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Trends in drug-drug interactions for new drug clinical trials in China over the past 10 years (2013–2022)

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Abstract

The number of drug-drug interaction (DDI) clinical trials in China has increased rapidly in recent years. The aim of this study was to summarize and analyze DDI clinical trials in China over the past 10 years. We conducted a cross-sectional study of DDI clinical trials registered in the Chinese Center for Drug Evaluation (CDE) from September 6, 2013 to December 31, 2022. All related registration information disclosed on the CDE website were summarized and analyzed. Although the number of DDI clinical trials conducted before 2017 was relatively low, it increased markedly after 2017. The average duration of DDI clinical trials was 85.83 ± 100.99 days from 2013 to 2019 and 107.16 ± 98.57 days from 2020 to 2022. The duration of rifampicin use was 5–19 days, and the investigational drug was administered after 5–14 days of rifampicin use. Itraconazole was administered for 4–17 days, and the investigational drug was administered after 3–10 days of itraconazole use. Clinical trials of drug-drug interactions have recently increased due to the development of new drugs and the updated policies regulating drug registration and marketing. Although the designs of clinical trials comply with the new guidelines, the duration of the administration of interacting drugs still varies widely. Optimizing protocol designs can shorten the implementation period of clinical trials and reduce the costs of drug marketing.

Keywords Drug-drug interactions, Clinical trials, New drugs

Clinical trial number

Not applicable.

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Introduction

Pharmacokinetic drug interactions can give rise to severe side effects, leading to the early termination during drug development or the withdrawal of drugs from the market [1]. Hence, evaluating the risks of clinically significant drug-drug interactions (DDIs) during the development of new molecular entities is crucial. During the development of new drug, clinical drug interaction studies are conducted based on the potential drug interactions assessed by in vitro studies [2]. The risks of DDIs are minimized during the screening process by referring to the most up-to date information. If potential DDIs are identified during the drug development process, the information should be appropriately communicated to physicians and pharmacists [2]. Regulatory agencies, such as the US Food and Drug Administration (FDA), European Medicines Agency (EMA), and Pharmaceuticals and Medical Devices Agency (PMDA) have issued guidelines associated with the conduct of DDI studies including their timing and design, the interpretation of study outcomes, and the management of DDIs in patients [3–5]. These guidelines recommend integrated and mechanistic approaches for evaluating DDIs, which have dramatically transformed the assessment of potential clinically significant interactions during the pre- and post-marketing stages of drug development [6, 7].

During the period between 2010 and 2015, the number of applications for clinical trials of innovative drugs in China began to rise [8]. In July 2015, the introduction of China's regulatory reform measures alleviated the backlog of applications. In 2017, China joined the International Conference on Harmonization (ICH), which brought about an increase in cooperation with prominent international institutions. Meanwhile, China's new drug development system and clinical trial system have been increasingly improved and developed, and the number of first investigational new drugs (INDs) for innovative drugs that were applied for and approved rose greatly [8, 9]. As the number of innovative drugs has grown, the number of clinical trials for DDI also has also increased. In China, the Center for Drug Evaluation of the National Medical Products Administration (NMPA) issued guidelines for drug interaction research in 2021 [10]. In this study, we hypothesized that China's post-2017 regulatory reforms (ICH alignment and 2021 DDI guidelines) would significantly increase both the quantity and methodological rigor of DDI trials. We aimed to summarize and analyze the trends in DDI clinical trials in China from 2013 to 2022, and to provide necessary supporting data for researchers, pharmaceutical companies and policymakers to improve the efficiency of drug development.

Methods

All drug clinical trials in China must be registered on the Chinese Center for Drug Evaluation (CDE) platform (http://www.cde.org.cn/), which is the authoritative clin ical trial registration database. This database was established in 2013 by the NMPA in China. We carried out a cross-sectional study of DDI clinical trials registered with the Chinese Center for Drug Evaluation (CDE) from September 6, 2013 to December 31, 2022 by conducting a search on the CDE website with the keywords "drug interaction," "interaction," "drug-drug," and "DDI." The clinical trial registration information posted on the CDE website, including registration number, registration date, trial topic, investigational drug name, investigational drug classification, interacting drug name, duration of investigational drug use, duration of interacting drug use, lead clinical center, target number of healthy subjects, date when the first subject signed informed consent, trial completion date, and other relevant information, was collected. If the information was not posted, it was not included in the analysis.

Two authors (JZ and JW) independently extracted data and excluded clinical trials that were not regarded as a DDI clinical trial. If consensus on certain information could not be reached by the two authors, the issue was discussed with a third author (JL), and a decision was made by consensus. Our operational protocols focus on ensuring data accuracy through iterative validation. "Midazolam", "Rifampicin", "Itraconazole", "Warfarin", and "Digoxin" were included in the search for interacting or index drugs.

We used R software (version 3.6.2) for data processing and analysis. The counting data are expressed as composition ratios, the normal distribution measurement data are expressed as means ± standard deviations, and the abnormal distribution measurement data are expressed as medians (25%, 75%). The boxplot was utilized to visually represent the distribution of the data of the duration of DDI clinical trials. Group comparisons were analyzed using the Mann-Whitney U test.

This study employed a longitudinal time-series analysis on annual data (2013–2022) to investigate growth patterns and external impacts. Data preprocessing included anomaly retention for negative growth rates (e.g., 2016) and forward-filling to address zero-inflated counts (2013–2014). Trend decomposition via Seasonal-Trend-LOESS (STL) with a 5-year cycle revealed nonlinear growth trajectories. Two modeling frameworks were evaluated: (1) an autoregressive integrated moving average (ARIMA) optimized through stepwise AIC minimization, and (2) an exponential smoothing state-space model (ETS) with additive trend components. Intervention analysis integrated a dummy-coded structural break (2016) into a state-space model to quantify persistent

shock effects. Model performance was assessed using mean absolute percentage error (MAPE) on a 3-year holdout set (2020–2022). Changepoint detection (Binseg algorithm, L2-norm) identified critical discontinuities, while autocorrelation analysis evaluated residual dependencies. All computations were executed in Python 3.9 using statsmodels and pmdarima libraries, with significance thresholds set at $\alpha = 0.05$.

Results

Annual changes in drug-drug interaction clinical trials

The number of DDI clinical trials grew from zero in 2013 to five in 2014 and to 11 in 2015. There were 9 DDI clinical trials in 2016. In 2017, the number of DDI clinical trials ascended to 14, and saw rapid growth in 2019. The year-over-year growth rates for 2018 and 2019 were 28.6% and 55.6%, respectively. In 2020, the number of DDI clinical trials increased to a similar level as in 2018, indicating a stabilization in growth. In 2021, the number of DDI clinical trials increased by 50%, reaching a total of 54. However, in 2022, the figure declined by 20.3%, dropping to 43. (Fig. 1.). The time-series analysis revealed nonlinear post-2015 growth (CAGR:32%), interrupted by two structural breaks: a 2016 contraction (count:9 vs.11; $p = 0.03$) and a 2020 inflection point (changepoint detection, penalty = 10). The ETS model demonstrated superior predictive accuracy (MAPE = 15.2%) over ARIMA (MAPE = 18.5%), attributed to enhanced volatility adaptation ($\alpha = 0.8$). Intervention analysis confirmed prolonged suppression from the 2016 shock (Cohen's d = 1.8), with recovery requiring three years. Residual diagnostics indicated model adequacy (ACF$|\rho|$<0.3), while unexpected 2022 declines (count:43 vs.54) suggested emerging external pressures. Sensitivity analyses excluded data artifacts (ΔAIC < 2).

Geographical distribution of drug-drug interaction clinical trials

Among the 218 DDI trials analyzed, 197 (90.4%) explicitly enrolled healthy volunteers, while 21 (9.6%) involved patient populations. The principal investigators of these 218 trials were from different provinces or municipalities across China. The majority of the clinical trials (96.8%; 211 trials) were completed at a single clinical trial center, and seven trials (3.2%) were completed at two or more clinical trial centers. Among the leading clinical trial centers, Jilin, Beijing, and Jiangsu conducted the highest number of trials (26, 25, and 25 DDI clinical trials, respectively). Shanghai, Hunan Province, and Anhui Province carried out 24, 21, and 17 trials, respectively. Eighty-one clinical trial centers conducted DDI clinical trials. Among them, the First Hospital of Jilin University implemented 25 DDI clinical trial projects, the Shanghai Xuhui District Central Hospital conducted 10 DDI clinical trials, and the First Affiliated Hospital of Bengbu Medical College carried out 9 DDI clinical trials (Fig. 2.).

Duration of drug-drug interaction clinical trials

The trial duration was defined as the period from the moment when the first subject signed the informed

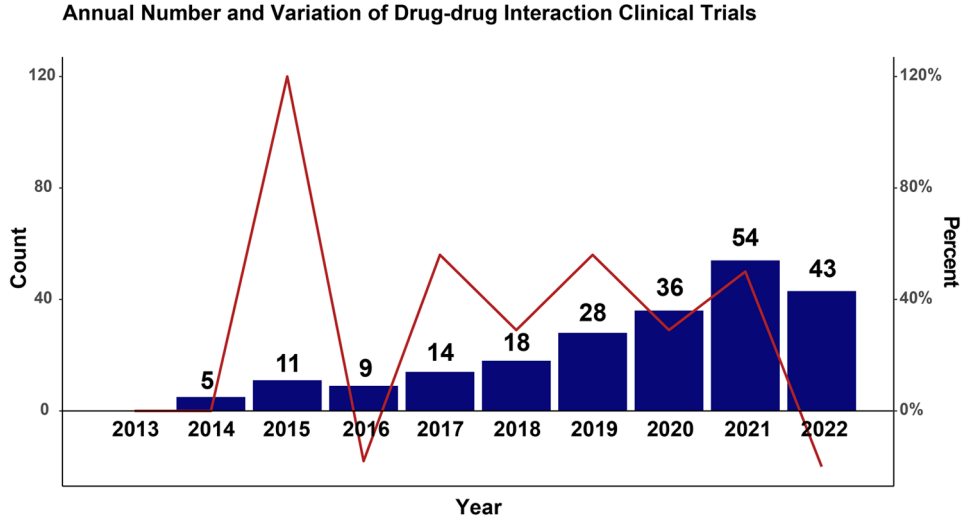
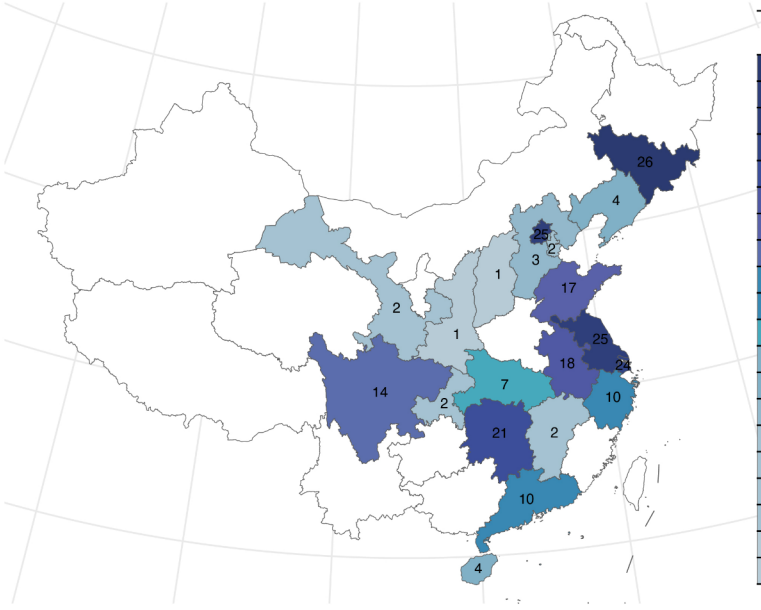


Fig. 1 Annual amount and fluctuations in clinical trials of drug-drug interaction. The numbers above the bars represent the number of DDI clinical trials each year, while the red line indicates the percentage change in the number of DDI trials compared to the previous year. In July 2015, the introduction of China's regulatory reform measures alleviated the backlog of applications. In 2017, China joined the International Conference on Harmonization, which brought about an increase in cooperation with prominent international institutions. The "Regulations on the Administration of Drug Clinical Trial Institutions" issued on November 29, 2019 and the amendment of the "Quality Management Practices for Pharmaceutical Clinical Trials" by the State Medical Products Administration and the National Health Commission on July 1, 2020. The "Technical Guidelines for Drug Interaction Research" published in January 2021 comprehensively describe the evaluation of drug interactions for drug research and development



Region	The number of drug-drug interaction clinical trials	2022 Resident population (million people)
Jilin	26	2347
Beijing	25	2184
Jiangsu	25	8515
Shanghai	24	2475
Hunan	21	6604
Anhui	18	6127
Shandong	17	10162
Sichuan	14	8374
Zhejiang	10	6577
Guangdong	10	12656
Hubei	7	5844
Liaoning	4	4197
Hainan	4	1027
Hebei	3	7420
Chongqing	2	3213
Tianjin	2	1363
Jiangxi	2	4527
Gansu	2	2492
Shaanxi	1	3956
Shanxi	1	3481

Fig. 2 Geographical distribution of clinical centers conducting drug-drug interaction clinical trials across various regions in China. This map includes Taiwan; however, clinical trial data from Taiwan were excluded from this study due to the existence of its independent drug regulatory authority, the Taiwan Food and Drug Administration (TFDA)

consent to the completion of the study. If the start and completion times were not posted on the CDE website, the duration of the clinical trial was excluded in the analysis, and a total of 43 clinical trials were excluded. If the start and completion dates were not available on the CDE website, the clinical trials were excluded from the analysis due to the inability to calculate their duration, resulting in a total of 43 excluded trials. As a result, 175 DDI clinical trials that included trial durations, were included in the analysis. The "Regulations on the Administration of Drug Clinical Trial Institutions" issued on November 29, 2019 and the amendment of the "Quality Management Practices for Pharmaceutical Clinical Trials" by the State Medical Products Administration and the National Health Commission on July 1, 2020 [11, 12], promoted the standardization and scientific design of drug clinical trial protocols in China. The revised provisions explicitly mandate that clinical trials prioritize the assessment of drug-drug interaction risks, particularly in studies involving multi-drug combination therapies, such as anti-tumor or antiviral treatments, and require systematic DDI evaluations to be conducted. Therefore, the statistics were divided into two groups: 2013–2019 and 2020–2022. The average durations of DDI clinical trials in the periods of 2013–2019 and 2020–2022 were 85.83 ± 100.99 days and 107.16 ± 98.57 days, respectively, as shown in Fig. 3. Group comparisons were performed using the Mann-Whitney U test, indicating no statistically significant difference between 2013 and 2019 and 2020–2022 groups ($p = 0.13$, Wilcoxon $r = 0.18$). Despite the lack of statistical significance, the median duration in the 2020–2022 group was 15% higher than in 2013–2019, suggesting a potential trend warranting further investigation with larger samples.

Drug-metabolizing enzyme-specific inducers

The selection of CYP enzyme inducers, inhibitors, and pointer substrates for drug interaction clinical trials is guided by the recommendations from guidelines of NMPA (2021) [10], FDA (2020) [3], EMA (2022) [4], and PMDA (2019) (Table 1). Among the CYP enzyme inducers, rifampicin, phenytoin, and carbamazepine are recommended for the CYP3A enzyme. Both NMPA and EMA recommend phenytoin and rifampicin as inducers for CYP1A2, with EMA also mentioning smoking as an inducer. For CYP2B6, all guidelines recommend rifampicin as a moderate inducer. While NMPA additionally includes carbamazepine, and EMA recommends both carbamazepine and efavirenz. Rifampicin is also recommended across all guidelines for CYP2C8, CYP2C9, and CYP2C19 enzyme inducers. Additionally, NMPA recommends phenytoin as a moderate inducer for CYP2C19.

Rifampicin is an index inducer of multiple cytochrome P450s (CYPs), including CYP2B6, 2C8, 2C9, 2C19, and 3A4/5, and an inhibitor of OATP1B transporters (single dose) [13, 14]. In 33 DDI clinical trials, rifampicin was selected as the inducer of drug metabolism. The duration of rifampicin use ranged from 5 to 19 days, and the investigational drug was administered after 5–14 days of rifampicin use. Moreover, 17 trials started 7 days after rifampicin use and 6 trials started 6 days after rifampicin use (Fig. 4.).

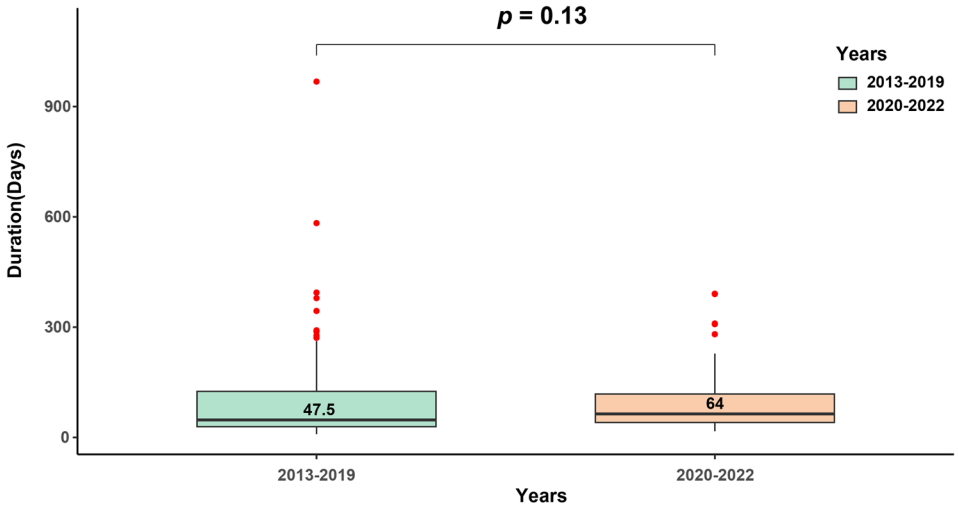


Fig. 3 Box plot of the duration of drug-drug interaction clinical trials. Boxplots show the median (horizontal line), interquartile range (boxes), and data range (whiskers). Median values are labeled above each box. Group comparisons were performed using the Mann-Whitney U test, indicating no statistically significant difference between 2013–2019 and 2020–2022 groups ($p = 0.13$, Wilcoxon $r = 0.18$). Sample sizes: 2013–2019 ($n = 82$), 2020–2022 ($n = 63$)

Table 1 A comparison of the final in vivo DDI guidance documents from NMPA, FDA, PMDA and EMA

	NMPA	FDA	PMDA	EMA
Index substrates for CYP enzymes				
CYP1A2	Caffeine, Tizanidine	Caffeine, Tizanidine	Caffeine, Tizanidine	Caffeine
CYP2B6	-	-	-	Bupropion
CYP2C8	Repaglinide	Repaglinide	Repaglinide	Repaglinide
CYP2C9	S-warfarin*, Tolbutamide*	S-warfarin*, Tolbutamide*	S-warfarin, Tolbutamide	Flurbiprofen*, S-warfarin*
CYP2C19	Lansoprazole*, Omeprazole	Lansoprazole, Omeprazole,	Lansoprazole*, Omeprazole	Omeprazole
CYP2D6	Desipramine, Dextromethorphan, Metoprolol, Nebivolol	Desipramine, Dextromethorphan, Nebivolol	Desipramine, Dextromethorphan, Nebivolol	Desipramine, Dextromethorphan, Nebivolol
CYP3A	Midazolam, Triazolam	Midazolam, Triazolam	Midazolam, Triazolam	Midazolam, Triazolam
Index inhibitors for CYP enzymes				
CYP1A2	Enoxacin, Fluvoxamine, Ticlopidine	Fluvoxamine	Fluvoxamine	Fluvoxamine
CYP2B6	-	-	-	-
CYP2C8	Clopidogrel*, Gemfibrozil	Clopidogrel, Gemfibrozil	Clopidogrel, Gemfibrozil	Gemfibrozil
CYP2C9	Fluconazole*	Fluconazole*	Fluconazole*	Fluconazole*
CYP2C19	Fluconazole*, Fluvoxamine, Fluoxetine, Ticlopidine	Fluvoxamine	Fluvoxamine	Fluconazole, Fluvoxamine
CYP2D6	Fluoxetine, Paroxetine, Quinidine	Fluoxetine, Paroxetine	Fluoxetine, Mirabegron*, Paroxetine	Fluoxetine, Paroxetine
CYP3A	Clarithromycin, Itraconazole, Ketoconazole, Ritonavir	Clarithromycin, Itraconazole	Clarithromycin, Erythromycin*, Fluconazole*, Itraconazole, Verapamil*	Clarithromycin, Itraconazole
Inducers for CYP enzymes				
CYP1A2	Phenytoin*, Rifampicin	-	-	Phenytoin*, Rifampicin*, Smoking*
CYP 2B6	Carbamazepine, Rifampicin*	Rifampicin*	Rifampicin*	Carbamazepine, Efavirenz*, Rifampicin*,
CYP2C8	Rifampicin*	Rifampicin*	Rifampicin*	Rifampicin*
CYP2C9	Rifampicin*	Rifampicin*	Rifampicin*	Rifampicin*
CYP2C19	Rifampicin, Phenytoin*	Rifampicin	Rifampicin	Rifampicin
CYP3A	Carbamazepine, Phenytoin, Rifampicin	Phenytoin, Rifampicin	Phenytoin, Rifampicin	Carbamazepine, Efavirenz*, Phenytoin, Rifampicin

*, moderate

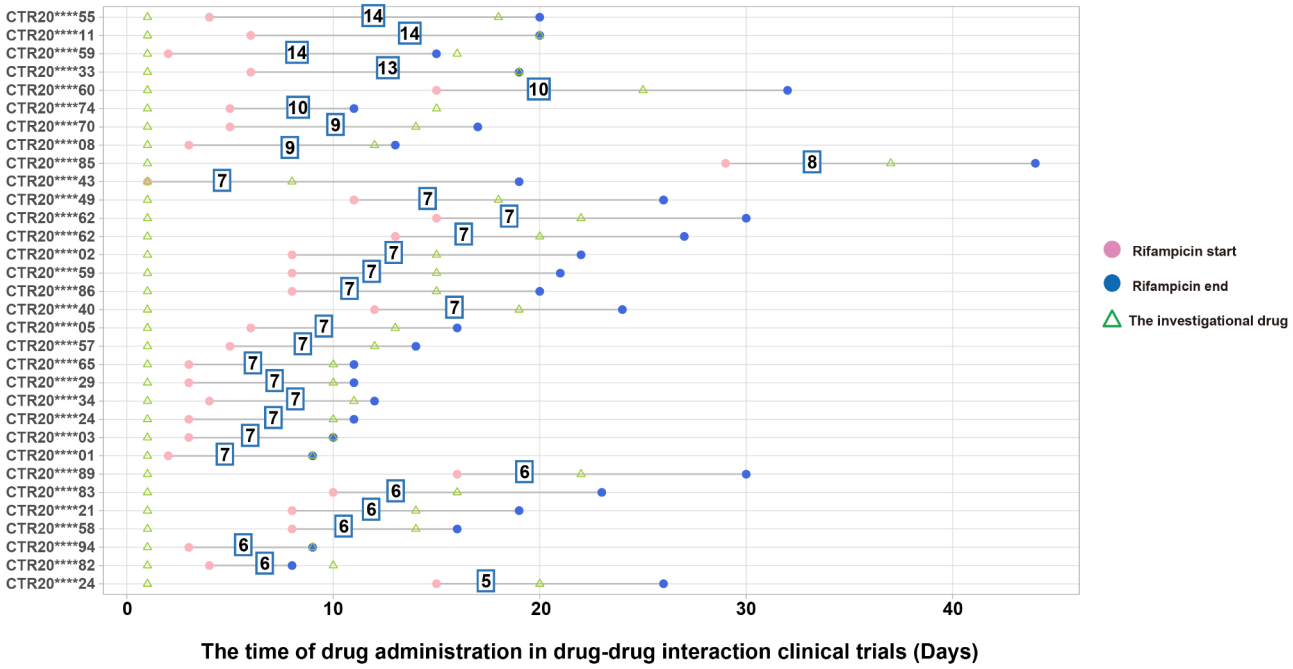


Fig. 4 Administration time points for rifampicin and investigational drugs. Green triangles indicate the dosing times for investigational drugs, red circles mark the start of rifampicin administration, and blue circles denote its end. The numbers in the blue boxes represent the time interval from the start of rifampicin to the administration of the investigational drug

Drug-metabolizing enzyme-specific inhibitors

For CYP3A inhibitors, all guidelines recommend clarithromycin and itraconazole. NMPA additionally recommends ketoconazole and ritonavir, while PMDA recommends erythromycin, fluconazole, and verapamil. In CDE-registered DDI clinical trials, itraconazole is the most commonly selected inhibitor, with a total of 41 clinical trials. Clarithromycin is mainly used in clinical trials related to helicobacter pylori combined therapy. Other recommended inhibitors for CYP1A2, CYP2B6, CYP2C8, CYP2C19, and CYP2D6 as outlined by NMPA, FDA, PMDA, and EMA, are listed in Table 1.

Itraconazole is an enzyme inhibitor of CYP3A, P-glycoprotein (P-gp), and breast cancer resistance protein [15–18]. Itraconazole was selected as an inhibitor of drug-metabolizing enzymes in 28 DDI clinical trials. The duration of itraconazole use ranged from 4 to 17 days, and the investigational drug was administered after 3–10 days of itraconazole use; further, 13 trials started after 3 days of itraconazole use, 6 trials started after 4 days of itraconazole use, and 5 trials started after 5 days of itraconazole use (Fig. 5.).

Drug-metabolizing enzyme probe substrates

Midazolam and triazolam are recommended as the probe substrate of CYP3A enzyme according to the guidelines. In Chinese DDI clinical trials, midazolam is mostly used as the probe substrate. For CYP1A2, caffeine and tizanidine are recommended as probe substrates by NMPA, FDA, and PMDA, while the EMA recommended only caffeine. The EMA also notes that caffeine is a NAT (N-acetyltransferase) substrate [19]. Additionally, probe substrates for CYP2B6, CYP2C9, CYP2C19, and CYP2D6 enzymes, as recommended by the guidelines of NMPA, FDA, PMDA, and EMA are listed in Table 1 for details.

Midazolam is a CYP enzymes probe substrate for CYP3A [20]. It was selected as the CYP enzymes probe substrate in 6 DDI clinical trials. Midazolam was administered twice in 3 DDI clinical trials, three times in 2 DDI clinical trials, and four times in one DDI trial. The duration of the investigational drug use ranged from 7 to 51 days (Table 2).

Digoxin is the probe substrate for the P-gp transporter and OATP1B3 [21, 22]. In 5 DDI clinical trials, digoxin was selected as the probe substrate for the P-gp transporter. The duration of the investigational drug use ranged from 9 to 22 days (Table 3).

Warfarin is a moderately sensitive substrate of CYP2C9 [23]. Warfarin was selected as the probe substrate of CYP2C9 in 6 DDI clinical trials. The duration of the investigational drug used ranged from 11 to 51 days (Table 4).

Discussion

Trends in clinical trials of drug-drug interactions in Mainland China

With the advancement of clinical development and substantial policy support from the government, drug

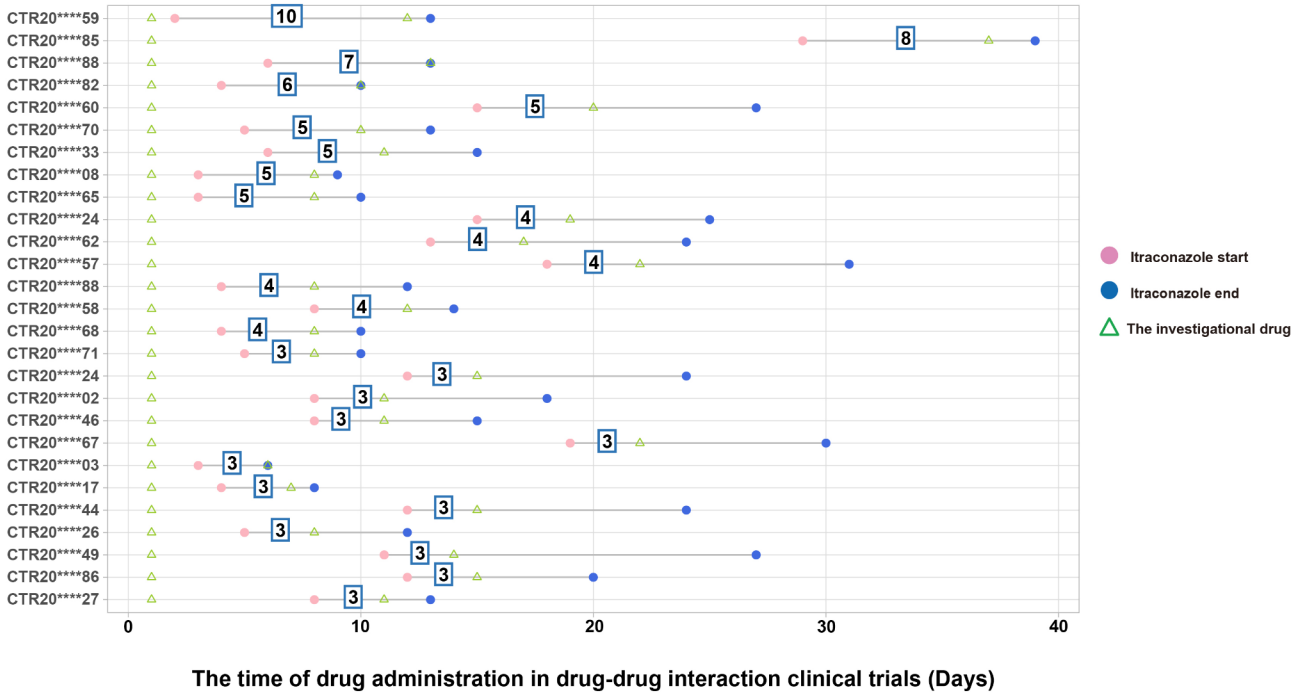


Fig. 5 Administration time points for itraconazole and investigational drugs. Green triangles indicate the dosing times for investigational drugs, red circles mark the start of itraconazole administration, and blue circles denote its end. The numbers in the blue boxes represent the time interval from the start of itraconazole to the administration of the investigational drug

Table 2 Administration times for Midazolam and the investigational drug

Number	Investigational drug start (Day)	Investigational drug end (Day)	The first dose of midazolam (Day)	The second dose of midazolam (Day)	The third dose of midazolam (Day)	The fourth dose of midazolam (Day)
CTR20****12	3	14	1	3	18	-
CTR20****33	6	19	1	6	19	21
CTR20****90	6	56	1	22	-	-
CTR20****91	8	28	1	8	22	-
CTR20****01	3	9	1	9	-	-
CTR20****86	7	26	1	21	-	-

Table 3 Administration times of Digoxin and the investigational drug

Number	Investigational drug start (Day)	Investigational drug end (Day)	The first dose of digoxin (Day)	The second dose of digoxin (Day)
CTR20****52	6	15	1	10
CTR20****64	6	27	1	22
CTR20****18	6	14	1	10
CTR20****86	7	26	3	23
CTR20****21	5	16	1	12

Table 4 Administration times for warfarin and the investigational drug

Number	Investigational drug start (Day)	Investigational drug end (Day)	The first dose of warfarin (Day)	The second dose of warfarin (Day)
CTR20****52	15	26	1	19
CTR20****40	14	24	1	18
CTR20****52	9	24	3	16
CTR20****91	8	28	1	22
CTR20****90	6	56	1	22
CTR20****86	7	26	1	21

development in China has made rapid progress [24]. The increased number of trials and new drugs in China illustrates the innovative advances from 2011 to 2020 [24]. The increased number of new drugs and the updated guidelines for innovative drugs have led to more clinical

trials on drug interactions. We collected the data for DDI clinical trials conducted in mainland Chinese from September 6, 2013 to December 31, 2022.

Only a few DDI clinical trials were conducted before 2015. After 2017, DDI clinical trials increased greatly. This coincided with the introduction of China's regulatory reform measures in July 2015, which eased the backlog of applications and encouraged pharmaceutical innovation [8]. The 50% increase in DDI trials post-2021 guidelines (54 vs. 36 trials annually) directly informed NMPA's ongoing efforts to harmonize with ICH M12 standards. This trend reduced reliance on foreign data, accelerating domestic drug approvals [8]. After 2019, the Regulations on the Administration of Drug Clinical Trial Institutions in 2020 promoted the standardization and scientific design of drug clinical trial protocols in China, and the number of DDI clinical trial registrations increased [11]. The "Technical Guidelines for Drug Interaction Research" published in January 2021 comprehensively describe the evaluation of drug interactions for drug research and development [10]. These guidelines, which were implemented through public consultations as a pilot procedure in China, reflect the latest scientific knowledge and recommendations on appropriate methods for evaluating DDIs during new drug development and the provision of information about DDIs in the drug specifications. The guidelines include a list of substrates, inhibitors, and inducers of cytochrome P450s and transporters that should be used as index drugs or typical drugs in DDI clinical trials. The implementation of these regulatory policies has mandated comprehensive DDI clinical trials as a prerequisite for new drug approval while establishing standardized guidelines for protocol design, thereby enhancing the technical and operational efficiency of DDI clinical evaluations. This regulatory advancement ensures systematic characterization of drug interaction profiles through scientifically rigorous trial designs, ultimately strengthening the evidence base for therapeutic safety assessments throughout drug development pipelines.

In 2022, the number of DDI clinical trials in China decreased, which we speculate may be the result of a combination of factors. These include increased global economic uncertainty leading to budget cuts for DDI trials by companies, advancements in computer simulations (such as PBPK) and in vitro research technologies that allow DDI clinical trials to be replaced by simulation techniques or in vitro experiments, and the impact of the COVID-19 pandemic. Looking ahead, it is anticipated that the number of DDI trials may experience a resurgence as the policy environment undergoes optimization, technological methodologies continue to advance, and market demands are recalibrated. Nevertheless, the landscape of research is expected to evolve, with a shift towards more diversified and efficient forms and methods of investigation.

The trends in DDI clinical trials exert significant dual implications for both regulatory frameworks and clinical practice. From a regulatory perspective, shifts in DDI clinical trial paradigms have necessitated updates to evidence-based guidelines, refinements in risk-benefit assessment methodologies, and optimization of drug labeling protocols. These trends further drive adaptations in post-marketing surveillance systems, particularly through risk evaluation and mitigation strategies (REMS), when real-world polypharmacy data reveal emergent interaction risks requiring urgent regulatory intervention. In clinical practice, systematic evaluation of DDI patterns informs the adoption of evidence-based prescribing practices, facilitates the development of therapeutic monitoring algorithms, and strengthens patient education initiatives targeting preventable interactions, collectively reducing the burden of adverse drug events. These findings underscore the translational significance of DDI clinical trial data in bridging pharmacovigilance systems with clinical safety optimization, thereby advancing the integration of drug safety surveillance into precision therapeutic decision-making.

The clinical centers conducting DDI clinical trials were unevenly distributed in China. Jilin, Beijing, and Jiangsu carried out the largest number of DDI clinical trials. This geographical disparity reflects the uneven distribution of clinical research resources in China, with resources being given priority to principal investigators [24]. The First Hospital of Jilin University of Jilin Province conducted the largest number of DDI clinical trials. This disparity may lead to limitations in the generalizability of research findings and exacerbate regional disparities in research capabilities. Moving forward, the implementation of policy support, the promotion of multicenter studies, the application of digital technologies, and the enhancement of clinical research capacities in resource-limited regions hold promise for achieving a more balanced allocation of resources.

The average implementation time of DDI clinical trials from 2020 to 2022 was 107.16 days, which was 21.33 days longer than the average implementation time of DDI clinical trials from 2013 to 2019. The longer implementation times is potentially related to a more standardized and scientific protocol design. The prolonged implementation timelines of DDI clinical trials from 2020 to 2022 may be attributed to heightened regulatory scrutiny, the impact of the COVID-19 pandemic, and increased trial complexity. While these factors extended trial timelines, they concurrently reflect advancements in the scientific rigor and standardization of DDI research. Future efforts should prioritize optimizing trial workflows to achieve

an equilibrium between methodological robustness and operational efficiency.

Design of drug-drug interaction clinical trials

As the development of innovative drug research thrives, the number of DDI clinical trials is on the rise. Many DDI trials have been carried out in accordance with the guiding principles, but protocol designs still need further improvements. Clinical trials of DDIs related to inducers of CYP3A were often conducted with rifampicin. The maximum hepatic CYP3A4 induction after continuous administration of rifampicin was identified from the drug interaction database of the University of Washington [25]. To evaluate the maximum hepatic CYP3A4 induction, oral rifampicin (600 mg per day) should be administered for more than 10 days. However, in the current DDI clinical trial registration research in China, the duration of rifampicin using to achieve induction effects varied greatly, ranging from 5 to 14 days. In most trials, rifampicin was administered for only 6–7 days to achieve the induction effect. Additionally, the time for administering other inducers and probe substrates also varied. Although the technical guidelines for DDI studies do not explicitly specify the dosing duration of rifampin, they clearly state that the administration period of enzyme inducers should be optimized based on the induction kinetic characteristics of target enzymes and study design to ensure stable enzyme induction effects. According to previous studies, the inductive effect of rifampin on CYP3A4 typically reaches steady-state after 5 consecutive days of administration [26]. Meanwhile, shorter durations of rifampin use can reduce adverse reactions such as hepatotoxicity. In summary, these considerations explain why most DDI clinical trials adopt a rifampin dosing period of 6–7 days. Determining the appropriate administration time can shorten the duration of clinical drug trials and reduce marketing costs.

Clinical DDI trials focused on the inhibition of CYP3A were often conducted with ketoconazole. Due to safety concerns for ketoconazole, itraconazole is commonly used in the United States and Japan in clinical trials [16]. In all DDI clinical trials in China, itraconazole was used as an inhibitor of the drug-metabolizing enzyme. Various itraconazole dosing regimens were used or proposed for DDI studies. These include 100 mg once daily for 4 days, 200 mg once daily for 4 days, 200 mg twice on day 1 followed by 200 mg once daily, and 400 mg as a single dose [27–29]. The Clinical Pharmacology Leadership Group (CPLG) recommends an itraconazole dosing regimen of 200 mg once daily, with a 3-day run-in period before co-administering the substrate. After the substrate co-administration (on day 4), itraconazole dosing should continue for 4–5 substrate half-lives [20]. In most cases, 14 days of itraconazole dosing is sufficient to eliminate the substrate, based on the persistence of inhibition after itraconazole administration. Furthermore, azoles, including ketoconazole and itraconazole, often inhibit P-gp, breast cancer resistance protein, and CYP3A. Thus, intestinal interactions may not be due to CYP3A inhibition alone [17, 27].

The 2021 DDI guidelines state that DDI clinical trial simulation studies can prospectively predict possible drug interactions by integrating system-specific and drug-specific parameters using modeling and simulation techniques and software, such as physiologically based pharmacokinetic (PBPK) models. For example, to predict the effects of a moderate to weak inhibitor/inducer on a drug (usually after knowing that the inhibitory agent or inducer can significantly affect the drug), the PBPK model should be fully validated with clinical DDI pharmacokinetic data for the inhibitor/inducer [30, 31]. The validated PBPK model can then be used to predict the effects of moderate to weak inhibitors/inducers. The feasibility of using the PBPK model should be discussed with the regulatory authorities. At present, many studies have focused on the construction of drug interaction prediction models, but the sensitivity and specificity of these models should be verified [32–35].

The frequency of pharmacokinetic DDIs may be higher than that implied by the PBPK models because in vitro studies for these enzymes have not been routinely conducted until recently. Thus, only limited clinical DDI studies have been performed [2]. In the case of a drug with significant metabolic contributions from polymorphic P450 enzymes, genetic polymorphisms should also be considered when designing protocols for DDI clinical trials.

We acknowledged three primary limitations in this study: First, the cross-sectional design precludes causal interpretation of temporal trends. Second, ethnic pharmacogenomic factors influencing DDI susceptibility were not captured in registry entries. Third, the predominance of healthy volunteer studies (90.4%) may limit generalizability to patient populations, particularly for drugs with disease-state-dependent pharmacokinetics. Future trials should prioritize patient-centered assessment of DDI in late-stage studies, and follow-up studies should integrate real-world therapeutic drug monitoring data to address these gaps.

Conclusions

This study summarized the clinical trials on drug interactions in China. As the number of innovative drugs continues to grow and the guidelines on drug registration and marketing are updated, clinical DDI trials have gradually increased in recent years. The design of new clinical DDI trials is based on the guidelines; however, the duration of interacting drug administration still varies widely.

Optimizing protocol designs can shorten the implementation period of clinical trials and reduce the costs of drug marketing.

Abbreviations

DDI	Drug-drug interaction
CDE	Center for Drug Evaluation
FDA	The US Food and Drug Administration
EMA	European Medicines Agency
PMDA	Pharmaceuticals and Medical Devices Agency
ICH	The International Conference on Harmonization
INDs	Investigational new drugs
CYPs	Cytochrome P450s
P-gp	P-glycoprotein
CPLG	The Clinical Pharmacology Leadership Group
PBPK	Physiologically based pharmacokinetic

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Data availability
No datasets were generated or analysed during the current study.

Declarations

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Not applicable.

Consent for publication
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Competing interests
The authors declare no competing interests.

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