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Research Article
Clinical Development Success Rates for Innovative Drugs in China

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Abstract

Background and Objective: In Mainland China, there exists rapid economic development, a huge demand for medication and remarkable progress in the development of innovative drugs. Thus, it is of great practical significance to evaluate the efficiency of drug innovation in China by measuring clinical development success rates. **Materials and Methods:** This study retrospectively analyzed the status of investigational new drug (IND) submissions for innovative drugs filed in mainland China between January 1, 2003 and May 31, 2019, calculating the phase transition probability and approval probability of 1,076 innovative drugs from 506 applicants. **Results:** This study found the overall approval probability of innovative drugs is 21%. The phase transition probability and approval probability vary by drug class, therapeutic class and applicant type. By drug class, the approval probability of therapeutic biologics (29%) is higher than that of preventive biologics (20%) and chemical drugs (19%). By therapeutic class, the approval probability of gastrointestinal and metabolic drugs (28%) is higher than that of antineoplastic and immunologic agents (26%) and systemic anti-infective (21%). The approval probability of drugs produced by applicants from economically-developed Eastern China (24%) and large-scale enterprises (30%) are leading in the overall industry. **Conclusion:** This study discovered an increasing number of IND submissions and revealed recent innovations concentrated on therapeutic biologics and medications for cancer and immunological disorders. It also suggested that China will play a significant role in future global pharmaceutical innovation with sustained policy optimization and expansion of the domestic pharmaceutical industry.

Key words: Clinical development success rates, innovative drugs, phase transition probability, approval probability, China

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

For the risky, costly, lengthy drug innovation, the clinical development success rate is an important indicator of innovation efficiency. Accurate and timely evaluation of clinical development success rate is of great practical significance for researchers and investors to correctly identify risks and make rational decisions. Traditional countries and regions engaged in drug innovation confer great importance to studying the success rates of new drug development[1-6]. The relevant research outputs have been shown to positively impact the optimization of drug innovation policy. However, in China, where there exists an ageing population with growing demand for drugs, a rapidly developing economy and great progress in innovative drug development, this kind of research is quite scarce.

Over the past two decades, an ecosystem for pharmaceutical innovations in China has been developed considering the factors such as market expansion[7], policy optimization[8], talent accumulation[9] and investment increase[10]. At the government level, with the launch of the National Science and Technology Major Project for New Drug Development in 2008[11], public investment in pharmaceutical innovation has further expanded. In 2015, the government implemented the Drug Review and Approval System Comprehensive Reform[8], which harmonized China's innovative drug registration regulations with international practices through policies including Priority Review and Approval, Pilot Plan on the Marketing Authorization Holder System, Implied Clinical Permission. China also became a member of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) in 2017. In terms of payment, the dynamic adjustment mechanism of the National Reimbursement Drug List has opened a timely passage for coverage of innovative drugs under the national medical insurance system[12]. A considerable number of domestic Chinese companies have increased their investment in drug R&D and recruitment of western-experienced returnees[13]. The Chinese Drug Evaluation Reports released by the center for drug evaluation (CDE) of the National Medical Products Administration (NMPA) showed an increasing number of innovative drugs approved and under development in China. On November 14, 2019, the BTK inhibitor zanubrutinib became the first new chemical entity discovered in China to receive approval by the US Food and Drug Administration (FDA), based primarily on data from a pivotal study conducted in China[14]. This is a promising start for Chinese companies which are actively exploring overseas markets. In summary, China has continued developing more innovative drugs, providing more choices for patients worldwide[15] while meeting domestic clinical needs.

Current studies on the research and development of innovative drugs in China focus on policy adjustment[8,16] and innovation-influencing factors[17]. There are few research studies conducted on the R&D project level. Qi *et al.*[18] analyzed the general landscape of innovative drugs in clinical trials and NDAs/BLAs (New Drug Applications/Biologic License Applications) in China between 2003 and 2010. Li *et al.*[19] systematically reviewed the status of clinical trials for new cancer drugs development in China between 2009 and 2018. However, specific research on the clinical development success rates of the innovative drug in China is still lacking and there is an urgent and unmet need to optimize specific strategies on the efficiency of innovative drug development in China.

In the current study, the clinical development success rates of 1,076 innovative drugs with Investigational New Drug (IND) submissions filed by 506 applicants between January 1, 2003 and May 31, 2019, were analyzed by drug category, therapeutic class and applicants' characteristics. Current research results intend to help policymakers optimize regulatory policies, guide R&D strategies in the industry and strengthen investment valuation and assessment models.

MATERIALS AND METHODS

Study period: China's Provisions on Drug Registration (Interim) came into effect on December 1, 2002, marking the official establishment of the drug registration system in China. Thus, used January 1, 2003, as the starting time point of the study and May 31, 2019, as the ending point of the study.

Inclusion criteria: The China NMPA registers drugs according to their category and degree of innovation. Drugs are classified into chemical drugs, biologics and traditional Chinese medicine (TCM), biologics are further classified into therapeutic biologics and preventive biologics. By innovation, drugs are classified into innovative drugs, modified drugs, generic drugs (biologics including biosimilar products), drugs marketed overseas but not in China and so on, corresponding to registration Class 1-15. The innovative drugs analyzed in this study include chemical drugs in Class 1 (drugs that are not marketed overseas and domestically, which refers to a clinically valuable drug containing a new compound that has a well-established structure and pharmacologically activity) and biologics in Class 1 (biologics that are not marketed overseas and domestically). Innovative traditional Chinese medicines (TCM) were not analyzed in this study.

Table 1: Registration class of innovative drugs in different time periods

Registration category	Time period	Government regulation	Class	Class description	Circumstances
Chemical drugs	01 January, 2003-04 March, 2016	Provisions on drug registration (Interim, 2002) 2007	1.1	Drugs not yet approved or sold in China or other countries	Drug substances and associated drug products prepared by synthesis or semi-synthesis
			1.2	Drugs not yet approved or sold in China or other countries	New effective monomers and associated drug products extracted from natural substances or by fermentation
	04 March, 2016-current	Reform plan for chemical drug registration classification 2016	1	Innovative drugs that have not been marketed in China or oversea	A clinically valuable drug containing a new compound that has a well-established structure and pharmacologically activity
Therapeutic biologics	01 January, 2003-current	Provisions on drug registration (Interim, 2002) 2007	1	Biologics not yet approved or sold in China or other countries	/
Preventive biologics	01 January, 2003-current	Provisions on drug registration (Interim, 2002) 2007	1	Vaccines not yet approved or sold in China or other countries	/

It is noteworthy that the current registration classification of chemical drugs was launched after the Comprehensive Reform of the Drug Review and Approval System in 2015. The current chemical drug in class 1 covers the former chemical drugs in Class 1.1 and 1.2 before the reform, clarified by the Drug Evaluation Report 2016 of CDE (https://www.nmpa.gov.cn/yaopin/ypjgdt/20170317082401656.html.). In detail, the registration classes of innovative drugs included in this study across different periods are shown in Table 1. The registration classification of chemical drugs and biologics of NMPA was concluded and compared in Supplementary 1.

Notably, in China, the innovative drugs were limited to "globally innovative" drugs, so the scope of our research is narrowing compared to new molecular entities (NMEs) used by the US FDA. For example, if an innovative chemical drug was first approved by the FDA or the European Medicines Agency, it would not be recognized as an innovative drug by the NMPA when its approval is later sought in China. It would be reviewed as a chemical drug in Class 3 (generic drugs applied by the domestic applicant, with an innovative drug that has been marketed overseas but not marketed domestically) or in Class 5 (domestic application for an innovative drug that has been marketed overseas).

Data extraction: In this study, information was extracted from 2 official databases of the CDE. From the progress tracking platform for drug registration (http://sq.nmpa.gov.cn/datasearch_nmpa/schedule/search.jsp?tableId=43&tableName=TABLE43&columnName=COLUMN464,COLUMN475&title1), thus, we collected a total of 3,790 IND submissions for innovative drug products updated as of May 31, 2019. As multiple submissions may be filed for different formulations and specifications of the same drug products, we have merged such submissions. After merging, a total of 1,076 unique drug submissions were obtained. We extracted the detailed review information about these innovative drugs, including drug name, applicant, indication, review and approval status, application acceptance time, phase start time, etc. It is common in China for an innovative drug submission to be jointly filed by multiple organizations. These organization types include pharmaceutical companies, research institutes, universities, etc. Whatever organization, listed first in the submission list, was considered as the first applicant. For pharmaceutical company-submitted INDs, if the submission was filed in the name of a subsidiary, branch or holding company, the parent company was defined as the applicant. Thus, a total of 506 applicants were identified.

From another database, the Registration and Information Disclosure Platform for Drug Clinical Studies (http://www.chinadrugtrials.org.cn.), clinical trial information updated as of May 31, 2019, for 1,076 innovative drugs were extracted, including clinical trials' subject enrollment time, phase development progress, etc. The CDE established this online information platform in September, 2013 and any clinical trial approved to be conducted in China must be registered on this platform and relevant information disclosed as per regulatory guidelines. Retrospective registration is required for clinical trials initiated before 2013 that are still in progress and registration for clinical trials initiated after 2013 must be completed within one month of obtaining IND approval.

Finally, we combined information from the 2 databases to determine the latest research progress (phase development or regulatory) of these innovative drugs. When the information on research progress was found clear and specific, the relevant information was directly extracted, when information had not been updated or was missing, logical judgments were made on research progress as per relevant guidelines of trial registration administration. The "latest research progress" of innovative drugs can be categorized in the following stages: IND submission (IND_Sub), IND suspended (IND_Sus), IND approved (IND_App), phase I, phase I suspended (Phase I_Sus), phase II, phase II suspended (Phase II_Sus), phase III, phase III suspended (Phase III_Sus), NDA/BLA submission (NDA/BLA_Sub), NDA/BLA suspended (NDA/BLA_Sus), NDA/BLA approved (NDA/BLA_App). Detailed information about data extraction and logical judgements regarding innovative drugs' "latest research progress" is given in Supplementary 2.

Calculation of clinical development success rates: Based on the "latest research progress" of innovative drugs, the cumulative numbers of innovative drugs were deduced in each research progress phase. Using the clinical development success rate calculation methods reported by DiMasi *et al.*[1] and Hay *et al.*[4], phase transition probabilities and approval probabilities were calculated.

The probability of the innovative drugs whose successful transition from one phase (i) to the next phase (i+1) of development occurred was referred to as the phase transition probability.

$$\text{Calculation: Phase transition probability} = \frac{\text{Cumulative number of innovative drugs that successfully entered phase (i+1)}}{\text{Cumulative number of innovative drugs in-phase (i)- Number of innovative drugs remaining under investigation in-phase (i)}} \times 100\%$$

An innovative drug, from the time of IND submission, to the final approval for sale in the market, the probability is termed approval probability. To calculate the approval probability, we take the product of a drug's phase transition probabilities at each stage of the drug development process, from IND submission to approval in Supplementary 3.

RESULTS

Clinical development success rates: This study conducted a retrospective analysis of IND submissions and NDAs/BLAs in China during the study period. According to Fig. 1a, over 16 years, the number of IND submissions has been generally increased, especially in the past 5 years. Two notable submission peaks can be observed: The first peak was relatively small, occurring in 2003-2004 due to the implementation of the Administrative Provisions on Drug Registration (Interim) in December, 2002. The second peak occurred in 2016-2019 after the Drug Review and Approval System Comprehensive Reform launched in October, 2015. The number of IND submissions was increased to 150 in 2017, with an increase of 56% over 2016 submissions. For the year 2019, only data before May 31 have been included and, despite the slowing increasing rate, the total number is expected to surpass that in 2018. At the same time, the

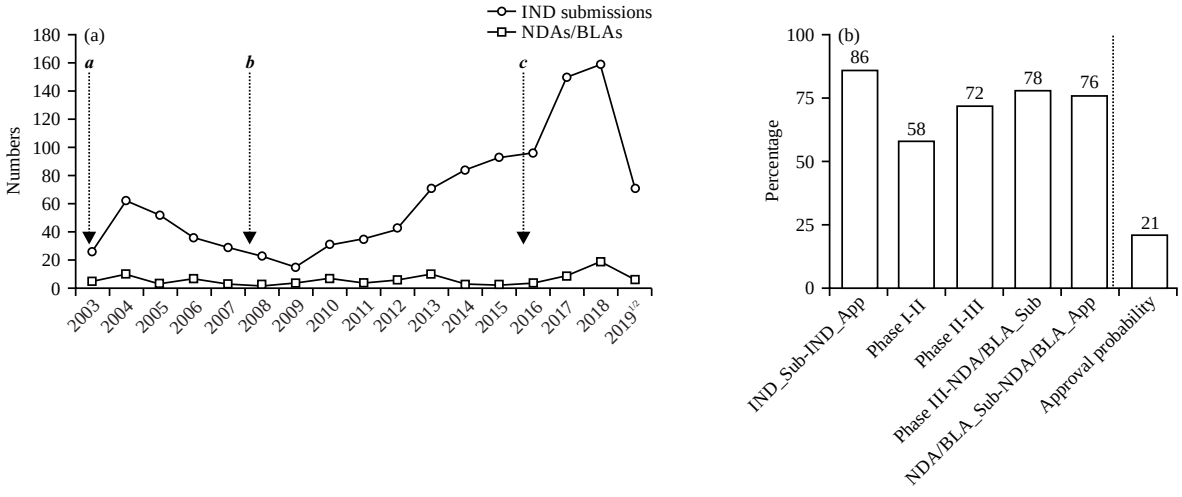

Fig. 1(a-b): Trends in innovative drug submission and clinical development success rate, (a) Number of IND submissions and NDAs/BLAs for innovative drugs and (b) Phase transition probability and approval probability

Submission time refers to the time when the CDE accepted the submission for review, ***a***: Implementation of the administrative provisions on drug registration (Interim) in December, 2002, ***b***: Revision to the administrative provisions drug registration in December, 2007 and ***c***: Drug review and approval system comprehensive reform launched in October, 2015

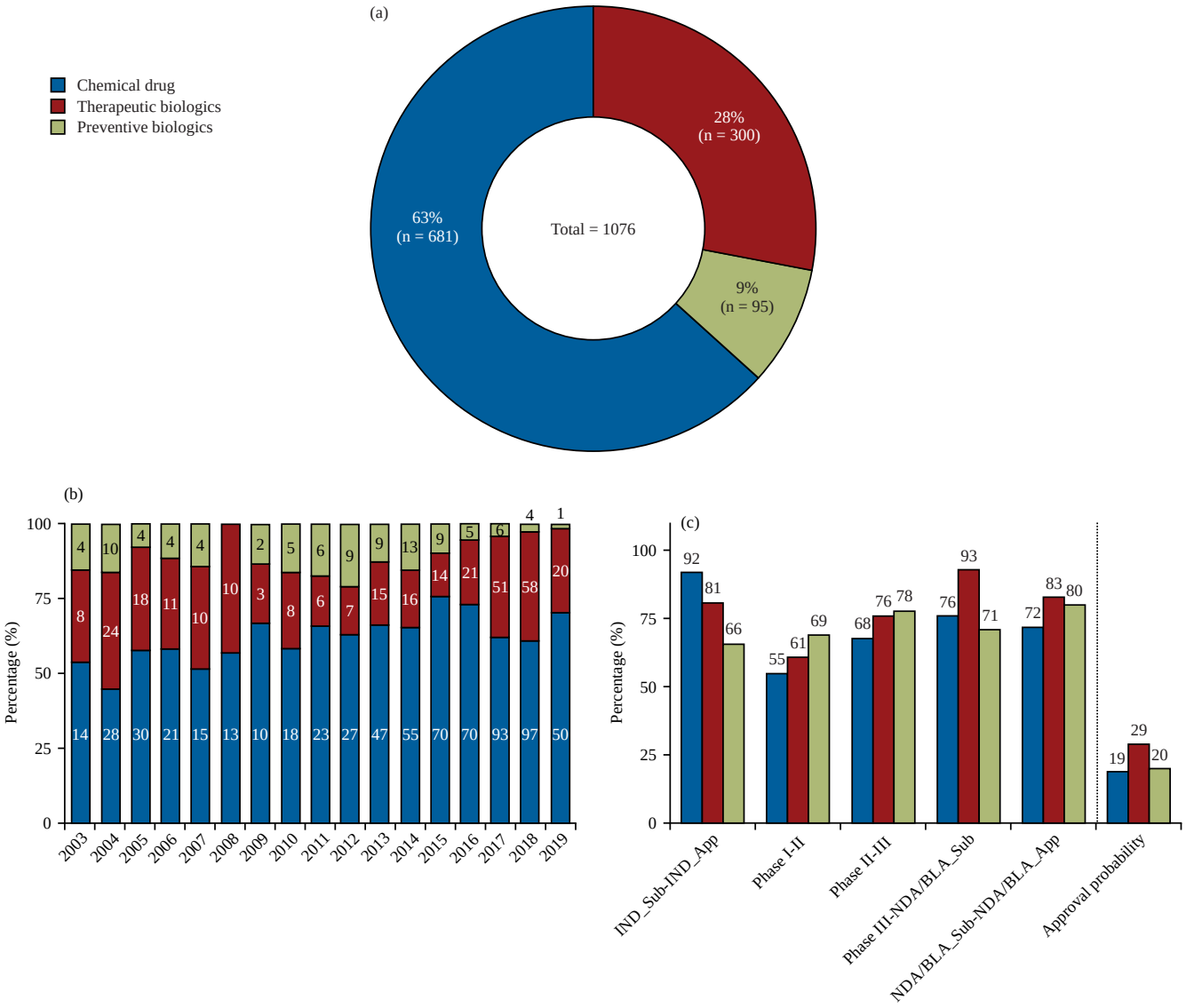

Fig. 2(a-c): IND submissions and clinical development success rates by drug category, (a) Number of IND submissions by drug category, (b) Annual percentage of IND submissions by drug category and (c) Phase transition probabilities and approval probabilities by drug category

Detailed numbers of IND submissions in each year were presented using white numbers in columns

number of NDAs/BLAs reached a record number of 19 in 2018, with a 90% increase over the previous record of 10 in 2017. This study also observed an incline in submissions in 2008-2010, attributed to an NMPA revision to the Administrative Provisions on Drug Registration in December, 2007 that tightened the standards for review and approval.

This study showed that, in China, the approval probability of an innovative drug from IND submission to NMPA approval is 21% (n = 1076). The phase transition probabilities of the 5 stages of drug development assessed in this study are 86% (IND_Sub-IND_App), 58% (Phase I-II), 72% (Phase II-III), 78% (Phase III-NDA/BLA_Sub) and 76% (NDA/BLA_Sub-NDA/BLA_App) in Fig. 1b. The phase transition probability was lowest for Phase I-II (58%). For the 2 stages requiring NMPA review, the NDA/BLA _Sub-NDA/BLA_App approval probability was 76%, 10% lower than the IND_Sub -IND_App approval probability (86%).

Clinical development success rates by drug category: The number of IND submissions of chemical drugs, therapeutic biologics and preventive biologics was analyzed during the study period. As shown in Fig. 2a, Chemical drugs were the

most common, accounting for 63% of the total (n = 681), followed by therapeutic biologics, accounting for 28% (n = 300). Preventive biologics ranked lowest, accounting for 9% (n = 95). Fig. 2b shows the changes in numbers of IND submissions for these three classes of innovative drugs over time. Chemical drugs persistently accounted for most drugs under development, while the number of submissions for preventive biologics considerably declined in the past 5 years. At the same time, the number of submissions for therapeutic biologics increased rapidly, reaching 58 in 2018 and accounting for 36% of the total.

It can be seen from Fig. 2c that the phase transition probabilities and approval probabilities of the three-drug categories varied considerably. The approval probability of chemical drugs, which dominated the number of IND submissions, was the lowest at 19%, close to the approval probability of preventive biologics (20%). In contrast, the approval probability of therapeutic biologics was much higher, reaching 29%.

Clinical development success rates by therapeutic class: According to the anatomical therapeutic chemical (ATC) classification system, analysis by indication showed that the distribution of IND submissions by therapeutic class in China is extremely uneven in Fig. 3a. Applications for antineoplastic/immunologic agents accounted for half of the total (n = 547, 51%), followed by systemic anti-infective (n = 195, 18%), gastrointestinal/metabolism drugs (n = 82, 8%), central nervous system (CNS) drugs (n = 56, 5%), cardiovascular drugs (n = 42, 4%) and drugs for blood and blood forming organs (n = 42, 4%).

A retrospective analysis of IND submissions showed that the unevenness of ATC class is intensifying over time in Fig. 3b. The number of submissions for antineoplastic/immunologic agents raised continuously over time, reaching a peak of 107 and accounting for 67% of total submissions in 2018. The number of submissions for systemic anti-infective has increased and decreased over time, consistently taking second place. However, its proportion has dropped from the highest point of 35% in 2010 to the lowest point of 10% in 2019. Gastrointestinal and metabolism drugs have consistently ranked third and the rankings of CNS, cardiovascular and blood and blood-forming organs drugs interchange year-to-year and the number of submissions is very small (<10).

Phase transition probabilities and approval probabilities also varied by therapeutic class in Fig. 3c. Based on sample size, analyzed the top three classes were separate while the other classes were analyzed together. It was found that, although the number of IND submissions for antineoplastic/immunologic agents was the largest, this group's approval probability was not the highest (26%). However, the phase transition probability for this ATC class in the IND_App and NDA/BLA_App stages were high, reaching 93%. The trend for systemic anti-infectives was the opposite. The phase transition probabilities were high in all clinical stages for this ATC class but low in the two regulatory stages, with a final approval probability of 21%. The approval probability of gastrointestinal/metabolism drugs was the highest (28%) and phase transition probability reached 88% in Phase II-III. The other therapeutic classes had low phase transition probabilities in all stages, resulting in a final approval probability of only 15%.

Clinical development success rates by applicants' characteristics: From the perspective of industry, to present the clinical development success rates of innovative drugs in China the characteristics of all 506 applicants were further analyzed in this study.

Firstly, in applicants' type and size, the 506 applicants were first classified by type into pharmaceutical companies and academic organizations. Pharmaceutical companies were further classified by size into "top companies" and "other companies" based on whether their 2017 sales revenue exceeded 5 billion yuan (about $726 million). Table 2 describes the detailed classification numbers. Found that "top companies" had good performance in both the number of IND submissions and phase transition probability, with the final approval probability reaching 30% in Fig. 4a. The approval probability of smaller "other companies" was 22%. The academic organizations were very low (only 6%).

Secondly, according to the National Bureau of Statistics' criteria for the division of economic regions, this study analyzed applicants' geographic location across China in Fig. 4b. Overall, East China was lead with 864 IND submissions, accounting for 80% of the total. The top six provinces by IND submission were all located in East China. In Jiangsu Province (ranked No.1), there were as many as 236 submissions, exceeding the total number of submissions (n = 212) from 18 provinces and municipalities in Northeast China, West China and Central China. Following Jiangsu by the number of submissions is Shanghai (177), Beijing (126), Guangdong (110), Zhejiang (91) and Shandong (54). The number of submissions recorded among other regions was very small.

Approval probabilities also varied substantially by region and were consistent with the geographic trend in the number of IND submissions. The highest number recorded was in East China, reaching 24%, followed by 19% in Central China and the lowest 8% in Northeast China.

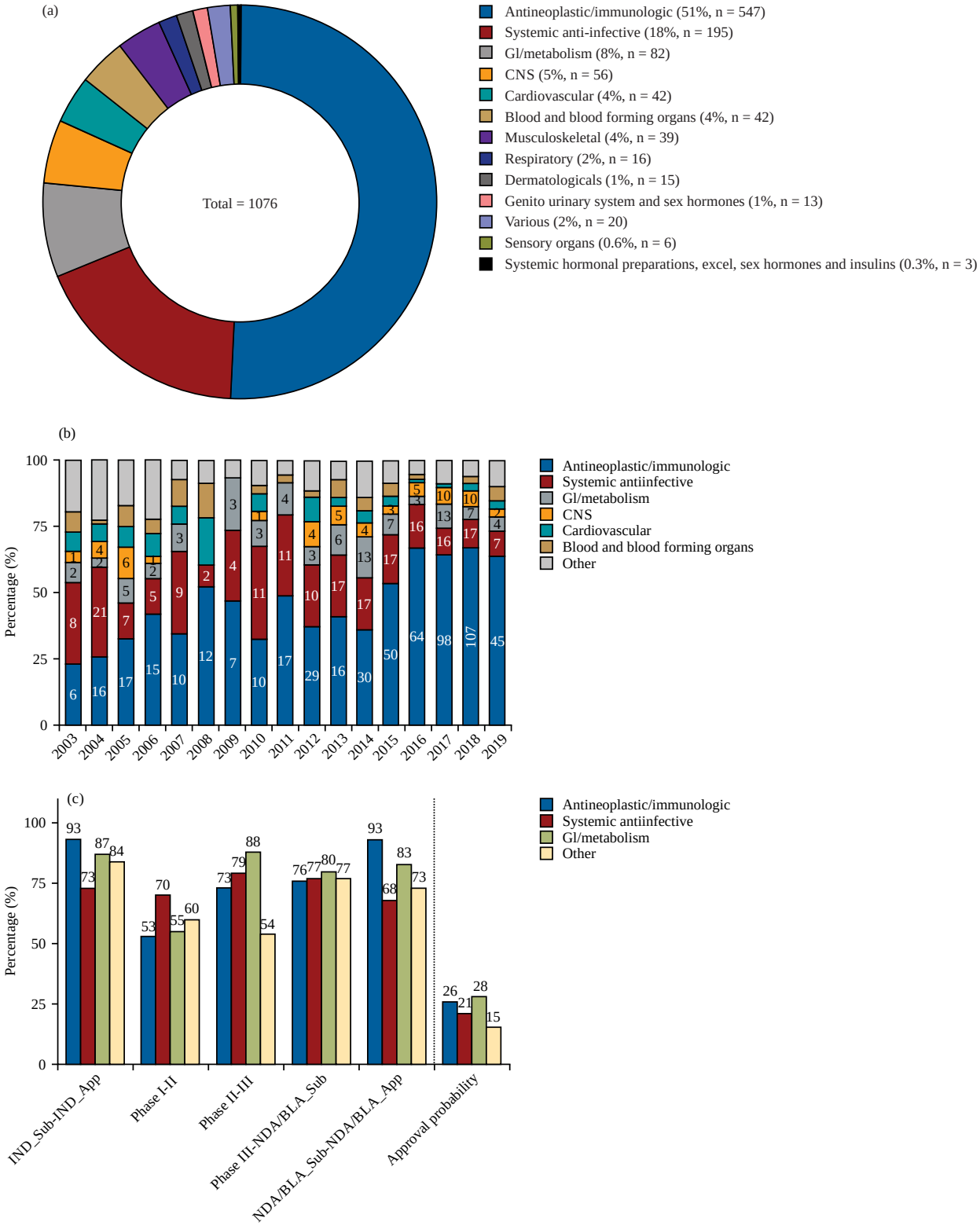

Fig. 3(a-c): IND submissions and clinical development success rates by ATC Class (a) Numbers of IND submissions by ATC Class, (b) Annual percentage of IND submissions by ATC Class and (c) Phase transition probabilities and approval probabilities by ATC Class

Detailed numbers of IND Submissions in each year were presented using white numbers in columns

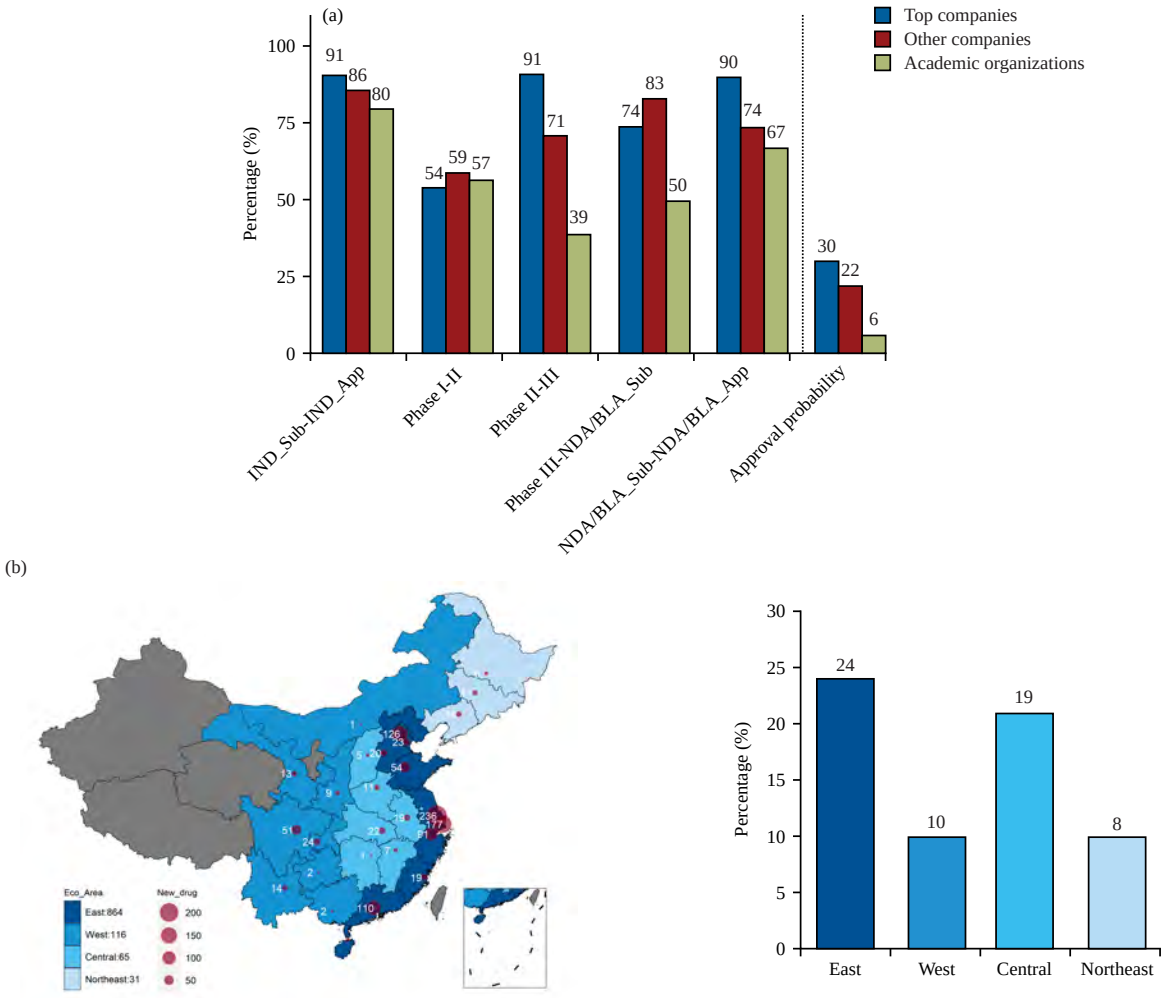

Fig. 4(a-b): IND submissions and clinical development success rates by applicants' characteristics, (a) Phase transition probabilities and approval probabilities by applicants' type and size and (b) Numbers of IND Submissions and Approval Probabilities by Companies' Geographic Location

Table 2: Analysis of applicant's type and size

		Applicants		IND submissions	
Types	Sizes	Numbers	Percentage	Numbers	Percentage
Pharmaceutical company	Top	24	5	182	17
	Others	458	90	807	75
Academic organization		24	5	87	8
Total		506		1076	

DISCUSSION

This study analyzed the number of IND submissions and NDAs/BLAs as well as clinical development success rate by drug category, therapeutic class and applicant since the establishment of the drug registration system in China. It reveals that considerable progress has been made in China's innovative drug development, but many challenges remain.

It is found that innovative drug development activity in China is highly sensitive to adjustment of registration policies (Fig. 1). In light of the high risks, huge time consumption and great investment in innovative drug development, it is extremely important to establish a stable innovative drug registration system in line with international standards. The NMPA-led drug review and approval system reform, initiated in 2015, has boosted domestic drug innovation, winning

commendations from industry and the international community. In the long run, sustained innovation depends on the constant evolution of the drug innovation ecosystem. An important policy challenge soon will be how the NMPA, National Department for Medical Insurance, National Health Commission, Ministry of Industry and Information Technology and other government agencies cooperate and seamlessly integrate regulations related to the access, pricing, payment, usage and public investment in innovative drugs, building a stable drug development environment.

It is also found that, in China, the approval probability of an innovative drug from IND submission to NMPA approval (21%) is very close to the study results of DiMasi *et al.*[1] (19.0%) and Wong *et al.*[6] (22%). Currently, innovative drug development in China remains in the stage of gradual transition from fast-follow projects to first-in-class projects. However China's innovative drug clinical development success rate has not significantly surpassed global levels, suggesting that there remains much room for improvement in the country's innovative drug development capability. For phase transition probabilities, the situation in China is quite different from other international studies. The lowest in Phase I-II (58%) and the NDAs/BLAs approval probability was only 76%. Internationally, the lowest phase transition probability occurs in Phase II-III (30-40%) and NDAs/BLAs approval probability reaches as high as 80-90%[1,4,5]. This correlates with drug developers' distribution of costs throughout the entire drug development timeline. In 2016, DiMasi *et al.*[20] found that the cost of innovative drug development was mainly concentrated in the later clinical phases, the mean out-of-pocket cost of phase III was USD 250 M, accounting for 75% of the total clinical out-of-pocket cost. Thus, drug developers will conduct a rigorous analysis of success in the early phases of development and carefully carry out later research to ensure success rates in phase III and NDA/BLA_App remain relatively high[5,21]. According to available data, this trend is not obvious in China, suggesting that the drug developers in China are not yet sufficiently grown in their management of pipeline products. This is possibly due to inadequate experience in clinical trial design or limited pipeline product options.

Analysis by therapeutic class indicates a noticeable uneven in the development of innovative drugs in China. There is an excessive focus on anticancer drugs, over the past 4 years, IND submissions for antineoplastic/immunologic agents accounted for more than 60% of the total. China's growing ageing population presents a huge market for oncology drugs, thus attracting many applicants and investors. According to the current study (Fig. 3c), the high success rate of this therapeutic class (26%) has also highly contributed to this field. Over-concentration of submissions in one therapeutic class will inevitably reduce the post-approval pay-back of innovative drugs. Drug developers' failure to adjust development strategies in a timely, responsive manner will result in inadequate motivation for sustained innovation.

This study also indicated that the innovative drug R&D industry in China is not very concentrated. A study conducted by Hay *et al.*[4] in 2014 showed that between January 1, 2003 and December 31, 2011, a small number (33) of large pharmaceutical companies (4% of total) with sales revenue exceeding USD 5 billion were responsible for 47% (2,075) of the total number of drugs are under development worldwide. In China, only 17% (182) of all innovative drugs are being developed by "top companies (2017 sales revenue >$726 M)", accounting for 5% (24) of all pharmaceutical companies (Table 2). This study also showed a markedly uneven geographical distribution of applicants across China. The majority of applicants engaged in pharmaceutical innovation in the developed regions of East China and the clinical success rate is also higher. Overall, these results are consistent with the clinical trial activity of new cancer drugs in China, as analyzed by Li *et al.*[19]. Instead of uneven population or patient distribution, this geographical disparity is the direct manifestation of the uneven distribution of high-quality medical resources used for clinical research, such as talent, funding and technical resources. This poses a challenge to the Chinese government's policy for coordinating development across the country. Narrowing the innovation gap between Central, West and East China is an important topic worthy of exploration by policymakers.

CONCLUSION

This study conducted the first retrospective analysis to investigate innovative drugs' clinical development submissions and success rates in China from 2003-2019. It discovered an increasing number of INDs submissions and revealed recent innovations concentrated on therapeutic biologics and medications for cancer and immunological disorders. It also suggested that China will play a significant role in future global pharmaceutical innovation with sustained policy optimization and expansion of the domestic pharmaceutical industry.

SIGNIFICANCE STATEMENT

This study discovered the phase transition probability and approval probability of 1,076 innovative drug development from 506 applicants in China from 2003-2019, which can beneficial for readers to learn more about the efficiency and

characteristics of current innovation drug development in China. In recent decades, advanced technology, improved legislation and higher investment have fueled the acceleration of China-based pharmaceutical innovation. This research is the first to analyze whole-industry clinical development success rates since establishing the drug registration system in mainland China. It also suggested that the sustained policy optimization and expansion of the domestic pharmaceutical industry will promote China to play a more significant role in future global pharmaceutical innovation. Thus, a new first-hand valuable reference for researchers, clinicians, enterprises and policymakers worldwide who are interested in innovative drug clinical development in China may be arrived at.

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SUPPLEMENTARY

Supplementary 1: Registration classification of chemical drugs and biologics of NMPA

Registration classification of chemical drugs

04 March, 2016-current: The registration classification of chemical drugs includes innovative drugs, modified new drugs, generic drugs and chemical drugs overseas marketed but not domestically marketed, please refer to the following 5 classifications:

- **Class 1:** Innovative drugs that are not marketed overseas and domestically. It refers to a clinically valuable drug containing a new compound which has a well-established structure and pharmacologically activity
- **Class 2:** Modified new drugs that are not marketed overseas or domestically. It refers to a drug that has obvious clinical advantages by optimizing its structure, dosage form, formulation and manufacture process, route of administration, indication(s), etc., on the basis of known active ingredient(s)
    - A new drug that contains an optical isomer of a known active ingredient by resolution or synthesis or etc., an ester or a salt (including a salt containing a hydrogen bond or coordination bond) of a known active ingredient, an alternative salt with change of acid radical/base/metal element to a known active ingredient, or other non-covalently bonded derivatives (e.g., complexes, chelates, or clathrates) of a known active ingredient, which has obvious clinical advantages
    - A new drug with new dosage form (including new drug delivery systems), new formulation and manufacture process, new route of administration, which contains a known active ingredient and has obvious clinical advantages
    - A new combination drug containing a known active ingredient, which has obvious clinical advantages
    - A drug for new indications, which contains a known active ingredient
- **Class 3:** Generic drugs applied by domestic applicant, with an innovative drug that has been marketed overseas but not marketed domestically. Such drugs should be consistent with the quality and efficacy of the reference listed drug (RLD)
- **Class 4:** Generic drugs applied by domestic applicant, with an innovative drug that has been marketed domestically. Such drugs should be consistent with the quality and efficacy of the RLD
- **Class 5:** Domestic applications for drugs overseas marketed
    - Domestic application for an innovative drug or a modified drug that has been marketed overseas. The modified drug should have obvious clinical advantages
    - Domestic application for a generic drug that has been marketed overseas

The innovative drug refers to the first drug approved for marketing domestically and overseas, which has complete and sufficient safety and efficacy data as the basis for marketing. A RLD refers to a reference drug used in the development of a generic drug that has been evaluated and confirmed by the national drug regulatory authorities. The selection and publication of the RLD are in accordance with the relevant provisions of the national drug regulatory authorities

January, 2003-04 March, 2016:

- **Class 1:** New chemical entity never marketed in any country
    - Drug substance and its preparations made by synthesis or semi-synthesis
    - Chemical monomer (including drug substance and preparation) extracted from natural sources or by fermentation
    - Optical isomer (including drug substance and preparation) obtained by chiral separation or synthesis
    - Drug with fewer components derived from marketed multi-component drug
    - New combination products
    - A preparation already marketed in China but with a newly added indication not yet approved in any country
- **Class 2:** Drug preparation with changed administration route and not marketed in any country
- **Class 3:** Drug marketed ex-China, including:
    - Drug substance and its preparations and/or with changed dose form, but no change of administration route
    - Combination preparations and/or with changed dose form, but no change of administration route

- Preparations with changed administration route and marketed ex-China
- A preparation already marketed in China but with a newly added indication approved ex-China

- **Class 4:** Drug substance and its preparation with changed acid or alkaline radicals (or metallic elements), but without any pharmacological change and the original drug entity already approved in China
- **Class 5:** Drug preparation with changed dose form, but no change of administration route and the original preparation already approved in China
- **Class 6:** Drug substance or preparation following national standard

Registration classification of biological products for therapeutic
January, 2003-January, 2020:

- **Class 1:** Biological products not yet marketed at domestic or overseas
- **Class 2:** Mono-clonal antibody
- **Class 3:** Gene therapy, somatic cell therapy as well as the preparations
- **Class 4:** Allergen products
- **Class 5:** Multi component products with bioactivity extracted from or by fermentation from human and/or animal tissues and/or body fluid
- **Class 6:** New combination product made from the already marketed biological products
- **Class 7:** A product that is marketed already overseas but not yet marketed domestic
- **Class 8:** Some of the strains used for preparing of micro-ecological products not yet approved
- **Class 9:** Products with not completely same structure with the already marketed products and not yet marketed at domestic or overseas (including amino acid locus mutation/absence, modification caused by a different expression system, deletion, changed interpretation, as well as chemical modifications of the product)
- **Class 10:** Products with a method of preparation different with the already marketed one, (such as use of different expression system, host cells)
- **Class 11:** Products first time made with DNA recombination technology (such as use of recombination technology to replace the synthesis technology, tissue extraction or fermentation technology)
- **Class 12:** Products transformed from non-injection into injection or topical use into systemic use and not yet marketed at domestic or overseas
- **Class 13:** The marketed products with a change in dosage form but no change in route of administration
- **Class 14:** Products with a change in route of administration (excluding the above Category 12)
- **Class 15:** Biological products admitted with National Standards

Registration classification of biological products for preventive
January, 2003-January, 2020:

- **Class 1:** Vaccine not yet marketed at domestic or overseas
- **Class 2:** DNA vaccine
- **Class 3:** A already marketed vaccine with new adjuvant change of carrier of combined vaccine
- **Class 4:** Non-purified vaccine or full cell vaccine (bacteria, virus) changed into purified vaccine or combined vaccine
- **Class 5:** Vaccine with strains not yet approved in China (except for vaccine for influenza, vaccine for leplospirosis and others)
- **Class 6:** Vaccine already marketed overseas but not yet marketed domestic
- **Class 7:** Combined vaccine prepared with vaccine already marketed domestic
- **Class 8:** Re-combination vaccine with protective antigen spectrum different with the marketed one
- **Class 9:** Vaccine manufactured with the change of the other approved expression or the other approved cellular stroma. Vaccine using new process, which is proved to improve the safety and effectiveness of the vaccine based on the data of laboratory
- **Class 10:** Vaccine with change of de-activator (method of deactivation) or de-toxicitor (method of de-toxicity)
- **Class 11:** Vaccine with change in the route of administration
- **Class 12:** A domestic marketed vaccine with change in dosage form but no change in route of administration
- **Class 13:** Vaccine with dosage of immunity or immunity procedure
- **Class 14:** Vaccine with an enlarged group of people (enlarged age range)
- **Class 15:** Vaccine admitted with National Standards

Supplementary 2: A detailed description of data extraction and logical judgment

Latest research progress	Data source	State description	Corresponding time	Judgment method
IND_Sub	CDE registration review and approval information	The applicant has filed the initial IND application to CDE and the handling state published by CDE is "for evaluation", "under evaluation", "under evaluation, review and approval", "for review and approval", "under review and approval", "review and approval completed-certificate to be made" or "certificate making completed-approved to be issued"	Undertaking time	Directly extract data
IND_Sus	CDE registration review and approval information	The handling state published by CDE is "for evaluation", "under evaluation" "under evaluation, review and approval"	State start time	No subsequent state update information is available and the period between "corresponding time" and 31 May, 2019 is longer than the average review and approval duration[a]
	CDE registration review and approval information	The state published by CDE is "approval issued"	State start time	No subsequent state update information is available and the period between "corresponding time" and 31 May, 2019 is longer than 3 years[b]
IND-App	CDE registration review and approval information	The state published by CDE is"approval issued"	State start time	No subsequent state update information is available and the period between "corresponding time" and 31 May, 2019 is not longer than 3 years[b]
Phase I	Registration and information disclosure platform for drug clinical studies	The state published on the platform is Phase I	Date of enrollment of the first subject [c]	Directly extract data
Phase I_Sus	Registration and information disclosure platform for drug clinical studies	The state published on the platform is Phase I	Date of enrollment of the first subject	The duration between "corresponding time" and 31 May, 2019 is not longer than 19 months[d]
Phase II	Registration and information disclosure platform for drug clinical studies	The state published on the platform is Phase II, Phase I/II, Phase IIb	Date of enrollment of the first subject	Directly extract data
Phase II_Sus	Registration and information disclosure platform for drug clinical studies	The state published on the platform is Phase II, Phase I/II, Phase IIb	Date of enrollment of the first subject	The duration between "corresponding time" and 31 May, 2019 is not longer than 25 months[d]
Phase III	Registration and information disclosure platform for drug clinical studies	The state published on the platform is Phase II/III, Phase III	Date of enrollment of the first subject	Directly extract data
Phase III_Sus	Registration and information disclosure platform for drug clinical studies	The state published on the platform is Phase II/III, Phase III	Date of enrollment of the first subject	The duration between "corresponding time" and 31 May, 2019 is not longer than 30 months[d]
NDA/BLA_Sub	CDE registration review and approval information	The handling state published by CDE is "for evaluation", "under evaluation", "under evaluation, review and approval", "for review and approval", "under review and approval", "review and approval completed-certificate to be made" or "certificate making completed-approved to be issued"	State start time	Directly extract data
NDA/BLA_Sus	CDE Registration Review and Approval Information	The state published by CDE is "approval issued"	State start time	No drug approval number has been granted
NDA/BLA_App	CDE Registration Review and Approval Information	The state published by CDE is "approval issued"	State start time	A drug approval number has been granted

[a]The average duration between IND_Sub and CDE completion of IND review and approval is calculated based on available data. The IND submission is defined as suspended if the average duration for review and approval is surpassed. The average duration for IND review and approval is 316 days for innovative chemical drugs and 506 days for innovative biologics. [b]On 06 September, 2013, the NMPA issued an Announcement on the Registration and Information Disclosure Platform for Drug Clinical Studies (No. 28), requiring that if valid drug clinical trial approval was obtained before this date, the applicant shall complete information registration within 3 months of announcement issuance, for a clinical trial that was newly granted approval, the applicant shall complete pre-registration within 1 month after obtaining approval. If this information disclosure is not completed within 3 years, the approval shall be automatically cancelled. [c]Priority order of time extraction: first extract "date of enrollment of the first subject"; if missing, extract "date of initial EC review"; if still missing, extract "date of initial information disclosure". [d]Average durations of clinical trial phases of innovative drugs based on literature review[1]: Phase I, 19 months, Phase II, 25 months, Phase III, 30 months

Supplementary 3: Calculation of clinical development success rates.

Using the clinical development success rates calculation methods reported by DiMasi *et al.*[1] and Pammolli *et al.*[2], phase transition probabilities and approval probabilities were calculated.

Definition and calculation of phase transition probability: The phase transition probability refers to the probability that innovative drugs successfully transition from one phase (i) to the next phase (i+1) during development.

$$\text{Calculation: Phase transition probability} = \frac{\text{Cumulative number of innovative drugs that successfully entered phase (i+1)}}{\text{Cumulative number of innovative drugs in phase (i)-number of innovative drugs remaining under investigation in phase (i)}} \times 100\%$$

For example: Among there are 100 innovative drugs in phase I development. 70 go on to enter phase II, 10 studies are suspended and 20 remained under investigation in phase I studies. Thus, the phase transition probability from phase I to phase II would be 88% (70/(100-20)=88%).

Definition and calculation of approval probability: Approval probability refers to the probability that an innovative drug, from the time of IND submission, is finally approved for sale on the market. To calculate the approval probability, we take the product of a drug's phase transition probabilities at each stage of the drug development process, from IND submission to approval.

For example: If the phase transition probability of an innovative drug is 85% from IND_Sub to IND_App, 75% from IND_App to Phase I, 70% from Phase I to Phase II, 60% from Phase II to Phase III, 80% from Phase III to NDA/BLA _Sub and 90% from NDA/BLA _Sub to NDA/BLA_App, the approval probability of this innovative drug is 19% (85%×75%×70%×60%×80%×90% = 19%).

Latest research progress	Current numbers	Number IND_App but logically determined to be in a suspended state*	Cumulative Numbers	Phase transition probability/approval probability
IND_Sub	85		1076	86%
IND_Sus	134			
IND_App	258 (154+104)	154	857	
Phase I	248		703	58%
Phase I_Sus	117	75		
Phase II	73		263	72%
Phase II_Sus	33	21		
Phase III	46		136	78%
Phase III_Sus	12	8		
NDA/BLA_Sub	19		70	76%
NDA/BLA_Sus	12			
NDA/BLA_App	39		39	
Total	1076			21%

0.86 x 0.58 x 0.72 x 0.78 x 0.76 = 0.21

39/(70-19) = 0.76

*We observed 258 drugs in the IND_App stage but with no relevant information retrieved for any subsequent development or regulatory stage. Based on the timing of clinical approval, 154 of them are in preparation for clinical trials and 104 are in suspension. We allocated the 104 drugs to each phase of clinical suspension in proportion to the existing data