency across laws and regulations. The documents point out the direction for changing a series of concepts and innovating mechanisms. 1. Change the role of government**.** Reduce administrative review and approval and give more responsibilities to companies, institutions, and the market under the precondition that safety is ensured. For example, review and approval procedure for clinical trial applications is changed to notification-based, qualification of clinical trial site is changed to filing-based. 2. Transform the concept of innovation**.** A regulatory science system is proposed that takes a scientific approach to treating the associated risks of drug development. For example, continuously optimize the process to accelerate regulatory review and approval. With regard to drugs urgently needed, the drugs can be conditionally approved. 3. Persist in opening up and aligning with international standards**.** The former State Food and Drug Administration joined ICH[4] in 2017 and was successfully elected as a member of the management committee in 2018, gradually implementing the highest international technical standards and guidelines, demonstrating China's determination to enhance innovation capabilities and international competitiveness of the drug industry. 4. Encourage private party participation and market competition**.** For example, encourage private investments to establish clinical trial institutions to increase the number of clinical trial sites to meet rapid growing demand. 5. Clarify the importance of intellectual property protection to encourage pharmaceutical innovation and propose to explore the establishment of a drug patent linkage system and patent period extension protection, and improve the protection of drug trial data. 6. Strengthen process supervision and management of the entire life cycle of drug products. For example, it is made clear that the marketing authorization holder (MAH) of a drug is responsible for the drug throughout the entire life cycle. 7. Strengthen communication mechanism and social governance. During the process of preparing a policy, communications between government and regulatory authorities and the industry are increased to ensure transparency of the decision-making process; during the process when a policy is implemented, feedback from the industry collected in time to make the communication mechanism work on a regular basis.

[4] The International Council for Harmonization of Technical Requirements for Drugs for Human Use

Strengthen the legal framework and encourage protection of intellectual property

The revised Drug Administration Law (DAL) in 2019 clearly points out the direction to encourage innovation and support of clinical value-oriented pharmaceutical innovations. It also stipulates that an MAH system should be established to make MAHs take responsibility for drugs throughout the life cycle and optimize the allocation of resources. In the revised DAL, many provisions were added to accelerate new drug approval. The new law also strengthened regulation on drug safety and life cycle management.

In the **revised *Patent Law*** passed in 2020, patent extension system that is in line with international practice was introduced to appropriately compensate for the time required to obtain approval of innovative drugs. In the revised Patent Law, arrangement is made about patent linkage (linking application of Gx to the patent status of its originator). It is stipulated in the law that the drug regulatory authorities, in conjunction with the patent administration department, will formulate specific measures for resolving the dispute during drug registration approval process, and establish an early settlement mechanism.

Formulate and implement policies to drive improvement of key elements of innovation

1. Regulatory review and approval

The series of measures and supporting plan for regulatory review and approval system reform reflected the guiding principles laid out in the Document of the Two Offices. The number of products that receive accelerated approval with priority review has increased from 7 in 2016 to 82 in 2019[5]. Four accelerated approval pathways for new drug registration are clearly stipulated in the new edition of *Drug Registration Regulation* in 2020, including breakthrough therapy, conditional approval, priority review, and special approval. Before the regulatory reform in 2015, the approval process of a new drug in China was five to seven years longer than that of US FDA. The time taken to approve a clinical trial application of a new drug was the bottleneck for new drug regulatory review and approval. In 2018, the 60-day notification based CTA and single approval for phase I-III trial were remarkable progress. A series of policies to accelerate regulatory system reform greatly shortened time for new drug approval and made it possible for new drugs to be simultaneously developed / approved in China vs. global. The implementation of the national "Major Project for New Drug R&D" in 2008 and the reform of the drug regulatory review and approval system that began in 2015 have directly led to a substantial increase in the number of new drugs approved in China in the past five years. During the 13th Five-Year Plan (2016-2020), the total number of innovative drugs approved has reached 200 (including innovative small molecules and biologics that have not been approved globally, and originators that have been approved overseas but not yet in China).

[5] National Medical Products Administration, 2019 Drug Review Annual Report

Regulatory mechanism gradually integrating with global. The former China Food and Drug Administration (now National Medical Products Administration) joined the International Council for Harmonization ("ICH") in 2017 and was elected a member of its Management Committee in 2018. The technical guidelines issued by ICH are not only used among its members, but also accepted and transformed by many non-member national drug regulatory agencies, becoming an important international rule-making mechanism in the field of drug registration. This greatly pushed the China's standards for drug registration to become more scientific and step up coordination and consistency in technical requirements for drug registration in China and international requirements. It is of great significance for improving the ability and level of drug supervision and the international competitiveness of China's drug industry. PhIRDA and RDPAC, as representatives of China in the International Federation of Drug Manufacturers Associations (IFPMA), have actively participated in the formulation of ICH technical guidelines and the implementation in China. As of November 2020, 54 industry experts have been recommended to 18 ICH working groups to participate in the formulation of ICH technical guidelines, of which 17 representatives served as team leaders, 10 served as alternate team leaders, and 149 were selected to dozens of ICH working groups at CDE.

Strengthened regulatory review capabilities and drive development of regulatory science. There were about 150 reviewers in the Center for Drug Evaluation at the end of 2015 and the number had increased to about 700 in 2018; at the same time, panels of review experts consisting of 626 external experts (including 35 academicians) were convened. Continuous improvements have been made in the quality and efficiency of regulatory review and approval process, with the focuses on the principles of "science-driven", "fairness" and "transparency".

2. Clinical research

Support hospitals and institutions to conduct clinical trials: assessment of infrastructure and capabilities of conducting clinical trials has been included in the medical institutions ratings. A separate evaluation and assessment system is established for medical institutions conducting clinical trials. Medical institutions are encouraged to establish a special department for clinical trials. Incentive mechanisms related to clinical trials are improved to encourage participation. The capabilities of clinical institutions and investigators have been improved with experience gained.

Implementation of filing-based clinical trial site qualification: certification-based qualification used to constrain the quantity and capabilities of clinical trial sites. Filing-based qualification implemented has encouraged the participation of clinical trials, with number of sites increased from 375 in 2015 to ~1,000 in 2020.

3. Payment

Improve the payment and reimbursement mechanism for innovative drugs in basic medical insurance: The basic medical insurance funding for urban employees and urban & rural residents increased from RMB 1.4 trillion in 2015 to RMB 2.3 trillion in 2019. The frequency of updating National Reimbursement Drug List (NRDL) has been continuously improved, from no update 8 years before 2017 to the dynamic adjustment in 2020; the inclusion mechanism has also been continuously optimized, from expert nomination to company application. The optimized NRDL listing mechanism allows broader coverage and more rapid inclusion of innovative drugs, resulting in improved accessibility for patients. For the 31 western drugs included in 2017 NRDL update, the average time from launch to NRDL listing was 7.8 years; while for the 66 western drugs included in 2020 NRDL update, the average time from launch to NRDL listing dropped to 3.7 years, among which 14 drugs were approved in 2020.

Establish a multi-tiered payment coverage system. Commercial health insurance, as an important part of the multi-tiered healthcare payment system, has rapidly developed in the past five years. Premium income of commercial health insurance grew from RMB 241 billion in 2015 to RMB 706.6 billion in 2019, with multiple forms of reimbursement-based commercial health insurance products playing critical complementary role to cover innovative drugs.

4. Basic research

A series of laws/regulations were released to encourage translation of Scientific and Technological Achievements. Firstly, the *Law on Promoting the Translation of Scientific and Technological Achievements* was revised; secondly, *Provisions on Implementing the Law on Promoting the Translation of Scientific and Technological Achievements* were introduced to clarify supporting rules; thirdly, specific tasks were deployed by adopting the *Action Plan for Promoting the Transfer and Translation of Scientific and Technological Achievements*. In accordance with these laws/regulations, the relationship among the government, research institutions and researchers were clarified, and the right of usage, disposal and earnings from scientific and technological achievements were delegated to scientific research institutions.

5. Intellectual property protection

Regulatory authorities and other administrative departments for patents of the State Council collectively solicited experts' input from industry and academia, to drive implementation of patent linkage and extension, and completed revision of the *Patent Law* and prepared for drafting of other related laws and regulations.

Chapter 3
Capital Investment Increased

The " Major New Drug Development Program" has played an important role in leading and catalyzing the development of China's drug R&D, and helped the transformation from a large drug manufacturing country to a strong pharmaceutical innovation country. As an critical part of China's mid-and long-term science and technology development plan, the "Major New Drug Development Program" was launched in 2008. With the progress during the 11th and 12th Five-Year Plan periods, the innovative R&D platform and technology platform have been initially established; during the 13th Five-Year Plan period, the focus was "cultivate key products, address key needs, and solve key problems" to achieve breakthrough. Implementation of three phases of the project will come to an end in 2020. The central government has invested a total of 23.3 billion yuan, provided support for more than 3,000 subjects, and achieved remarkable results in pharmaceutical innovation is targeting 10 major diseases. Government's continuous investment in pharmaceutical innovation will help further drive science and technology innovation to keep up with the global pace of the next generation of pharmaceutical innovation technology.

The remarkable improvement in innovation policy environment has greatly boosted the confidence and enthusiasm of private capital to invest in innovative drugs. Venture capital and private equity investments in China's healthcare were only 12Bn RMB in 2015, which increased 15-fold to 185Bn RMB in 2020 (with one-third focusing on innovative drugs)[6]. The China BioMed Innovation and Investment Conference inaugurated in 2016 has become an influential platform in APAC for partnership between pharmaceutical innovation industry and investors.

Another indication of the enthusiasm to invest in innovative drugs is the growth in the number of biotech companies going public and their total market capitalization. In 2020, there were over 20 biotech companies listed in China, and the total market cap of China biotech companies listed on Shangwhai's STAR Market, HKEX and NASDAQ soared from less than 10Bn RMB in 2016 to over 1 Trillion RMB by the end of 2020. High recognition of China innovative drug companies and market potential by global investors, as shown in 2020 global top 50 biopharma companies ranking[7], six China companies are listed including Hengrui, Hansoh, WuXi Biologics, Sino Biopharmaceuticals, CSPC, and BeiGene.

Under current wave of investment in innovative drugs, it is necessary to focus on the long-term, from investment stimulated to market return driven, thus to ensure the sustainability of the pharmaceutical innovation industry. The investment in innovative drug R&D is huge (not considering risk, the average R&D cost of a single innovative drug is as high as 1.5 billion RMB). After a new drug is launched, if it cannot obtain a reasonable economic return in time due to factors such as market access, pricing and payment, intellectual property protection, etc., it will severely dampen the enthusiasm of investors and pharmacos to further invest in R&D. Sustainable development of the pharmaceutical innovation industry is closely tied to well-developed payment system and intellectual property protection system for innovative drugs.

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[6] ChinaBio, 2020 China Life Science Investment Hits New Records

[7] Endpoints News March 2020

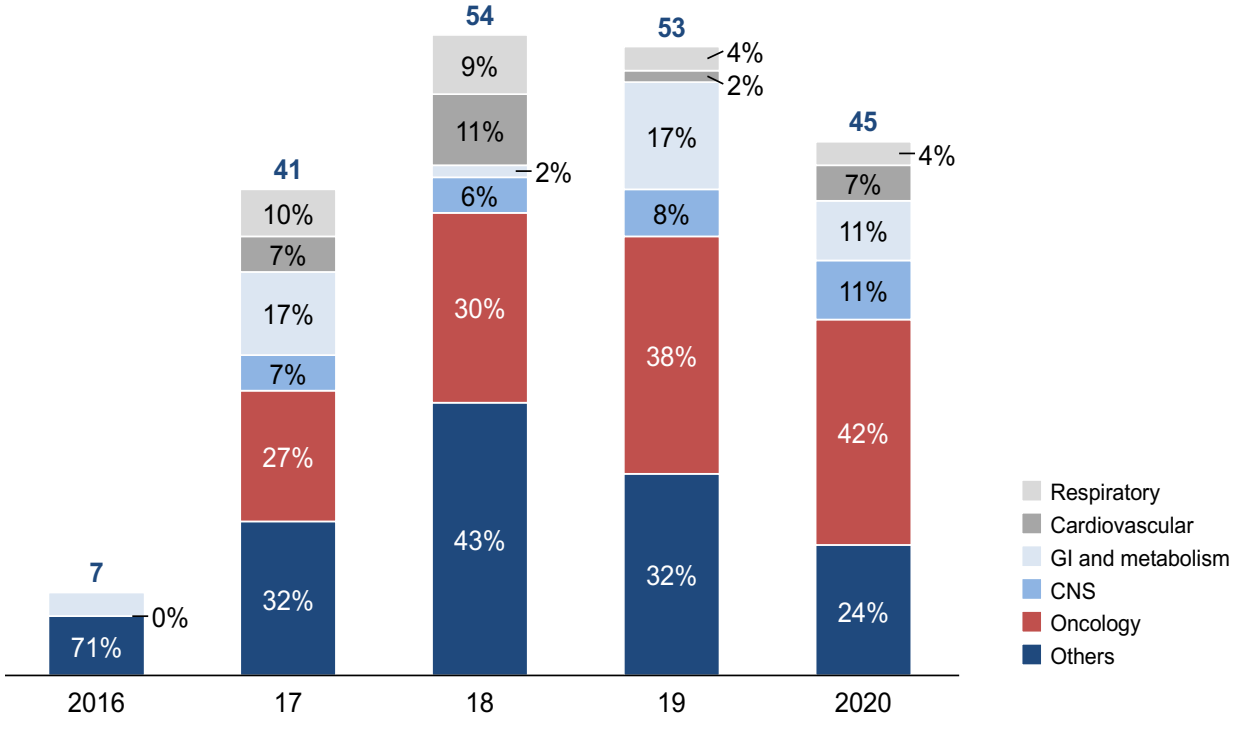
Chapter 4
Elevated Innovators' Capabilities

Innovative drugs launched by both local companies and MNCs address patients' unmet medical needs in China

In the past five year, 200 innovative drugs have been approved iwn China, focusing on diseases with highest burden and fastest growth to address patients' unmet medical needs, including oncology, GI and metabolism, respiratory, CV etc. (Figure 1).

Figure 1

Innovative drugs launched in China 2016-2020, focusing on diseases with highest burden and fastest growth



1. Including innovative drugs/ biological products not launched in China or overseas, and innovative drugs/ biological products that launched overseas but not launched in China

Source: GBI

Local companies gradually establish innovation capabilities, and have achieved early breakthrough in globalization

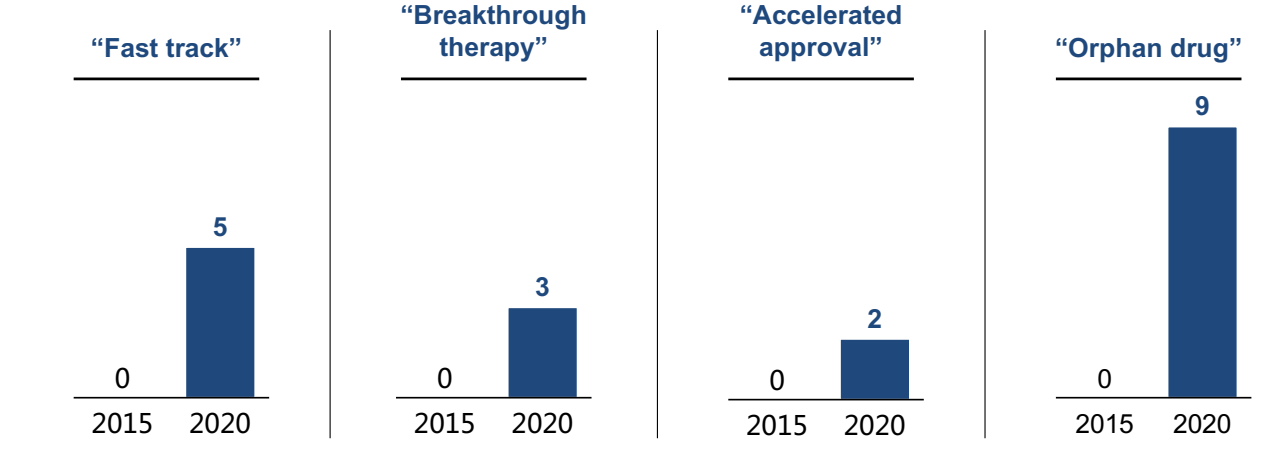
Several large local pharmacos have annual R&D expenditure over RMB 1 billion, accounting for more than 10% of annual revenue. Leading local companies have also established R&D centers in and outside China to develop a complete innovation system. Increasing numbers of Class I innovative drugs developed by local companies have been approved in the past three years: 10 in 2018, 12 in 2019 and 15 in 2020. Successful development of COVID-19 vaccines also demonstrated China pharmaceutical innovation capabilities. As of Feb 2021, five technical routes were taken in parallel for COVID-19 vaccine development in China, with 7 in phase 3 and 4 obtained conditional approval; oversea orders for China vaccines from 50+ countries/regionals have passed 500 million doses, showing global acceptance of China vaccine regarding safety and efficacy.

The number of international multicenter clinical trials sponsored by China companies increased from 48 in 2015 to 131 in 2019[8]; and the number of countries/regions covered increased from 14 in 2015 to 51 in 2019. China innovative drug companies have been granted multiple accelerated reviews and orphan drug designations by the US FDA (Figure 2). Of these, the oncology drug zanubrutinib by BeiGene is the first innovative drug developed by a China company that obtained marketing authorization in the US through expedited pathways. Additionally, licensing partnerships also help China innovative drugs reach global markets. Representative cases in 2020 include Innovent's out-licensing ex-China commercialization rights of TYVYT (anti-PD-1 mAb) to Eli Lilly, and I-Mab's out-licensing ex-China development and commercialization rights of TJC4 (an anti-CD47 mAb) to AbbVie.

Figure 2

China pharmaceutical innovation gradually gain recognition from overseas regulators, and has achieved early breakthrough in globalization

Number of China innovative drugs granted by the US FDA by types of designations



Source: Press search

[8] Clinicaltrials.gov

MNCs upgrade China innovation center, and form broad local partnerships

For MNCs, the role of R&D in China has transitioned from mainly for drug registration and commercialization to making China an innovation hub for simultaneous development of innovative drugs with US and EU. MNCs have established 25 R&D centers in China, with an annual R&D investment of over RMB 12 billion[9]. R&D centers in China have been key component of MNCs' global R&D, and at the same time helped R&D talent cultivation in China. For example, the 863Mn RMB Roche Innovation Center Shanghai has been opened, making it the third largest strategic center for Roche globally, potentially to bring innovation in China to global in the future; Sanofi has set up its first global research institute in Suzhou China, with an expected annual investment of 160Mn RMB over the next five years; Pfizer's China R&D Center, established in Shanghai back in 2005, has gone from providing functional support to participating in the Pfizer's global development of innovative drugs.

MNCs' China R&D centers are working closely with international institutions and experts in various fields, and the model of introducing new drugs by China participation in global simultaneous development is gradually being realized. For instance, three new indications for nintedanib esilate soft capsules, an antifibrotic agent, all achieved simultaneous submission in China, and were approved in China based on the results of phase III global MRCT with Chinese patients' participation.

MNCs are active in leveraging diversified cooperation models, to cooperate with universities, scientific research institutions, and biotech companies to discover new technologies and new therapies; through licensing deals, to strengthen cooperation with local drug companies in R&D; through investment funds, to tap into local innovation at earlier stage. For example, JLABS @ Shanghai is the first incubator established outside North America by Johnson & Johnson to serve as an efficient and flexible innovation platform; INNOVO is an innovation platform in Beijing established by Novo Nordisk to increase partnership with local academic institutions and start-ups regarding innovation in China; I•Campus in Wuxi is a life science campus co-built by AstraZeneca and the government. 2020 is a milestone year for globalization of China innovation, the number (80+), scale and quality of cooperation between local companies and MNCs have reached unprecedented heights.

Elevated clinical research capabilities

I**ncrease in number of articles published in top clinical journals**: the number of articles published by China KOLs in top clinical research journals such as *The Lancet* and *The New England Journal of Medicine* is on the rise, from 137 in 2015 to 302 in 2020.

Increase in number of PIs involved in clinical trials: approximately 1,300 Chinese investigators participated in clinical trials between 2017 and 2019, and 10% of them have participated in at least one international multicenter clinical trial. Taking oncology as example, number of oral presentations given by Chinese PIs at the annual meeting of American Society of Clinical Oncology increased from one in 2015 to six in 2019.

Improved basic research output

Increase in number of articles published in top journals of basic research: 150+ research articles led or co-led by Chinese research teams were published in top academic journals including *Nature, Science*, and *Cell* in 2020.

Leading in number of patent applications related to pharmaceutical innovation: according to the WIPO's Intellectual Property Statistics, China ranked among the top 2 between 2015 and 2019 with 9,500 biotechnology patent applications, 18,800 drug patent applications and 16,600 medical technology patent applications filed[10].

[9] RDPAC, as of June 2020

[10] WIPO, Intellectual Property Statistics

Chapter 5

Output of China Pharmaceutical Innovation – "Quantity" Increase Achieved and "Quality" Improvement Expected

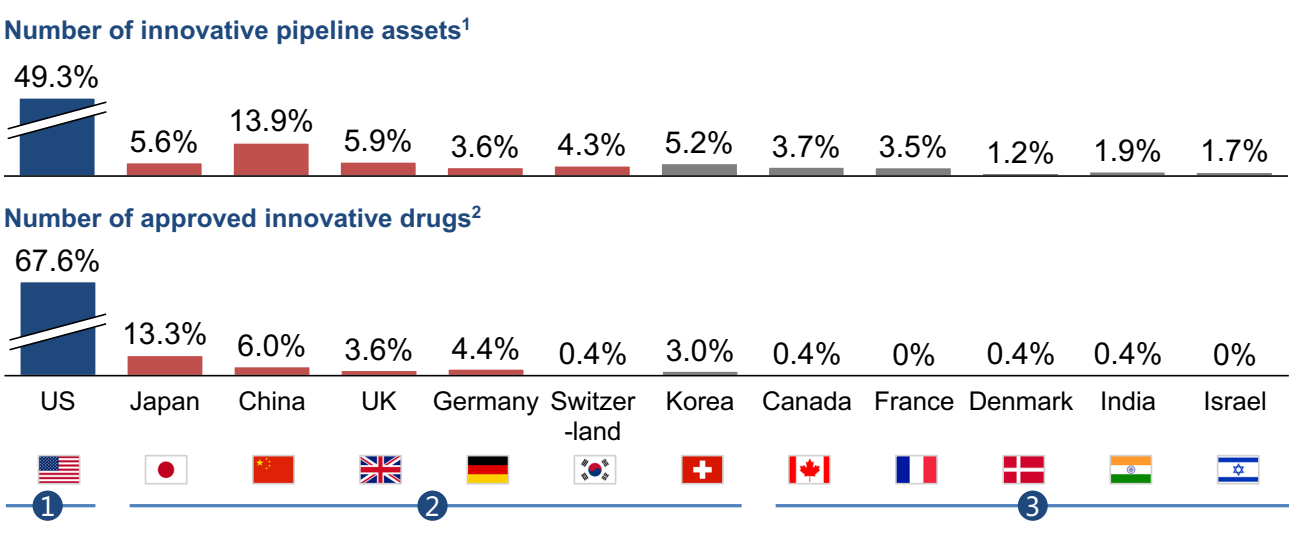
"Quantity": Contribution to global innovative pipeline and innovative drug launches rose to second and third in rankings

Quantitative measures of contribution to global pharmaceutical innovation include two indicators: the number of innovative pipeline assets under development and the number of approved innovative drugs. China contributed 13.9% of global innovative pipeline assets in 2020 (based on the number of assets at preclinical, clinical phase I to III and pre-market registration status as of February 2020, by country where companies are headquartered), compared to 4.1% in 2015 and 7.8% in 2018. China is now leading tier 2 countries, and the gap with the only tier 1 country, US (49.3% in 2020), has been narrowed.

If measured by number of innovative drugs approved (2015-2019, counting only new molecular entities, by country where companies are headquartered), China ranks among top 3 globally among 12 major benchmark countries, with a 6.0% share. This percentage contribution has also increased compared to historical levels (only 2.5% over 2007-2015). Despite the great momentum, there is a still significant gap between China and the US (67.6%) ranking the first and Japan (13.3%) in the second place (Figure 3).

Figure 3

China is now leading tier 2 countries in terms of innovative pipeline assets and approved innovative drugs



1. Number of innovative pipeline products in preclinical, phase I to phase III, and pre-registration as of Feb., by country where companies are headquartered; only the listed countries are considered for contribution %, and the total is 100%
2. 2015-2019, % of first-to-market innovative drugs, counting only new molecular entities; only the listed countries are considered for contribution %, and the total is 100%

Source: Pharmaprojects

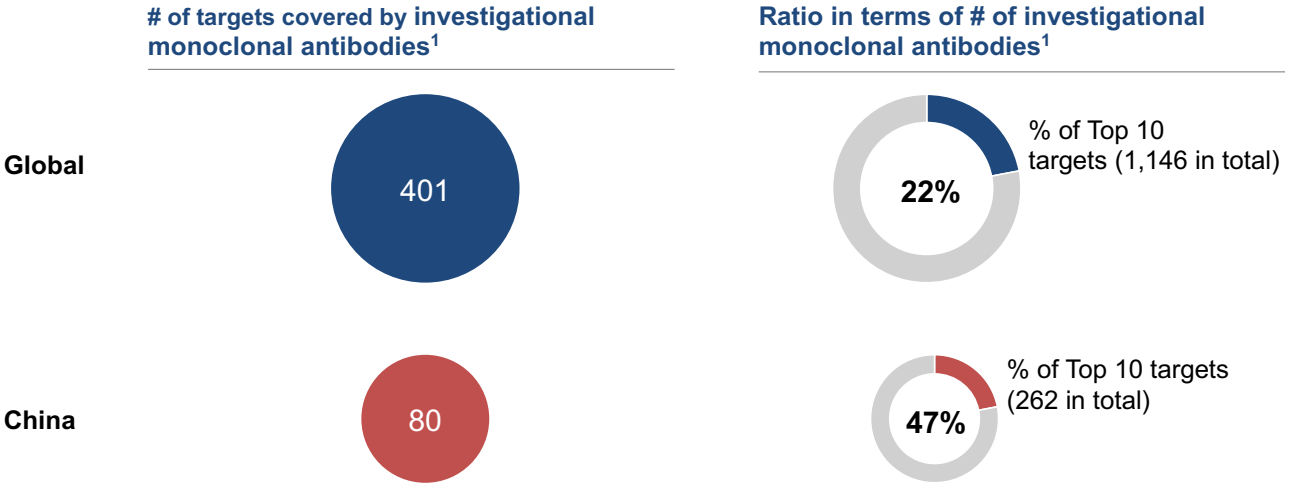
"Quality": mostly fast followers, breakthrough innovation yet to come

China is currently at the stage of incremental innovation with fast followers. The time to market for China's local innovative drugs lagging behind global first-in-class drugs is gradually shortening, with the gap in 2020 reduced by nearly half the time on representative drug targets compared to 2015 (from 8-10 years to 4-6 years). However, the number of global first-in-class innovative drugs remains very limited, with only three out of 37 class I local innovative drugs approved between 2018-2020 having innovative mechanism of action (not yet approved in the US).

Local innovation is highly concentrated around hot targets. Taking monoclonal antibody as example, there are currently about 400 targets overall covered by active investigational monoclonal antibodies worldwide, of which only one-fifth are covered by pipelines of China local companies. R&D around mature "hot" targets is more concentrated in China, e.g., the number of investigational monoclonal antibodies against the top 10 targets is 22% globally, but 47% in China (Figure 4). The reason is due to limited capabilities for breakthrough innovation and risk aversion by capital investment; in the long run, as China's local R&D and innovation capabilities continue to improve and the market returns for differentiated innovation emerge, the situation of concentrated innovation will be alleviated.

Figure 4

Local innovation is highly concentrated around hot targets, with insufficient differentiation



1. As of Nov. 2020, only innovative drugs, excluding dosage form innovation or biosimilars

Source: Pharmaprojects

Chapter 6
Outlook for the Ecosystem in 2021-2025

The guiding principle of China's development of science and technology has shifted from the "three facings" in 2016 to the "four facings" in 2020. "Facing life and health of the people" has risen to the same height as "Facing frontiers of world's science and technology" and "Facing main economic battlefield", and "Facing major national needs." Driven by multiple factors such as the complicated international environment and growing domestic economic development and health demands, China's pharmaceutical innovation has become more strategically important in social and economic development. Through more than ten years of "innovation-driven strategy" and continuous efforts, innovative development has achieved high consensus of the whole society. At present, China is at an important historical turning point from a major drug manufacturing factory to a strong pharmaceutical innovation powerhouse. Only through continuous institutional innovation and increasing government support and investment, can the creativity of scientific and technical talents be stimulated, and the global competitiveness of products and the trust from the public be enhanced. We should adhere to the solemn mission of protecting and promoting public health, and use systematic thinking to enable systematic construction of public health in accordance with forward thinking, holistic planning, strategic layout, and comprehensive advancement. We can promote the rapid development of pharmaceutical innovation and industry along the direction of scientization, legalization, internationalization, and modernization.

The drug industry is carrying an unprecedented responsibility on a global scale. The development of vaccines and effective treatments has become a key to restarting the economy. China's successful research and development of a COVID-19 vaccine is attracting worldwide attention, and the world is looking at China's rising medical innovation power from a new perspective. This will further enhance China's position in the field of international pharmaceutical innovation, promote international cooperation between China and other countries in science and technology, integrate China into the global innovation network, and finally make China a platform for global science and technology cooperation. On one hand, innovative medicine supply will match local demands; meanwhile, China innovation will benefit patients all over the world.

The COVID-19 pandemic has set another example of enormous social and economic impact led by health issues. Improving health is not just a cost and spending, but also an important investment for a national system. Improving people's health can increase their productivity and labor participation, and reduce illness and premature death. With improved health, people can enhance their wellbeing and generate large economic benefits. According to estimates[11], improved health status is expected to boost the global GDP by RMB 78 trillion and China's by RMB 12 trillion in 2040. In 2019, China's total health spending accounted for 6.6% of its GDP, still lower than the 8.2%[12] average of high-income countries, indicating room for further investment in the future.

Under this context, the pharmaceutical innovation ecosystem's development in China should focus on three key levers in the next five years (Figure 5). The first lever is to **enhance the industry's innovation competitiveness with "new drug launch" as the core**. The industry should deepen reform and embrace openness to achieve higher-quality development. In doing so, it has leaped from the past tier-3 followers to the current tier 2 and is expected to move into tier 1 to lead in the

[11] McKinsey Global Institute Report: Prioritizing health: A prescription for prosperity

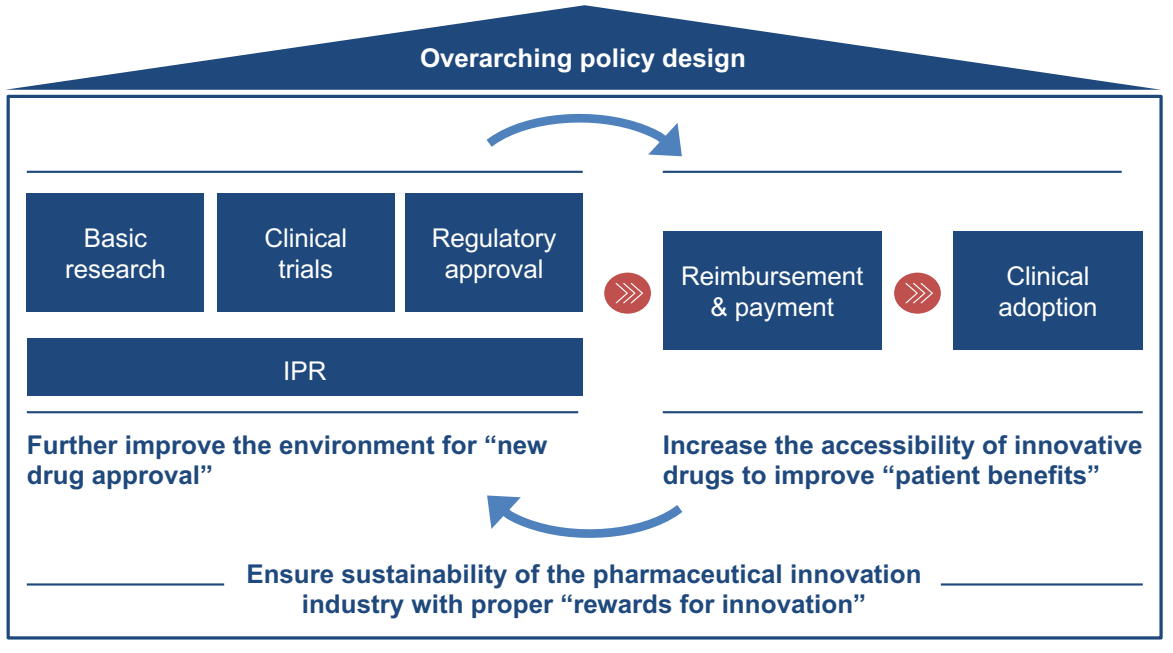
[12] 2016 data; based on WHO's report, Public Spending on Health: A Closer Look at Global Trend, in 2018

future. **The second lever is to improve the accessibility of innovative drugs with "patient benefits" as the core.** Higher health investment and capital utilization efficiency lead to wider adoptions of innovative drugs of higher clinical values and earlier disease diagnosis and prevention, which in turn achieves higher returns on investment and reduces disease burdens from cancer, chronic diseases, and infectious diseases. **The third lever is to ensure sustainable industry development with "reward for innovation" as the core.** Sustainable capital and R&D investments from drug players are key to benefiting patients with more breakthrough innovations.

Figure 5

China pharmaceutical innovation ecosystem (2021-2025):

strengthen the linkage among different elements to further improve "new drug approval", promote "patient benefits" and ensure "reward for innovation"



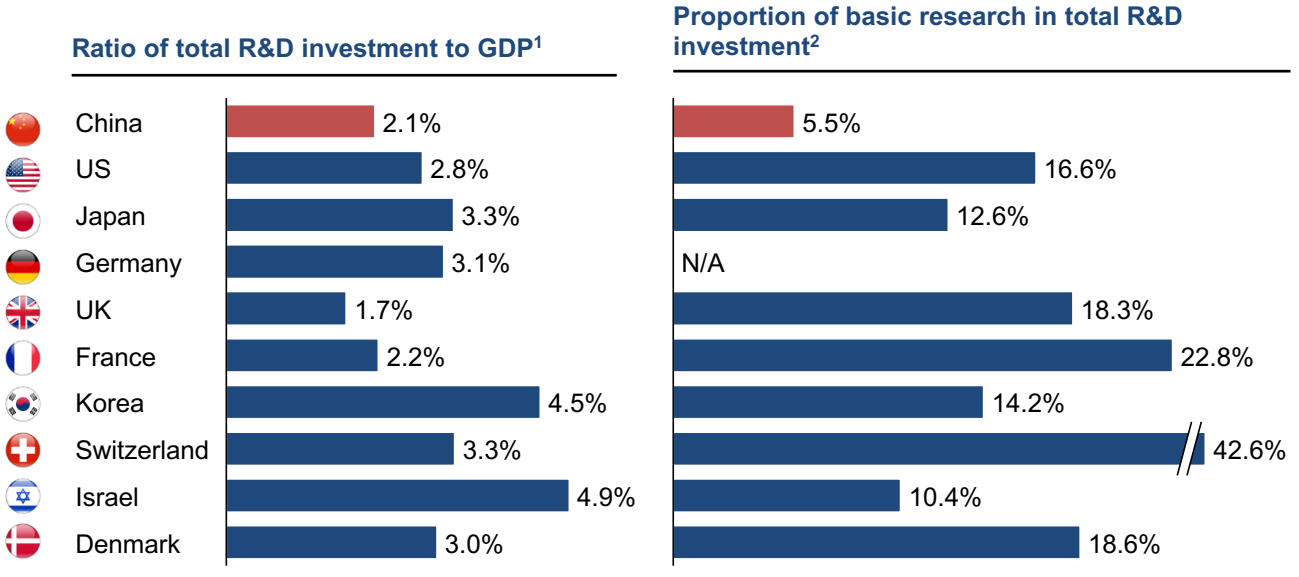
I. Enhance the industry's innovation competitiveness with "new drug launch" as the core

Strengthen the basic research system: Basic medical research is a highly valued strategic frontier by all countries. Developed countries such as the US, UK, France, Japan, and Australia have all developed national strategies for biopharmaceutical or life sciences, and continuously invested in the system to coordinate basic researches and stay ahead of the innovation curve. Basic research is open and uncertain to a large extent, which needs to be supported by continuous funding from the government. The total R&D investment in China accounts for 2.1% of GDP, in line with average level of the European Union, and close to 2.8% level in the US. However, in terms of the proportion of basic research in total R&D investment, the figure is 6% for China, significantly lagging behind the 15% plus level for US and EU countries (Figure 6)[13]. In addition, developed countries have established a management and coordination system for biopharmaceutical researches, while China

[13] OECD

Figure 6

In China, the ratio of R&D investment to GDP is comparable to that of developed countries, but investment in basic research needs to be strengthened



1. 2018 data (for Switzerland, 2017 as the latest data available)
2. 2018 data (2015 and 2017 as the latest data available for France, Switzerland and Denmark)

Source: OECD

lacks a centralized management infrastructure for wholistic planning and deployment of studies to ensure advanced and efficient medical researches. In the US, for example, the National Institute of Health (NIH) controls nearly USD 40 billion funds each year, 80% of which supports research institutions beyond hospitals, coordinated by 24 research institutes in each disciplinary area, aiming to promote cutting-edge medical researches. In France, the French National Institute of Health and Medical Research (INSERM) leads the French National Consortium for Life and Health Sciences to improve the consistency, creativity, and advancement of life and health science researches by coordinating research directions, research projects, and financial resources.

De-bottleneck the translation of basic research outcome: Although the number of top-level academic papers (e.g., in the three major journals including *Nature, Science*, and *Cell*) published by Chinese research institutions has exceeded 150, successful translation into R&D pipeline assets and new drugs launched remain limited. All biopharmaceutical R&D powerhouses recognize the importance of clinical practice in the development process, as the concept of outcome translation "from the laboratory to clinical practice" has been throughout all stages of national industry innovation and development. For instance, the US has established the National Center for Advancing Translational Sciences to build a bridge from basic medical research to clinical studies, and built a network of academic medical centers across US to promote the development of clinical translational medicine nationwide. In contrast to these powerhouses, China urgently needs to strengthen the innovation quality and application, to realize the contribution of basic research to first-in-class drugs' development.

Accelerate the application of emerging technologies : Artificial intelligence and big data will help improve the efficiency of innovative drugs' research and development, covering multiple steps such as target discovery, drug screening, and clinical research. The application of emerging technologies has raised higher requirements for the completeness, connectivity and quality of China's medical and health data, while further reforms and breakthroughs at the institutional level are still pending.

Improve regulatory review and approval: China should participate deeply in the bilateral and multilateral cooperation on global drug regulation, join the efforts to study and set global norms and standards, and advance the implementation and translation of ICH technical guidelines. While ensuring a sufficient, comprehensive and steady implementation, China should also drive the coordination with global advanced regulatory concept, approaches and standards and facilitate regulatory trust and mutual recognition as well as global integration. It should continuously reinforce and implement the concept of scientific and risk-based regulation and establish a big data-based end to end drug quality monitoring system. It should also advance the establishment of an efficient and streamlined review and approval management process and decision-making pathway, and establish mechanisms including effective communication, immediate claim response, fair dispute resolution, regular comment solicitation, and authoritative efficiency evaluation. To strengthen the regulatory review capabilities, China should build a talent appointment mechanism fit for its innovative and rapid growth, and improve the risk control system for drug approval, to ensure drugs made-in-China are publicly trusted and internationally recognized. Drawing from the global experience in pandemic response, China should build an independent review agency for biological products and promote the R&D of preventative and therapeutic vaccines. It should also continuously promote the development and implementation of Good Review Practice (GRP). Additionally, the post-approval re-evaluation and pharmacovigilance should be strengthened. It is essential to improve the regulatory system, refine the team setting and professional capability building of regulatory teams to ensure smooth communication channels within the industry, and ultimately to increase the participation in the social governance.

Strengthen post-marketing surveillance and research: China should encourage and strengthen post-marketing Phase-IV clinical and real-world data research, and standardize empirical monitoring of clinical use of new drugs, to tighten control over the safety and efficacy of innovative drugs and enhance drug use guidance.

Strengthen intellectual property protection: China should build and improve the legal systems for drug IP protection to ensure new drug patents and experimental data are truly protected across departments and value chains. The definition of new drugs should be clarified to distinguish from generic drugs in clinical trials, market authorization and use conditions.

Holistically improve clinical research capabilities: First of all, the clinical study system in China should be further enhanced, including the network of clinical study institutions and the incentive mechanism for clinical studies. Secondly, it is necessary to ensure close cooperation among all major stakeholders involved in the clinical studies (including research sponsors, research organizations/teams, and regulatory authorities) to improve protocol design quality as well as the safety and efficacy evaluation capabilities, especially for first-in-human experiments. China should also strengthen the end to end process management compliant to GCP to improve the risk management and control capabilities. It should apply emerging technologies to replace traumatic and subjective clinical indicators, and establish an effective ethics collaborative review and central review system. While facilitating the healthy and orderly development of third-party service providers, it should standardize the management of CROs and enhance integrity system to build high-level, internationalized CRO clusters. Lastly, from the perspective of mid to long term system construction, China should continuously promote training of clinical research talents and improve capabilities of supporting functions.

II. Improve the accessibility of innovative drugs with "patient benefits" as the core

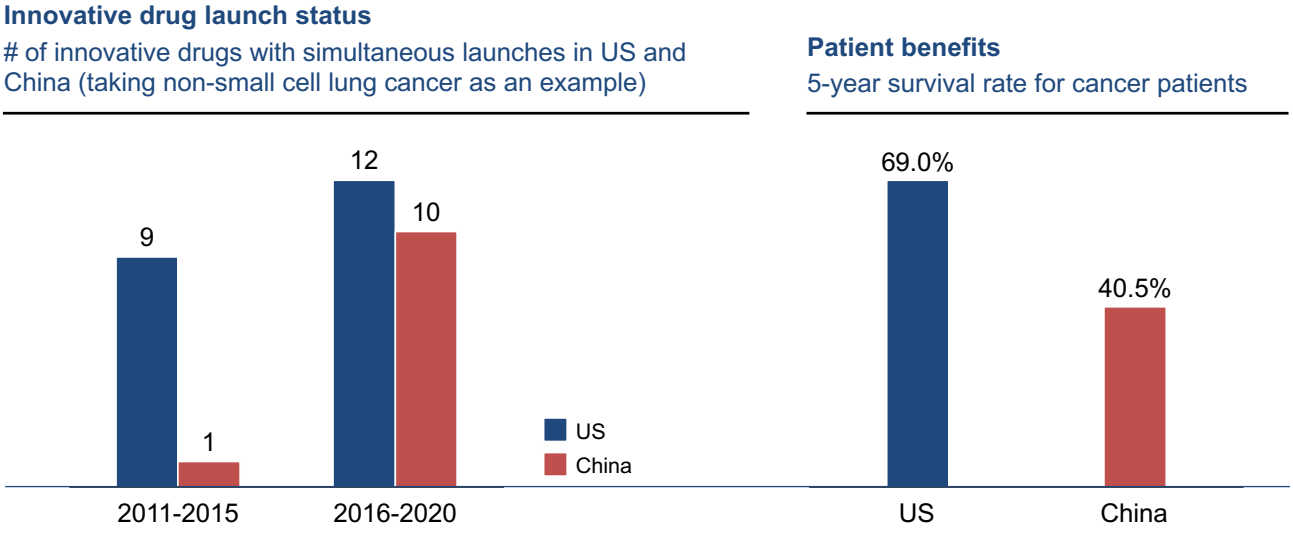
Pharmaceutical innovation is crucial to improving people's life and health. In the next decade, more and more people will be inflicted with chronic diseases such as cancers, cardiovascular and cerebrovascular diseases, diabetes and respiratory diseases; moreover, the outbreak of COVID-19 reminds us again that the threat of infectious diseases will still exist for a long time. Therefore, improving the prevention and treatment of cancers, chronic diseases and infectious diseases will effectively improve the health level of the entire population, and it is also a key lever for the innovative drug industry to help realize goals stated in "Healthy China 2030".

If the new drug launched cannot broadly benefit patients in need, it will not truly reflect the fundamental requirements of "people first and life first". After new drug launch has been significantly accelerated, ensuring that innovative drugs benefit more patients is the top priority of China's pharmaceutical innovation ecosystem. The gap between China and developed countries is constantly narrowing (taking non-small cell lung cancer as an example, most of targeted drugs listed in the United States in recent years have been registered and listed in China), as measured from innovative drugs launched in the market. However, there is still a big gap between China and developed countries including US if measured by patient benefits and treatment outcomes (Fig.7). For example: Although the five-year survival rate of cancers in China has increased from 30.9% to 40.5% in recent decade[14], it is still far behind the level of 66.9% in the United States. This gap is caused by a variety of reasons, such as poor prognosis of major types of high-incidence cancer in China and relatively limited coverage of cancer screening and early diagnosis and treatment in China, leading to a relatively high proportion of patients in the middle and advanced stages. Another key reason for the gap is that although the innovative drugs with better clinical efficacy have been listed in China, they only benefit a part of patients due to constraints on payment, admission to hospital and clinical diagnosis and treatment level, etc. This fact highlights the importance of the linkage among pharmaceutical innovation, payment and reimbursement and clinical use. At present, there are insufficient evidence in China on the impact and contribution of innovative drugs on the health outcomes of the Chinese population (for example, improvement of survival rate, reduction of mortality rate and extended life expectancy for cancers and other serious diseases). In the future, conducting an accurate research evaluation with scientific approaches will add significant values in guiding clinical use of innovative drugs.

[14] Report on Nutrition and Chronic Diseases in China (in 2020)

Figure 7

Global innovative drugs have accelerated launches in China, and the increase in clinical use will help further improve patient benefits



Source: FDA; GBI; 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.

Improve mechanism of National Reimbursement Drug List ("NRDL"): Basic medical insurance has made a lot of achievement in the past 5 years, with some key areas yet to be improved. For example, half of innovative drugs approved between 2016 and 2020 still have not been listed in NRDL. In the future, there are a few key areas for improvement: Firstly, gradually narrow the gap in financing and treatment between workers and residents in different regions by upgrading the overall planning mechanism, establishing a national dispensing fund, steadily improving the financing level of residents' medical insurance and strengthening the outpatient coverage, etc. Secondly, consider raising the cap on annual treatment costs for the NRDL listed drugs; Thirdly, further improve the science-driven and transparency of frameworks and methods for price calculation and medical insurance payment standard formulation, enhancing the weight and status of pharmaceutical innovation in the evaluation; Fourthly, explore innovative payment methods, such as risk sharing, and further improve the price confidentiality of certain negotiated drugs; Fifthly, explore the medication guarantee mechanisms including establishing specific fund, etc. for oncology and rare disease drugs.

Capture full potential of Commercial Health Insurance: As an important part of multi-level medical security system, commercial health insurance is still in the primary stage of development in China. The overall penetration rate of commercial health insurance in the general population is only about 25% ; Structurally, in the RMB 706.6 billion original premium income of health insurance in 2019, only 35% came from reimbursement type of medical insurance. The industry development faces challenges such as insufficient public awareness, serious product homogenization and lacking risk and cost control capabilities. In order to further develop commercial health insurance industry and realize the development goal of up to RMB 2 trillion premium income by 2025 set out by the government, we should consider unifying the standards in the commercial health insurance industry and clarifying the boundary line between basic medical insurance and commercial health

insurance. Efforts should be made to establish data infrastructure, promote legal and compliant use of big health data, and help health insurance companies to improve actuarial and product design innovation capabilities.

Promote clinical use of innovative drugs: Further streamline the intermediate steps from new drug application to clinical use, greatly simplify the hospital listing process of innovative drugs, optimize constraints such as drug proportion and prescription amount limit, and expand DTP pharmacy channel; Improve the diagnostic level, physicians' capabilities and patient compliance to ensure that patients can fully enjoy benefits from medical technology advancement and enhance their sense of gain. The innovative drug industry should continue anchoring on its expertise in disease areas, improving diagnosis and treatment level and practicing the "patient-centric" values to create end-to-end solutions for patients.

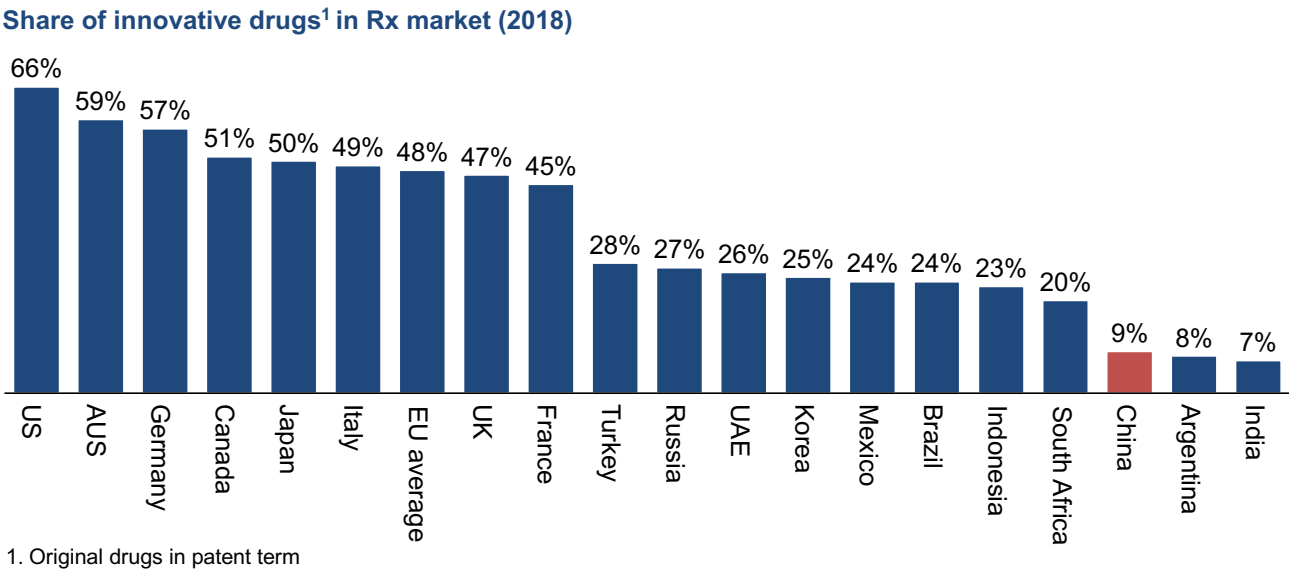
III. Ensure sustainable industry development with "reward for innovation" as the core

In the past five years, a large amount of capital had entered the innovative drug industry, and such investment had promoted the R&D and listing of innovative drugs. As innovative drugs continue to be approved and launched in the market, the importance of reasonable reward for innovation (including pricing and payment reimbursement) is becoming more and more prominent.

At present, China's innovative drug market size is limited. The share of innovative drugs in the overall drug market does not match with the level of economic development and the development goals of innovative drugs. Drug market data of G20 countries in 2018 showed that the share of innovative drugs was 66% in US, 59% in Australia, 57% in Germany, and only 9% in China, ranking the 18th place among 20 countries (Fig. 8).

Figure 8

The share of innovative drugs does not match with the level of China's economic development and the development goals of innovative drugs



1. Original drugs in patent term

Source: IQVIA

Improve payment for innovative drugs and encourage continuous investment in research and development: Drug industry has characteristics of large investments, long cycles and high risks. However, human beings have to conquer diseases via innovation, through ground-breaking prevention, diagnosis and treatments. Therefore, to develop into a highland of global pharmaceutical innovation, China has to offer a reasonable premium for innovative drugs to make a reasonable return, thereby encouraging the innovative industry to continuously investing in drug research and development and ultimately benefiting the people of China and the rest of the world.

In the past five years, China has built a vibrant pharmaceutical innovation industry with advanced concepts in the innovation ecosystem, overarching design vigorously promoted from top to bottom, and highly integrated innovative companies with fair competitions. Looking into the next five years, by strengthening basic research investment and capabilities, and improving translational capabilities, we can release more lasting and breakthrough innovation potential, which can benefit more Chinese patients. By optimizing the policy mechanism of regulatory review and clinical research, the efficiency and quality of R&D and the integration with international standards can be further improved. By strengthening the linkage among pharmaceutical innovation , payment and reimbursement, and clinical use, the people's health and well-being can be truly improved, and meanwhile, the innovative drug industry can obtain reasonable returns for further investment into innovation. A globally competitive pharmaceutical innovation industry will promote the sustainable development of China's economy and help achieve the grand goal of establishing a Human Health Community.