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Drug Safety Evaluation in China

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Abstract

Purpose of Review This review aimed to introduce the regulations management and current situations of drug safety evaluation in China.

Recent Findings The nationwide implementation of good laboratory practice and good clinical practice guarantees the quality of pre-marketing drug safety evaluation. In recent years, post-marketing drug safety monitoring is changing from passive mode to the combination of active and passive monitoring. A national adverse drug reaction monitoring sentinel alliance has been created to actively identify, report, and evaluate adverse reactions, with more than 1.4 million cases reported in 2017. But the quality of the reports is not optimal, with few reports from drug manufacturers, low rate of severe reports, and trend of lag reporting.

Summary Drug safety evaluation in China is transitioning from passive monitoring to a combination mode. Drug pharmacovigilance is a powerful tool for active monitoring, but participation by drug manufacturers would be essential to an effective drug safety evaluation system.

Keywords Drug safety evaluation · China · Good laboratory practice · Good clinical practice · Adverse drug reaction · Traditional Chinese medicine

Introduction

Drug is the basis for survival and development of human being. Drug safety, effectiveness, and quality controllability are the central working contents of national drug regulators, among which drug safety is especially important for public health and social stability, thus guaranteeing that safety is one of the vital duties of the government of each country.

The evaluation of drug safety includes both non-clinical and clinical components. Non-clinical safety evaluation contains all the tests done by an experiment system in the lab for the purpose of evaluating drug safety, mainly including safety pharmacological test, single and repetitive dose toxicity tests, reproductive toxicity test, carcinogenicity test, and toxicokinetic test. Clinical safety evaluation includes drug safety evaluation in clinical trials and post-marketing adverse drug reaction (ADR) monitoring [1]. In this review, we introduced the laws and regulations management for safety evaluation in different stages (Fig. 1) and analyzed current situation and existing problems in China.

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Non-clinical Safety Evaluation

Laws and Regulations Management

Good laboratory practice (GLP) is the main guideline which directs the drug non-clinical safety evaluation in China. It contains the basic principles that must be followed in each part of non-clinical studies. In 1972–1973, GLP was first implemented in Denmark and New Zealand. In 1976, Food and Drug Administration (FDA) of the USA also issued and implemented GLP [2]. In 1981, Organization for Economic Cooperation and Development (OECD) developed its principles of GLP, and the OECD member countries reached a consensus on Mutual Acceptance of Safety Data (MAD), deciding that data generated in the testing of chemicals in an

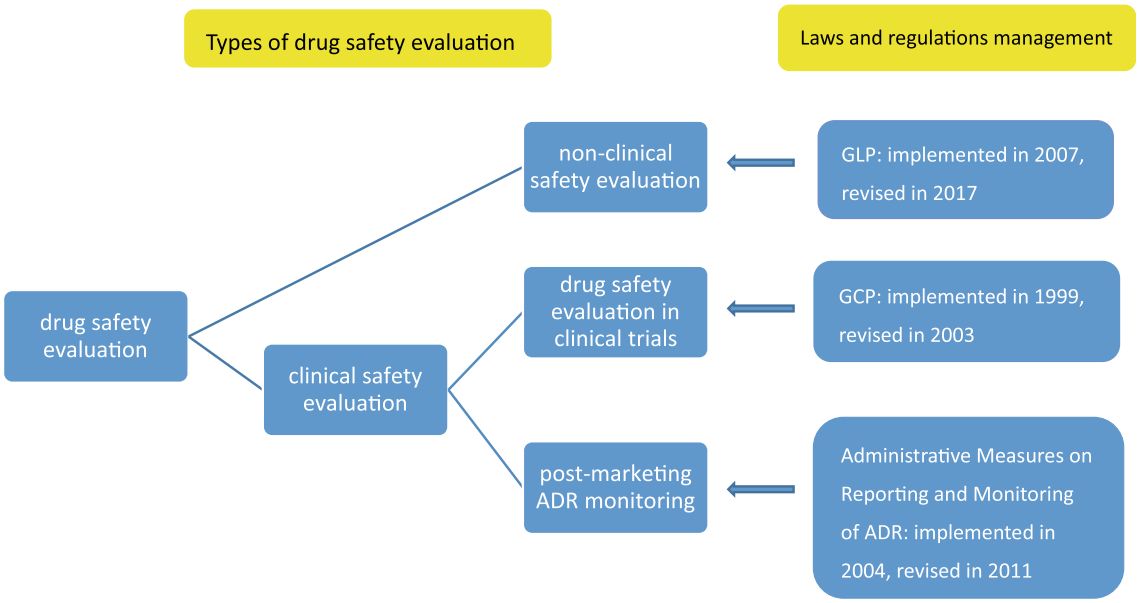

Fig. 1 The laws and regulations management for drug safety evaluation in China. GLP, good laboratory practice; GCP, good clinical practice; ADR, adverse drug reaction

OECD member country in accordance with OECD Test Guidelines and OECD principles of GLP should be accepted in other member countries, in order to avoid repeated tests and improve economic efficiency [3]. This made GLP become the international norm generally followed by the labs conducting new drug safety studies all around the world.

The GLP in China started late. Before 1985, new drug application in China required toxicology test data, and the Drug Administration Law of the People's Republic of China [4] implemented in 1985 provided detailed demands on toxicological evaluation. The conception of GLP had not been introduced to China until the end of 1980s [5]. The first formal draft of GLP was completed in September 1993. On December 11, 1993, good laboratory practice (proposed regulation) was issued officially by the State Scientific and Technological Commission of China [6]. Thereafter, China Food and Drug Administration (CFDA) summarized the practical experiences in the trial implementation, consulting the principles of GLP in developed countries and World Health Organization and revised GLP three times. In 2007, GLP was officially implemented in China [7] and is forcibly executed in all the non-clinical safety studies [8]. In 2017, CFDA revised GLP again and issued a new edition, with the number of articles increased from 45 to 50. The chapter of "Supervision and inspection" in the old edition was deleted, and chapters of "Nomenclature and relevant definitions," "Experiment system," "Quality guarantee," and "Entrusting party" were added in the new version. With the supplementation and detailing of the old contents, the new version of GLP was able to meet the growing needs of industry development and management [9].

Current Situation of Non-clinical Safety Studies in China

In recent twenty years, the implementation of GLP in China has achieved initial success, with the weak links including maintaining of equipment, analysis of test samples, and personnel training and management being paid increasing attentions. Since the first batch of four research institutions passed the pilot assessment in accordance with GLP of China in 2003, in total 70 research institutions conducting drug safety studies have acquired the certification of GLP from CFDA till June 2019 [10].

In the aspect of MAD of non-clinical studies, China was officially accepted as an OECD-GLP observer in 2005 and planned to apply for participating in the MAD system [11]. In recent years, the devices and technology in some research institutions have reached or approached advanced international standards. Several institutions including National Institutes for Food and Drug Control have successfully passed the GLP tests given by the FDA of USA, and some have started to undertake or have fulfilled the overseas commissions of drug safety evaluation. Until the end of 2017, 22 institutions in China had acquired or constantly possessed the certification of OECD-GLP [12].

Drug Safety Evaluation in Clinical Trials

Regulatory Management

China held a good clinical practice (GCP) seminar in 1994 and drafted a corresponding guidance document in 1995. GCP guidelines of China for clinical trials of new drugs were officially issued and implemented in 1999 [13]. The Drug Administration Law of 2001 clarified that implementation of good clinical practices in drug clinical trials was mandatory [4]. The State Council revised and issued a new edition of GCP in 2003, adding a detailed requirement of ADR monitoring [14].

Current Situation of Safety Evaluation in Clinical Trials

Most international and joint capital pharmaceutical companies and more and more Chinese companies have implemented clinical trial regimens according to the GCP requirements, as well as standardizing operating procedures and performing ethical reviews of proposed trials [15]. Widespread implementation of GCP in China is designed to ensure the quality of drug safety evaluation during clinical trials [16].

Post-marketing Drug Safety Evaluation

Importance of Post-marketing ADR Monitoring

Post-marketing surveillance plays an important role in improving drug efficacy and safety [17]. According to the Drug Administration Law of the People's Republic of China [4], drugs approved for clinical use are under surveillance for 5 years to monitor the incidence of ADRs. The types and occurrence rate of adverse reactions in pre-marketing clinical trial might be significantly different from those in post-marketing monitoring [18].

History of ADR Monitoring System in China

1980s ADR monitoring was initiated in 1988 in China, and the Center for Monitoring Adverse Drug Reactions of the Ministry of Health was established in 1989 and gradually included locations in Beijing, Shanghai, Hubei, Hunan, Zhejiang, Tianjin, Liaoning, Hebei, and Fujian et al. [19].

1990s China joined the Drug Monitoring Program of the World Health Organization in 1998. The CFDA and the Ministry of Health issued the Measures for Monitoring and Administration of Adverse Drug Reactions (proposed regulation) in 1999, providing the regulation guarantee for ADR monitoring in China [19].

2000s A national ADR information reporting system and ADR case reporting and notification system were established in 2001 [20••]. In 2004, the Ministry of Health and CFDA officially issued Administrative Measures on Reporting and Monitoring of ADR, claiming that ADR monitoring centers at each level should intensify supervision and improve the information system to realize convenient online reporting and rapid feedback [21].

2010s In 2012, the 12th Five-Year Plan for Drug Safety concluded that drug safety monitoring should be improved and that evaluation and warnings regarding ADRs should be strengthened [22]. Currently, post-marketing drug safety monitoring is mainly passive and based on ADR reports, resulting in under-reporting, missing and non-standard data, unclear descriptions of the reactions, or only focusing on severe drug safety events. Active monitoring would collect longitudinal observations, facilitating early detection and the recognition of non-severe or long-latency drug safety events [23]. The combination of active and passive monitoring will improve drug safety by highlighting adverse events requiring assessment of the continued presence of the drug on the market.

The increased use of electronic medical records provides a solid basis for active drug safety monitoring [24]. To harness electronic data in active monitoring, the State Adverse Drug Reaction Monitoring Center initiated the establishment of ADR monitoring sentinels in selected hospitals and created national ADR monitoring sentinel alliance. Sentinel hospitals are medical institutions certificated by national ADR monitoring center which can monitor ADR and re-evaluate related drugs through Chinese hospital pharmacovigilance system (CHPS) [25], which is a multifunctional information system assisting monitoring sites to identify, report, and evaluate ADR [26]. In the 13th five-year plan period, the target number of ADR monitoring sentinel hospitals in China is 300 [27].

In 2011, the Ministry of Health revised the Administrative Measures on Reporting and Monitoring of ADR [28], emphasizing the responsibility that a drug manufacturing enterprise should take in post-marketing ADR monitoring as the first person responsible for drug safety. The revised measures required regular analysis and evaluation of ADR reports collected and active research on drug safety from manufacturers [28, 29]. In 2018, CFDA issued the Announcement on Direct Reporting of Adverse Reactions by Drug Marketing License Holders, stressing the direct report of adverse reactions to the national ADR system by the manufacturers [30••].

Current Situation and Problems of ADR Monitoring in China

The national ADR monitoring system collects spontaneous case reports from drug manufacturers, medical organizations, and drug surveillance entities [31]. ADR monitoring centers

have been established in 31 provinces, the Xinjiang Uyghur Autonomous Region, and the armed forces [20••]. The number of registered adverse reaction monitoring network users has been over 340,000 [20••, 32]. Between 1999 and 2017, national network for monitoring ADRs received about 12,182,000 ADR reports, and around 1,429,000 of these reports were received (1068 reports/1,000,000 people) in 2017 [32, 33]. In 2003, the reports among 1,000,000 people was lower than 30 [34], so this number increased by more than 30 folds in 15 years. Table 1 summarized the characteristics of national annual reports of adverse drug reactions monitoring in China from 2012 to 2017 [32, 35–39].

Although the total number of ADR reports is large, the quality of the reports is not optimal. The reasons are as follows:

1) The source of the reports is typically medical organizations, and reports from drug manufacturers are relatively few. Hospitals accounted for 75%, 78%, and 82% of reports filed in 2012, 2013, and 2014, respectively, and only 1–2% of ADR reports were filed by drug manufacturers [40–43]. Besides, the proportion of new and severe cases reported by manufacturers is also much lower than the average level in China [44]. Most pharmaceutical companies do not have adequate systems for monitoring ADRs, owing to poor awareness of corporate responsibility, lack of initiative or incentive, and no infrastructure for collecting, verifying, and reporting ADRs [45, 46]. Regulatory oversight of drug manufacturers has recently been strengthened, aiming to increase their subjective initiative and making them become a new force or even the main force of pharmacovigilance system.
2) The rate of reporting new and severe ADRs is low. In the total 1, 317, 000 reports received in 2012, new and severe ADR reports only accounted for 22.1% [36]. The rate higher than 30% predicts good quality of whole ADR data in a country. However, this rate just reached 29.6% in China until 2016 [47], indicating that the quality of ADR monitoring in China still has a gap with that of developed countries. Increasing the number of sentinel surveillance hospitals and continuous improvement of pharmacovigilance, along with improved corporate action, should improve the quality of ADR data.
3) Lag and centralized reporting is a problem. The analysis of ADR data in Haidian District, Beijing, indicated that 10–15% of the reports showed a trend of lag and centralized reporting [48]. In ADR reports of the Autonomous Area of the Miao Buyi Ethnic Group in 2015, the percentage of overdue reports was 20.13% [49]. The possible reasons include: monitoring staff may be insufficient and often work part-time; awareness of reporting ADRs in a timely manner may not be high in hospitals; and monitoring work of drug safety in some institutions was not enrolled in the performance evaluation system resulting in lack of incentive. Thus, the number of monitoring staff should be increased, requiring training of special knowledge of ADRs. Also the work level of ADR monitoring should be involved in the performance appraisal system of hospitals, in order to guarantee effective pharmacovigilance.

Safety Evaluation of Traditional Chinese Medicine Treatments

Characteristics of TCM Treatment Adverse Reactions

The incidence of traditional Chinese medicine (TCM) treatment adverse reactions is a matter of great concern, and reports of adverse events have increased in recent decades. According to the literature, a total of 6061 cases were reported in 110 medical journals on TCM treatment poisoning and adverse reactions between1915 and 1994. If the data was

Table 1 The characteristics of national annual reports of adverse drug reactions monitoring in China from 2012 to 2017

Year	Total number of annual reports (million)	Proportion of new cases and severe cases (%)	Proportion of cases caused by chemicals (%)	Proportion of cases caused by traditional Chinese medicine treatments (%)	Proportion of cases caused by biologics (%)	Reported by medical institutions (%)	Reported by drug manufacturing enterprises (%)	Reported by drug managing enterprises (%)	Other sources (%)
2012	1.20	20.0	81.6	17.1	1.3	74.8	24.4		0.8
2013	1.32	22.1	81.3	17.3	1.4	78.4	1.4	19.6	0.6
2014	1.33	25.7	81.2	17.3	1.5	82.2	1.4	16.0	0.4
2015	1.40	28.2	81.2	17.3	1.5	82.2	1.4	16.0	0.4
2016	1.43	29.6	81.5	16.9	1.6	85.6	1.4	12.8	0.2
2017	1.43	30.3	82.8	16.1	1.1	88.0	1.8	9.9	0.3

divided based on a timeline, there were only 26 cases before 1950s, 147 in 1960s, 398 in 1970s, 2217 in 1980s, and 3273 between1991 and1994, showing a sharp increasing trend [50]. As indicated in the Chinese annual report of adverse drug reaction monitoring of 2017, the number of suspect cases caused by drugs was 1,571,000, with TCM treatments as the cause accounting for 16.1%. The number of reports for severe ADRs in 2017 was 161,000, and 10.6% of them could be attributed to TCM treatments, doubling the proportion in 2016 [32]. It is worth emphasizing that TCM injections appear to cause more adverse reactions than other forms of dosing in clinic, accounting for approximately 54.0% of ADRs associated with TCM treatments and 85.1% of severe reactions, as suggested in the national monitoring report of 2017 [32].

The safety evaluation principle of new TCM treatments is similar to that of assessing chemical drugs. However, TCM treatments still present unique challenges, such as unknown compound formulation, multiple effect pathways and targets, untested dose-response relationships [51], uncharacterized mechanism of action, unclear effective components or toxic components, and no defined pharmacokinetics and pharmacodynamics [52]. Thus, safety evaluation of TCM treatments requires non-clinical experiments, clinical trials, and ADR monitoring directing at their particularity.

Current Situation of TCM Safety Evaluation

1) Non-clinical safety evaluation

In 1992, the Ministry of Health and Drug Administration issued the Guide for the Research of New TCM Treatments. In 2005, CFDA issued multiple specific guidelines on non-clinical safety studies of TCM treatments and other natural medicine. These technical requirements are similar to those of the FDA and the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) [53].

With the advancement of modern science, the research technology of TCM treatment toxicity has also developed rapidly, changing from simple acute and long-term toxicity tests to serum pharmacology, toxicokinetics [54], molecular toxicology, and imaging toxicology. System biology is especially suitable for the analysis of complicated components and multiple action targets of TCM treatments [55–57], including genome, transcriptome, proteome [58], and metabolome [59].

2) Clinical safety evaluation

As to the management of clinical trials, CFDA issued General Principles of Clinical Research on New TCM Treatments in 2015 [60], proposing appropriate planning and clinical trial design and detailed requirements for exploratory research, efficacy index design, confirmation, and evaluation, along with specific indicators and standards of safety [61].

In the aspect of post-marketing safety evaluation, the Chinese government especially focuses on guaranteeing the safety of TCM injections. CFDA issued Notice on the Issuance of 7 Technical Guidelines including re-evaluation of TCM injection safety and evaluation of production technology and conducted a series of safety re-evaluation on TCM injections. In 2009, Shuanghuanglian injection and Shenmai injection were selected as the first batch of products for re-evaluation. In 2010, Houttuynia injection and Yujin injection were the second batch as the key work for re-evaluation of TCM injections safety [62]. The National Insurance Directory printed and distributed by the Ministry of Human Resources and Social Security in 2017 indicated that 26 TCM injections (such as Xiyanping injection) could only be used in qualified medical institutions [30••].

Conclusions

In summary, drug safety evaluation in China is transitioning from passive monitoring to a combination of active and passive surveillance. Drug pharmacovigilance is a powerful tool for active monitoring, but participation by drug manufacturers would be essential to an effective drug safety evaluation system.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights This article does not contain any studies with human or animal subjects performed by any of the authors.

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