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REVIEW

Changes in clinical trials of endocrine disorder and metabolism and nutrition disorder drugs in mainland China over 2010–2019

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Abstract

With the improvements in relevant policies, laws, and regulations regarding drug clinical trials in China, the quantity and quality of drug clinical trials have gradually improved, and the development prospects of drug clinical trials for endocrine disorders and metabolism and nutrition disorders are promising. Based on information from the clinical trials from the online drug clinical trial registration platform of the National Medical Products Administration, we aimed to review and evaluate the development of clinical trials of drugs for endocrine disorders and metabolism and nutrition disorders in mainland China from 2010 to 2019, as well as the trends over time. A total of 861 trials were carried out on 254 types of drugs for endocrine disorders and metabolism and nutrition disorders, among which 531 (61.67%) involved endocrine disorders, and 330 (38.33%) addressed metabolism and nutrition disorders. The annual number of clinical trials has been increasing gradually, with a significant increase in 2017. Among them, the proportion of clinical trials with Chinese epidemiological

Abbreviations: NMPA, National Medical Products Administration.

characteristics was relatively large (Wu, Annual Report on Development Health Management and Health Industry in China, 2018). The largest number of trials were for diabetes drugs (55.63%), followed by trials of drugs for hyperlipidemia (19.4%) and those for hyperuricemia (7.9%). It was found that the geographical area of the leading units also showed obvious unevenness according to the analysis of the test unit data. Based on the statistics and evaluation of the data, comprehensive information is provided to support the cooperation of global pharmaceutical R&D companies and research units in China and the development of international multicenter clinical trials in China. This work additionally provides clinical trial units with a self-evaluation of scientific research competitiveness and hospital development strategies. At the same time, it provides a reference with basic data for sponsors and stakeholders in these trials to determine their development strategy goals.

KEYWORDS
China, clinical trial, endocrine disorder, metabolism and nutrition disorder

1 | INTRODUCTION

According to the "China Health Management and Health Industry Development Report (2018)," the prevalence of major chronic diseases in the medically examined population in China was analyzed and the results showed the prevalence rates of dyslipidemia (38.64‰) and diabetes (34.02‰) in the medically examined population nationwide.[1] From 1990 to 2016, the prevalence of diabetes in all age groups ranged from 3.7% to 6.6%.[2] The increased incidence of endocrine disorders and metabolism and nutrition disorders has also led to the development of drugs to improve the prognosis and progression of patients. The provision of effective, safe, and economical medicines has become a priority for the Chinese government and related pharmaceutical enterprises.

Before 2013, China's innovative drugs were affected by the so-called "drug lag," including long review times, strict applications or delays in approval, which hindered pharmaceutical innovation.[3] According to the data, the average waiting time for clinical trial registration of innovative drugs was 15 months in 2013, compared with 14 months in 2014.[4] Over the past decade, a series of measures have been undertaken to encourage the development of innovative drugs.[5] At the same time, the National Medical Products Administration (NMPA) has strictly checked and supervised the quality of clinical trial data. China's clinical trial standards have come close to international standards, greatly improving China's clinical trial and new drug research and development capabilities. Good clinical trials should rely on the drug clinical trial institution of the clinical trial unit in China. China's drug clinical trial institutions should continue to strengthen the construction of management and quality systems to make greater contributions to China's drug clinical trials.[6]

The statistics of each data point should rely on the data platform. In 2013, the National Medical Products Administration (NMPA, formerly China Food and Drug Administration) established the "Registration and Information Disclosure Platform for Drug Clinical Trials" and implemented the registration and information publicity for drug clinical trials.[7] On July 22, 2015, NMPA issued an announcement on the self-inspection and verification of drug clinical trial data,[8] which became a milestone event for China in standardizing the quality of clinical trials and accelerating the review and approval process of clinical trials. In 2016, NMPA enacted the "Technical Guidelines for Clinical Trial Data Management" and "Guidelines for the Planning and Reporting of Drug Clinical Trial Data Management and Statistical Analysis" to render the management of clinical trial data in China more authentic, standardized, and complete.[9,10]

We examined the development trend of clinical trials of endocrine disorders and metabolism and nutrition disorder drugs in China from 2010 to 2019 based on the registration and information disclosure platform for drug clinical trials established in 2013. We explored all of the information on the clinical trials of endocrine disorders and metabolism and nutrition disorder drugs in China over the past 10 years. This systematic evaluation reveals prospects for clinical trials for drug development at home and abroad and provides basic data for sponsors and stakeholders to determine development strategy goals.

2 | DATA COLLECTION

2.1 | Data acquisition and evaluation

All the data were collected systematically from the National Registration and Information Disclosure Platform for Drug Clinical Studies registered from January 1, 2010, to December 31, 2019. NMPA established the "Registration and Information Disclosure Platform for Drug Clinical Trials" (www.chinadrugtrials.org.cn) in

2013. All drug clinical trials must be registered on this platform, including phase I–IV trials, bioequivalence studies and pharmacokinetic research, and registration of clinical trials before 2013 was required for supplemental registration. The earliest supplementary registration of clinical trials began on February 16, 2002. We collected all public information on the NMPA website, including registration number, trial name, indication, drug name, drug type, trial classification, trial stage, design type, randomization, blinding, trial scope, first public information date, date of the first enrollment, leading unit, participating unit, sponsor, funding source for the pilot project, etc. We only included clinical trials that were already registered because some clinical trials had already been registered online but had not actually been performed. We screened all clinical trials from 2010 to 2019 based on the "first subject enrollment date" in the database. We classified them according to the standard of MedDRA (MedDRA was developed by the International Technical Coordination Committee for Drug Registration. MedDRA is a rich and detailed medical standard terminology set) and extracted the clinical trial data on endocrine disorder and metabolism and nutrition disorder. All the data were obtained from the public website of the NMPA. Our evaluation was based only on clinical trial data from mainland China, excluding Hong Kong, Macao, and Taiwan.

2.2 | Statistical analysis

All the data analyses were performed using SAS software, version 9.4 (SAS). Frequencies and percentages were used to describe categorical variables. We analyzed the 10-year trends in our selected indicators, including the number of initiated trials, bioequivalence trials, trial stages, trial drugs, trial units, sponsors, and other relevant indicators. The annual rate of change was calculated for each indicator. The starting year of a trial was defined by the date of the first enrollment.

3 | RESULTS

3.1 | The number and types of drug clinical trials

A total of 861 endocrine disorder and metabolism and nutrition disorder drug trials were initiated from 2010 to 2019 in mainland China. Among them, there were 531 endocrine disorders and 330 metabolism and nutrition disorder trials. 13 in 2010, 21 in 2011, 50 in 2012, 54 in 2013, 57 in 2014, 62 in 2015, 63 in 2016, 130 in 2017, 201 in 2018, and 210 in 2019 (Figure 1). The annual number of clinical trials increased over time, with an average annual growth rate of 43.22%. The greatest increase was seen in 2017, with an increase of 106.3% compared to 2016.

Bioequivalence studies accounted for the largest proportion (416 [48.32%]), followed in order by phase I trials (205 [23.81%]), phase III trials (150 [17.42%]), phase II clinical trials (50 [5.81%]), and phase IV trials (10 [1.16%]), with the phase for the remaining 3.48% trials unknown. The numbers of phase I and bioequivalence studies increased year by year. The number of bioequivalence studies reached 151 in 2018, accounting for 36.3% of the total number of BE (bioequivalence) studies (Figure 2).

A total of 254 drugs for endocrine disorder and metabolism and nutrition disorder were in clinical trials during the decade, and 181 types kinds of chemical drugs, 66 types of biological products, and seven types of drugs were uncategorized (Figure S1). A total of 683 (79.33%) clinical trials were of chemical drugs, 141 (16.38%) of biological products and 37 (4.3%) were uncategorized. The number of clinical trials of chemical drugs and biological products showed an upward trend overall, and the growth rate of chemical drugs was faster than that of biological products (Figure S2).

The number of domestic multicenter trials increased gradually over the decade, whereas the number of international multicenter trials only increased in 2019 (Figure S3). Overall, the proportion of international multicenter trials decreased over time.

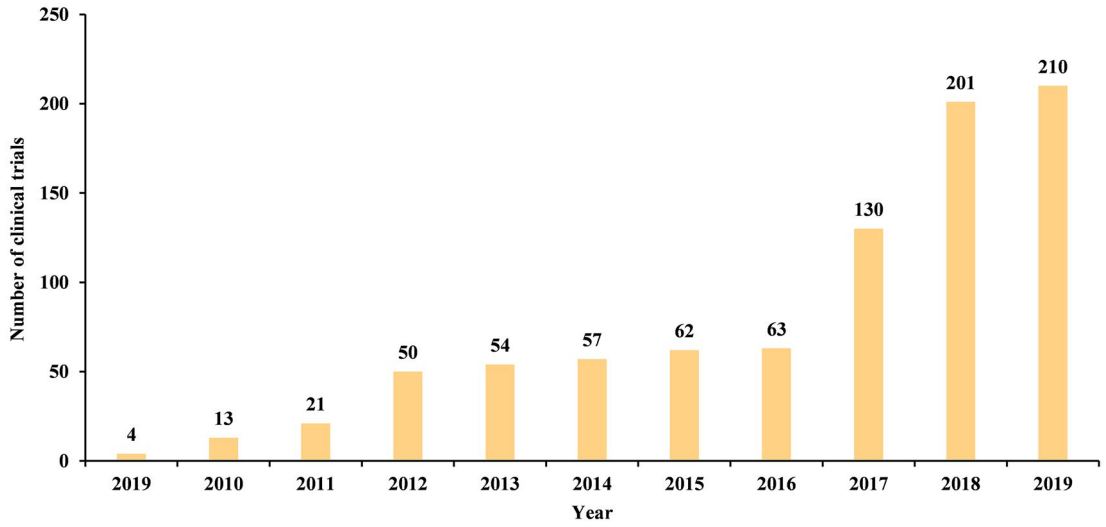

FIGURE 1 Number of endocrine disorder and metabolism and nutrition disorder drug trials from 2010 to 2019 in China

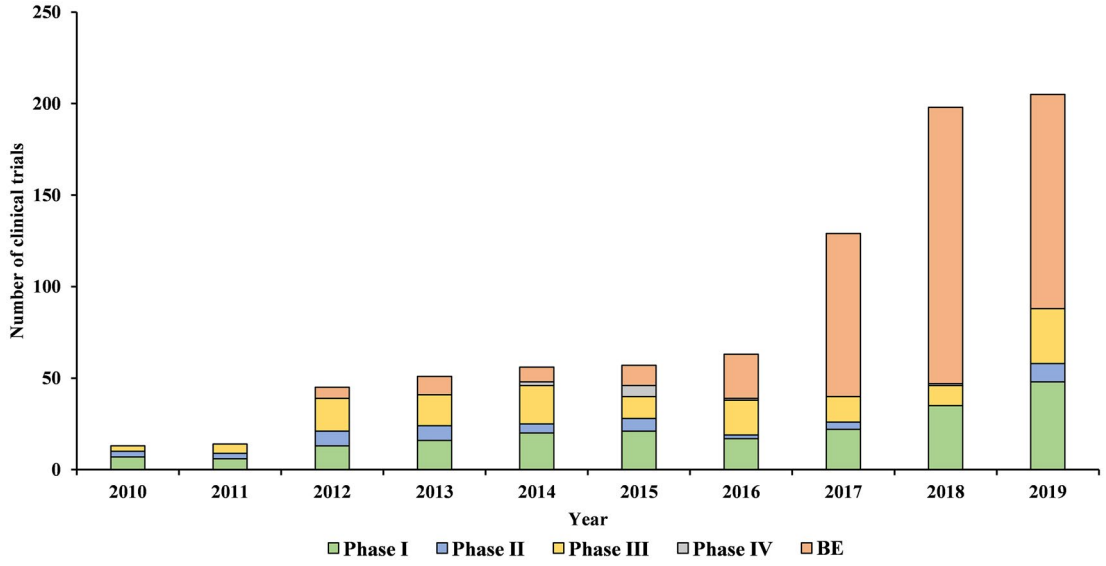

FIGURE 2 Number of endocrine disorder and metabolism and nutrition disorder drug trials in different phases from 2010 to 2019 in China

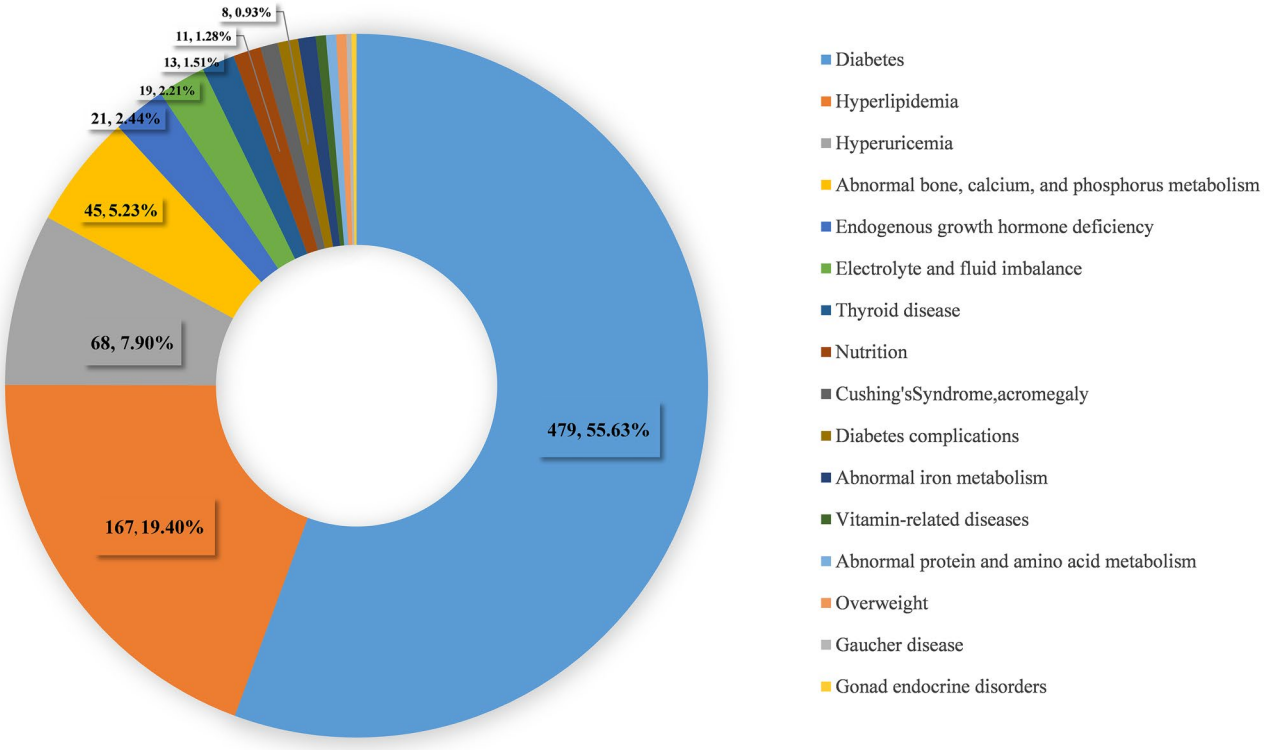

FIGURE 3 Number of trials classified by indication from 2010 to 2019 in China

We have classified the indications in detail according to MedDRA. From 2010 to 2019, we found that the largest number of clinical trials of diabetes drugs was 479 (55.63%), followed by 167 (19.4%) for hyperlipidemia and 68 (7.9%) for hyperuricemia There were fewer drug clinical trials for other diseases, including 479 (5.23%) for abnormal metabolism of bone, calcium, and phosphorus, 21 (2.44%) for endogenous growth hormone deficiency, and 19 (2.21%) for electrolyte and fluid imbalances (Figure 3).

3.2 | Leading clinical trial centers and sponsors

A total of 177 hospitals have carried out endocrine disorders and metabolism and nutrition disorder drug clinical trials as leading clinical trial units (Table 1). Among all leading clinical trial units, 117 hospitals carried out bioequivalence studies, of which 68 hospitals only carried out bioequivalence studies (Table S1). There are 67 hospitals as leading clinical trial units to carry out phase I clinical trials. (Table S2).

TABLE 1 Top 10 hospitals in number of clinical trials of leading clinical trial units from 2010 to 2019

Ranking	Trial unit	Number of trials
1	Peking University First Hospital	37
2	Peking Union Medical College Hospital	36
3	Peking University People's Hospital	34
4	Tongji Hospital, Tongji Medical College, Huazhong University of Science & Technology.	30
5	Shanghai Public Health Clinical Center	24
6	West China Hospital of Sichuan University	22
7	The First Medical Center of Chinese People's Liberation Army General Hospital	21
7	China-Japan Friendship Hospital	21
7	The Second Affiliated Hospital of Zhejiang University School of Medicine	21
10	Bethune First Hospital of Jilin University	20

A total of 344 enterprises applied as sponsors to perform clinical trials of endocrine disorders and metabolism and nutrition disorder drugs over the past 10 years (Table 2). There were also large differences in geographical distribution. Jiangsu Province, Beijing, and Shanghai were third in the number of clinical trials and the number of sponsor enterprises. A total of 213 enterprises performed BE studies. Zhengda Tianqing Pharmaceutical Group Co., Ltd., ranked first (Table S3). A total of 112 enterprises performed phase I clinical trials. Jiangsu Hengrui Pharmaceutical Co., Ltd., ranked first (Table S4). A total of 110 enterprises performed phase II and III clinical trials. Sanofi (China) Investment Co., Ltd., ranked first (Table S5).

3.3 | Clinical trials of diabetes drugs

A total of 479 clinical trials of diabetes drugs were performed, involving 126 drugs. There were 91 types of chemical drugs, 32 types of biological products and three unknown types, and the number of trials increased over time (Figure 4). We identified 16 types of hypoglycemic mechanisms. The most common diabetes drugs were DPP4 inhibitors (113 [23.59%]), biguanides (83 [17.33%]), insulins (53 [11.06%]), and SGLT inhibitors (53 [11.06%]) (Figure 5). In terms of trial phases, the number of BE studies was the largest at 250 (52.19%), followed by phase I at 117 (24.42%), and phase III at 93 (19.42%), with phases II and IV only accounting for 2.51% and 0.63%, respectively (Figure S4).

A total of 193 enterprises performed 479 clinical trials of diabetes drugs. Jiangsu Hengrui Pharmaceutical Co., Ltd. conducted a maximum of 26 trials, followed by the Jiangsu Haosen Pharmaceutical Group Co., Ltd., with 18 (Table 3). Fifty-four enterprises carried out clinical trials of DPP4 inhibitors. Jiangsu Hengrui Pharmaceutical Co., Ltd. also ranked first with 11. Clinical trials of GLP-1 receptor agonists/analogs were performed by 18 enterprises. Jiangsu Haosen Pharmaceutical Group Co., Ltd. was first on this list, with 10 trials.

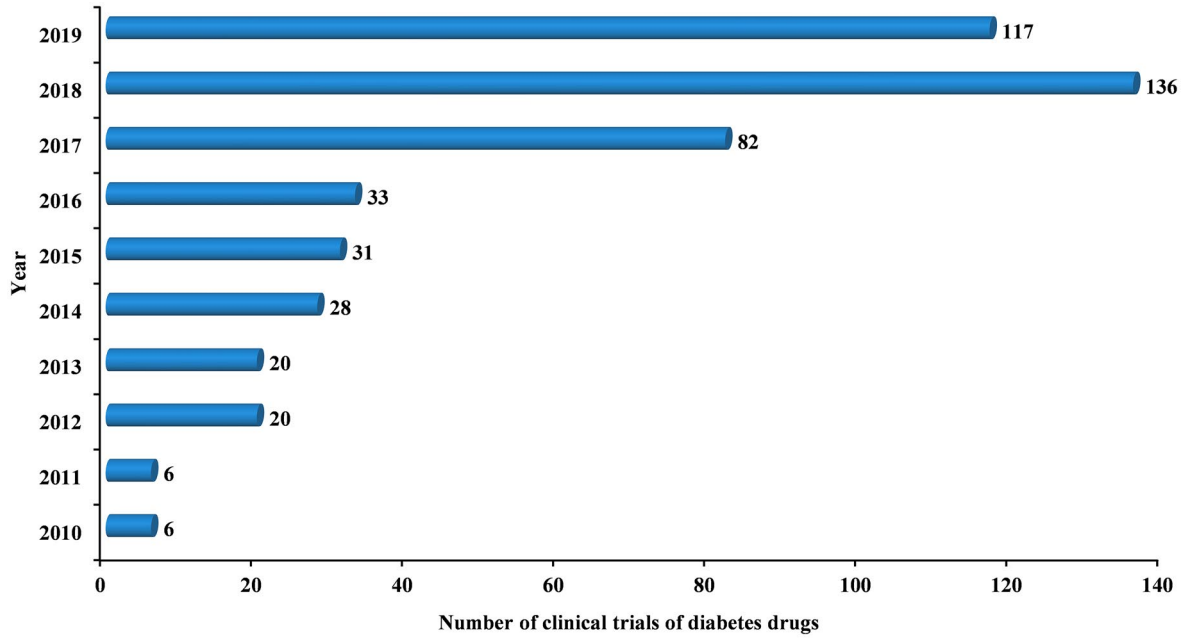

FIGURE 4 Number of diabetes drug trials from 2010 to 2019 in China

TABLE 2 Top 10 sponsors in the number of clinical trials from 2010 to 2019

Ranking	Sponsor	Number of trials
1	Jiangsu Hengrui Pharmaceutical Co., Ltd.	38
2	Jiangsu Haosen Pharmaceutical Group Co., Ltd.	18
2	Zhengda Tianqing Pharmaceutical Group Co., Ltd.	18
4	Sanofi (China) Investment Co., Ltd.	17
5	Zhejiang Hisun Pharmaceutical Co., Ltd.	16
6	Novo Nordisk (China) Pharmaceutical Co., Ltd.	14
6	Yangzijiang Pharmaceutical Group Co., Ltd.	14
6	GeneScience Pharmaceutical Co., Ltd.	14
9	Eli lilly Asia representative office in Shanghai	12
10	Shandong Xuanzhu Pharmaceutical Technology Co., Ltd.	11

4 | DISCUSSION

This systematic evaluation provides an overview of endocrine disorder and metabolism and nutrition disorder drug clinical trials from 2010 to 2019 in mainland China. Data such as the total number of clinical trials in mainland China, types of trial drugs, and numbers of leading clinical trial centers all increased significantly during this period. These results show that China has good development momentum in clinical trials for endocrine disorders and metabolism and nutrition disorder drugs, indicating that the speed of new drug research and development in China is accelerating. Moreover, China has undertaken efforts in international cooperation and mutual recognition of data, which can provide an important direction for the research and development of drugs for endocrine disorder and metabolism and nutrition disorder.

From 2009 to 2018, the number of endocrine disorder and metabolism and nutrition disorder drug trials in mainland China showed remarkable growth, with an average annual growth rate of 43.22%, suggesting the contribution of Chinese pharmaceutical enterprises and medical institutions to global drug research and development. These findings are also evidence that China's new drug development system and clinical trial system have increasingly improved and developed rapidly. China's "Eleventh Five-Year," "Twelfth Five-Year," "Thirteenth Five-Year," and other national-level policy plans have supported the development of hundreds of innovative drugs and the construction of hundreds of drug clinical trial platforms. These policies aim to address the serious lag in drug R&D in China and foster more innovative drug R&D enterprises and more internationally compatible clinical trial institutions with GCP (Good Clinical Practice) regulatory systems and capabilities.

On July 22, 2015, NPMA issued an announcement on the self-inspection and verification of drug clinical trial data to further strengthen the supervision of the authenticity, completeness, and standardization of clinical trial data and address the backlog of new drug approvals in China.[8] Since then, the quality of clinical trials in China has been better guaranteed. The China State Council released "Opinions on Reforming the Review and Approval System for Drugs and Medical Devices" in 2015. It was a landmark reform.[11] Subsequently, a series of regulatory policies were promulgated and implemented; in particular, the General Office of the CPC Central Committee and the General Office of the State Council issued "the opinions on deepening the reform of the review and approval system to encourage the innovation of drugs and medical devices" on October 8, 2017.[12] The number of clinical trials has increased

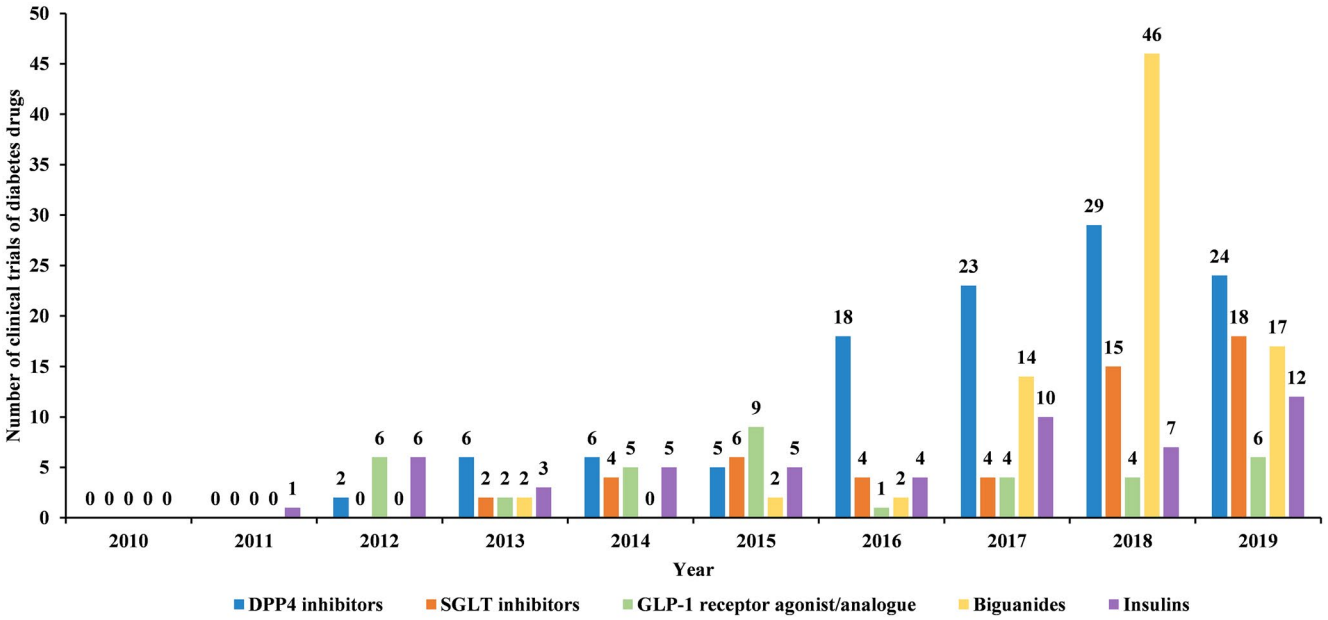

FIGURE 5 Number of clinical trials of the top five drugs for hypoglycemic mechanisms from 2010 to 2019 in China

TABLE 3 Top 10 sponsors in the number of diabetes drug clinical trials from 2010 to 2019

Ranking	Sponsor	Number of diabetes drug trials
1	Jiangsu Hengrui Pharmaceutical Co., Ltd.	26
2	Jiangsu Haosen Pharmaceutical Group Co., Ltd.	18
3	Novo Nordisk (China) Pharmaceutical Co., Ltd.	14
3	Zhengda Tianqing Pharmaceutical Group Co., Ltd.	14
5	Sanofi (China) Investment Co., Ltd.	13
6	Eli lilly Asia representative office in Shanghai	12
7	Shandong Xuanzhu Pharmaceutical Technology Co., Ltd.	11
8	Gan & Lee Pharmaceutical Co., Ltd.	10
8	Hualing Pharmaceutical Technology (Shanghai) Co., Ltd.	10
10	Jiangsu Deyuan Pharmaceutical Co., Ltd.	9

significantly since 2017 and has contributed to meeting the health needs of one-fifth of the global population and to global collaboration on new drug development.

The registration management of imported drugs was relaxed, and the process of drug clinical trials was accelerated in 2017.[13] The National Medical Products Administration announced in 2018 that clinical trials could be started within 60 working days of the application if no negative and questionable review or opinion was received. The timing of this review cycle will render the NMPA's regulatory schedule similar to that of other countries.[14] This 60-day acquiescence system for new drug approval was further emphasized in the "Provisions for Drug Registration" issued in January 2020.[15] These improvements will encourage domestic and international enterprises to perform clinical trials of their drugs in China.[4]

The General Office of the State Council issued "the Opinions on the Evaluation of the Quality and Efficacy of Generic Drugs" in 2016,[16] which provided clear opinions on the consistency evaluation of generic drugs in China and encouraged enterprises to conduct bioequivalence studies. Based on this directive, the number of bioequivalence studies increased significantly after 2016. The number and growth trend of domestic trials are higher than those of international multicenter trials, showing that China still has much room for development in the international clinical trial platform.

We further classified endocrine disorders and metabolism and nutrition disorder drugs according to MedDRA. We found that the number of diabetes drug clinical trials exceeded half of all trials, ranking first, followed by hyperlipidemia and hyperuricemia drugs, over the past 10 years. Diabetes has become one of the 10 major diseases seriously endangering the health of people in China.[17] The prevalence rate of diabetes among adults aged 18 years old and older was 9.7% in 2012, and the prevalence rate was on the rise.[18] Ischemic heart disease was among the top three causes of death in China in 2017. Diabetes, hyperlipidemia, and hyperuricemia can significantly increase the risk of cardiovascular adverse events, and the relative risk of myocardial infarction and cardiovascular death is higher.[19] Diabetes increases the risk of vascular complications and premature death, placing an enormous economic burden on society. The burden associated with diabetes might be greater than in any other country.[20] China's aging population will inevitably lead to an increase in the proportion of chronic diseases common in the elderly.[21] Currently, the development trend of clinical trials in China is in line with the characteristics of disease epidemiology.

Diabetes accounted for 49.6% of all drugs for endocrine disorders and metabolism and nutrition disorders in clinical trials over the decade. We summarized the diabetes drugs according to the hypoglycemic mechanism. We found that the number of novel diabetes drug clinical trials, such as DPP-4 inhibitors, GLP-1 analogs, and SGLT inhibitors, was greater than that of traditional diabetes drugs, such as biguanide and insulin. DPP-4 inhibitors, such as sitagliptin, are effective in lowering blood sugar [22] and show cardiovascular safety.[23] The safety and tolerability of vildagliptin and allogetine were good.[24,25] They have potential as first-line treatments for patients with T2DM in Asia.[26] There is no increase in cardiovascular risk from the current evidence.[27,28] Liraglutide is a representative GLP-1 receptor agonist, and a large number of studies have confirmed its beneficial hypoglycemic effects and good safety profile.[29,30] Research on new hypoglycemic drugs is receiving increasing attention, and these drugs they could become the first-line drugs for diabetes in the future. In addition, we conducted statistical analysis of the phases of clinical trials of diabetes drugs. We found that BE studies accounted for 52.19%, whereas phase I clinical trials accounted for only 24.42%. China has achieved research and development of innovative drugs for diabetes, but there is huge space for further development. The data from clinical trials will provide a better idea and direction for the future development of diabetes drugs.

Our data further showed that the geographical distribution of the trial units in China is uneven, and the regional distribution of the number of trials is related to the regional economic level. This geographical difference is a manifestation of the uneven distribution of clinical research medical resources in China. At the same time, 38.42% of the trial units only performed bioequivalence studies. To some extent, this finding also showed that, although more clinical trial institutions have joined the group of leading units, the capacity of clinical trial institutions is uneven. Some clinical trial institutions lack experience participating in registered and listed clinical research or multicenter clinical research. These problems must be addressed and solved in the future for the rapid development of pharmaceutical innovation.

Another important role in clinical trials is the sponsor. The sponsor is the first responsible party in the clinical trial and the initiator of the clinical trial. It is necessary to manage the entire trial process. In our data review, both Chinese and foreign enterprises that conducted clinical trials of endocrine disorder and metabolism and

nutrition disorder drugs showed strong participation. Foreign pharmaceutical enterprises hope to accelerate the clinical trial processes for innovative drugs through international, multicenter clinical trials.[31] Domestic enterprises are also maintaining pace with innovation, especially Jiangsu Hengrui Pharmaceutical Co., Ltd., which ranked first in many of the data. There were 213 enterprises that conducted BE studies and 112 enterprises that carried out phase I clinical trials over the past 10 years. There will be more enterprises to sponsor clinical trials in the future. However, whether the capacity of existing or newly added pharmaceutical enterprises can quickly meet the requirements of drug R&D, especially the R&D of innovative drugs and international multicenter cooperative R&D, must be further examined. In clinical trials of diabetes drugs, the new hypoglycemic DPP-4 inhibitor drugs and GLP-1 drugs are research hotspots for various pharmaceutical enterprises. In addition, the incidence of hypoglycemic events with these drugs is low, and the weight loss or weight-neutral effects are better than those of sulfonylurea drugs.[32] These advantages point to future research directions for pharmaceutical enterprises.

Based on trials listed on the only mandatory registration platform for clinical trials in mainland China, we evaluated the overall landscape of endocrine disorder and metabolism and nutrition disorder drug research and development in mainland China for the decade of 2010–2019. Because there were a certain number of registered trial items that did not record the time of the first subject enrollment, the statistics of the data could have caused certain deficiencies. However, considering that the clinical trial approval issued by China must be implemented within three years or it will be invalid, although some trials had registration dates and ethical review dates, they were not actually performed. Therefore, we used the time of the first subject enrollment as the basis for selecting items to ensure that the data of the included items are more authentic. In the data statistics, the name of the trial unit was incorrectly entered, and not all blank items were counted. Some hospitals changed their names during this period, whereas others merged. We unified the names of the hospitals, and the merged hospitals included the data from all merged hospitals.

5 | CONCLUSION

China made rapid progress in the development of drugs for endocrine disorders and metabolism and nutrition disorders between 2010 and 2019. Both innovative and generic drugs will play a role in addressing China's medical needs. The number of patients with endocrine disorders and metabolism and nutrition disorders in China is enormous, and the economic burden is heavy. Chinese patients have benefited from global drug discovery and development, with growing clinical development capacity and substantial support from the government. We believe that China has become an advantageous location for drug research and the development of endocrine disorder and metabolism and nutrition disorder drugs, and it is ready to contribute to global drug research.

ACKNOWLEDGMENT

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CONFLICT OF INTEREST

No.

AUTHORS' CONTRIBUTIONS

Xin Liu and Yu Cao planned and drafted the paper, and contributed to data quality control, analysis, and interpretation. Haitao Niu provided methodological guidance and support with data interpretation. All authors reviewed and revised the manuscript.

DATA AVAILABILITY STATEMENT

All data were collected systematically from the National Registration and Information Disclosure Platform for Drug Clinical Studies registered from January 1, 2010 to December 31, 2019. NMPA established the "Registration and Information Disclosure Platform for Drug Clinical Trials" (www.chinadrugtrials.org.cn) in 2013. All drug clinical trials must be registered on this platform, including phase I-IV trials, bioequivalence studies and pharmacokinetic research, and require the registration of clinical trials before 2013 for supplemental registration, the earliest supplementary registration of clinical trials began on February 16, 2002. We collected all public information on the NMPA website, including registration number, trial name, indication, drug name, drug type, trial classification, trial stage, design type, randomization, blinding, trial scope, first public information date, date of the first enrollment, leading unit, participating unit, sponsor, funding source for the pilot project, etc. We just included clinical trials that had already been registered, because some clinical trials had already been registered online but had not actually been carried out. We screened all clinical trials from 2010 to 2019 based on the "first subject enrollment date" in the database. We classified them according to the standard of MedDRA, and extracted the clinical trial data of endocrine disorders and metabolism and nutrition disorders. The whole data were obtained from the public website information of the NMPA. Our evaluation was based only on clinical trial data from mainland China, excluding Hong Kong, Macao, and Taiwan.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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