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INVITED REVIEW

Pharmacovigilance in China: Evolution and future challenges

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Drug-related adverse reactions are among the main reasons for harm to patients under care worldwide and even their deaths. The pharmacovigilance system has been proven to be an effective method of avoiding or alleviating such adverse events. In 2019, after two decades of implementation of the drug-related adverse reaction reporting system, China formally implemented a pharmacovigilance system with the Pharmacovigilance Quality Management Standards and a series of supporting technical documents created to improve the safety of medication given to patients. China's pharmacovigilance system has faced many problems and challenges during its implementation. This spontaneous reporting system is the main source of data for China's medication vigilance activities, but it has not provided sufficiently powerful evidence for regulatory decision-making. In conformity with the health-centred drug regulatory concept, the Chinese government has accelerated the speed of examination and approval of urgently needed clinical drugs and orphan drugs along with the requirement to improve the safety supervision of these drugs after their listing. China's marketing authorization holders (MAHs) must strengthen their pharmacovigilance capabilities as the primary responsible departments for drug safety. Chinese medical schools generally lack professional courses on pharmacovigilance. The regulatory authorities have recognized such problems and have made efforts to improve the professional capacity of pharmacovigilance personnel and to strengthen cooperation with stakeholders through the implementation of an action plan of medication surveillance and the establishment of a patient-based adverse events reporting system and active surveillance systems, which will help China bridge the gap to bring its pharmacovigilance practice up to standards.

KEYWORDS

China, current situation, perspective, pharmacovigilance

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1 | INTRODUCTION

The Drug Administration Law of the People's Republic of China (2019 revision), promulgated on August 26, 2019, establishes the legal status of the pharmacovigilance system in China.[1] Article 12 stipulates that "The state shall establish a pharmacovigilance system to monitor, identify, evaluate and control adverse drug reactions (ADRs) and other harmful reactions related to drug use." This occurred 7 years after 2012, when the EU released their Good Pharmacovigilance Practice guidelines with an important update of the former EU regulatory framework,[2] and 17 years after the World health Organization (WHO) published its Importance of Pharmacovigilance document in 2002.[3]

Pharmacovigilance is centred on safety management throughout the entire life cycle of a medication. Medicinal products involve risks at all stages, from pre-approval clinical development to product registration, post-approval production, distribution, and clinical use and supervision, which may be rooted in the inherent risks of a drug or related to human factors, such as product quality defects, irrational prescription, nonappropriate use, and so forth. All of these factors have potential impacts on the health of patients. The purpose of establishing a pharmacovigilance system is to identify harmful drug-related reactions throughout the life cycle of the medicine in a timely fashion so that risk minimization measures can be issued. Spontaneous reports of ADRs have a certain value for the identification of potential safety signals,[4–9] but there are obvious limitations as well, such as serious underreporting,[10,11] poor quality of reports,[12] inability to quantify risk accurately and the unknowable number of the exposed population.[13,14] The inadequacy of the ADR monitoring system has led many countries to implement pharmacovigilance systems to enhance their risk management capacity. China also formally implemented a pharmacovigilance system in December 2019.[1] On May 13, 2021, the National Medical Products Administration (NMPA) promulgated Good Pharmacovigilance Practice, a milestone in the history of pharmacovigilance in China. However, China still faces many problems and challenges in reaching its ideal level of pharmacovigilance practice.[15]

2 | ORIGIN AND DEVELOPMENT OF PHARMACOVIGILANCE IN CHINA

2.1 | Understanding of drug safety among ancient Chinese scholars

The record of drug safety in China can be traced back thousands of years. The earliest medical classic in China, the Inner Canon of the Yellow Emperor (compiled between 800 and 200 BCE), classified medicines as toxic or nontoxic.[16,17] Shennong's Classic of Material Medical (compiled between 25 and 220 CE) divides traditional Chinese medicine (TCM) into the grades upper, middle and lower,[18] where most lower-grade drugs are considered toxic and should not be used over the long term. If toxic drugs are used in treatment, the lowest dose should be used first, and the drug should be discontinued or traded for an alternative medicine when the patient's condition improves.[17] In addition, many ancient Chinese medical texts describe processing and collocation with other drugs to reduce toxicity.[18,19]

2.2 | Pilot project of ADRs monitoring

In the 1950s, the Ministry of Health of China collected reports of adverse reactions to penicillin, including penicillin-induced anaphylactic shock and other serious adverse reactions.[20] In January 1988, the Ministry of Health instructed 10 hospitals in Beijing, Shanghai and other places to carry out a pilot project on ADR monitoring.[21] In 1994, 66 hospitals in 26 provinces of China were the first batch of key hospitals to be assigned the role of monitoring ADRs.[22]

2.3 | Implementation of the ADR reporting system

In 1999, the second year after China joined the World Health Organization's International Drug Monitoring Cooperation Program,[23] the National Medical Products Administration (NMPA) promulgated the Measures for Monitoring and Management of ADRs (for Trial Implementation).[24] The National Drug Adverse Reaction Monitoring Center was also officially established in the same year. Article 71 of the Drug Administration Law of the People's Republic of China (2001 revision), promulgated on February 28, 2001, stipulates the following: "The state implements a reporting system for ADRs".[25] The legal system of China's drug adverse reaction reporting system and the national drug adverse reaction monitoring network have been gradually improved.

2.4 | Exploration of the pharmacovigilance system

On September 30, 2018, the NMPA issued its Announcement on Direct Reporting of Adverse Reactions by Marketing Authorization Holders (No. 66 of 2018),[26] requiring marketing authorization holders (MAHs) to immediately report observed or confirmed ADRs through the China Adverse Drug Reaction Monitoring System (CADRMS), in accordance with the principle of reporting on suspicion. The scope of the report includes all harmful reactions that occur during drug use that are unrelated to the purpose of the medication and whose origin in the medication cannot be ruled out. These reactions include those caused by quality defects in the drugs and off-label use or overdose use.[26] This is very similar to the WHO's definition of pharmacovigilance,[3] although the previously stipulated reporting scope in China regarded "harmful reactions that are unrelated to the purpose of medication under rational guidance and dosage of qualified drugs".[27] This change demonstrates the attempt to change the ADR reporting system to the pharmacovigilance system.

TABLE 1 China's pharmacovigilance related laws and regulations

Type	Topic	Release/revision date
Laws	Vaccine administration law of the People's Republic of China	2 July 2017
	Drug administration law of the People's Republic of China	27 August 2019
Administrative regulations	Regulation on the control of narcotic drugs and psychotropic drugs	3 August 2005
	Regulations for the implementation of the drug administration law of the People's Republic of China	1 June 2016
	Regulations on protection of traditional Chinese medicines	30 September 2018
Departmental regulations	Provisions for drug package insert and labels	15 March 2006
	Provisions for drug recall	10 December 2007
	Provisions for adverse drug reaction reporting and monitoring	4 May 2011
	Provisions for drug registration	3 March 2020
	Measures for the supervision and management of drug production	3 March 2020
	Provisions for the change management of post-approval drugs	13 January 2021
Normative documents and others	National guideline for the surveillance of adverse events following immunization	3 June 2010
	Good manufacturing practice for drugs	17 January 2011
	Guidance for good clinical practice for vaccine (for trial implementation)	31 October 2013
	Measures for the reporting of serious adverse events in vaccine clinical trials (for trial implementation)	17 January 2014
	Inspection guidance for reporting adverse drug reactions and monitoring (for trial implementation)	2 July 2015
	Good supply practice for pharmaceutical products	20 July 2016
	Good laboratory practice	2 August 2017
	NMPA's announcement on directly reporting adverse drug reactions by MAHs	10 October 2018
	Guidance for individual case safety reports E2B (R3) regional specifications	22 November 2019
	Good clinical practice	26 April 2020
	NMPA's opinions on further strengthening the construction of the capability of adverse drug reaction monitoring and evaluation system	30 July 2020
	Implementation opinions of the General Office of the State Council on comprehensively strengthening the capacity building of regulatory supervision on medicinal product	10 May 2021
	Good pharmacovigilance practice	13 May 2021
	Measures for the administration of drug inspection (for trial implementation)	28 May 2021

TABLE 1 (Continued)

Type	Topic	Release/revision date
Guidelines, post-marketing	Guidance for preparation of drug periodic safety update report	6 September 2012
	Guidance for vaccine manufacturers reporting adverse events	26 July 2013
	Guideline for the collection and reporting of adverse drug reactions	19 December 2018
	Guideline for the evaluation of clinical safety literature for post-marketing medicine (for trial implementation)	23 May 2019
	Guidance on preparation of the pharmacovigilance annual report of marketing authorization holders (for trial implementation)	29 November 2019
	Guideline for preparation of pharmacovigilance delegation agreements (for trial implementation)	4 June 2020
Guidelines, clinical trials/other	Standards and procedures for expedited reporting of safety data during clinical trials	27 April 2018
	E2B (R2): Technical guidance for safety data transmission and ICSR reporting	30 July 2018
	Requirements on format and content of risk management plan of anti-tumor drugs for marketing authorization application	13 September 2018
	Technical guidelines on clinical changes for marketed chemical drugs and biological products	10 February 2020
	Guideline for safety information evaluation and management during clinical trials (trial implementation)	1 July 2020
	Guideline on management of development safety update report (for trial implementation)	1 July 2020
	Technical guideline for the preparation of safety summary for the new drug application of innovative anti-tumor products	31 December 2020

Note: Regulations related to medical devices are not listed in the table.

2.5 | Establishment of China's pharmacovigilance system

2.5.1 | Pharmacovigilance-related laws and regulations

A wide range of laws, administrative regulations, departmental provisions and normative guidelines on pharmacovigilance exist in China. The relevant laws are those enacted by the Standing Committee of the National People's Congress, such as the Drug Administration Law of the People's Republic of China (2019 Revision), administrative regulations are promulgated by the State Council, such as the Regulations on the Protection of Traditional Chinese Medicines, and departmental provisions and normative guidelines are formulated by the NMPA, such as the Regulation of Pharmacovigilance Management. In addition, technical departments affiliated with the NMPA, such as the Center for Drug Re-evaluation (CDR) and the Center for Drug Evaluation (CDE), have developed technical documents to guide pharmacovigilance (for some major pharmacovigilance (PV)-related laws and regulations see Table 1).

2.5.2 | Good pharmacovigilance practice

In May 2021, NMPA issued the Good Pharmacovigilance Practice (GVP) guidelines.[28] The GVP considers the requirements of the International Council for Harmonization of Technical Requirements for Registration for Pharmaceuticals for Human Use (ICH) Guidelines, including the scope, time limits and information source of adverse

reaction reporting, and is basically in line with ICH technical requirements and standards. At the same time, it draws on the mature experience of international organizations and other countries, such as the technical requirements of the Council for International Organizations of Medical Scientific (CIOMS) for signal detection, the EU pharmacovigilance system and its master files and relevant requirements, and the requirements of Japan and the EU for strengthening passive monitoring.[29] China's GVP has nine chapters and 134 articles, all of which are applicable to MAH and Drug Registration Applicants/Sponsors, with the approval to carry out clinical drug trials in China, as a guidance document for them to establish PV system and conduct PV activities.

2.5.3 | Pharmacovigilance during clinical trials

The Clinical Trials Management Office, which is subordinated to CDE, is specifically responsible for the reception, analysis and evaluation of suspected and unexpected serious adverse reactions (SUSAR) during clinical trials, as well as development safety update reports (DSURs) during the research and development of relevant drugs.[30] Following the guidelines of ICH E2A, E2B and E2F, among others, CDE has formulated and published a series of technical standards and normative documents based on the actual situation in China and constructed an electronic reporting system for SUSAR cases during clinical trials. CDE began to receive SUSAR reports from drug registration sponsors on May 1, 2018. On April 26, 2019, CDE opened the DSUR submission channel on its official website to receive DSUR reports from drug registration sponsors.[31] In 2020, overall 1775 copies of DSUR reports were submitted to CDE by the sponsors.

Based on the SUSAR case report, DSUR analyses and evaluations, and the evaluation of the risk management information submitted by the registration sponsors, CDE will issue a Notice on Risk Control of Clinical Trial, Notice on Suspension of Clinical Trials, Notice on Termination of Clinical Trials, and other relevant documents, and it will take corresponding supervision measures to better protect the safety of the subjects. In 2020, the CDE issued notifications for 18 clinical trials of medicinal products,[32]which never happened before and is significant for Chinese pharmacovigilance.

2.5.4 | Post-approval pharmacovigilance activities

China's drug adverse reaction monitoring network is divided into four levels, including the National Center for Drug Re-evaluation (CDR), 34 provincial drug adverse reaction monitoring centers, and hundreds of municipal and county-level institutions responsible for adverse drug reaction monitoring.[33,34] These institutions monitor and evaluate medical device-related adverse events, cosmetic adverse reactions and drug abuse, in addition to adverse drug reactions.[35] The role of China's adverse drug reaction monitoring agencies has gradually been shifted to pharmacovigilance management. In May 2019, China's first municipal pharmacovigilance institute was established in Shenzhen, followed by institutions in Inner Mongolia, Shanxi, Hebei, Linyi, and other districts and cities, based on the foundation of the existing CADRMS.

China has a nationwide CADRMS system. Over the past 20 years, the performance and functionality of CADRMS systems have gradually improved, and the number of ADR reports has also rapidly increased (Figure 1). At the beginning of the century, Chinese doctors needed to fill out paper ADR report forms. After 2003, CDR released stand-alone ADR monitoring report software, which allows ADRs to be reported by emails, and completed the construction of online

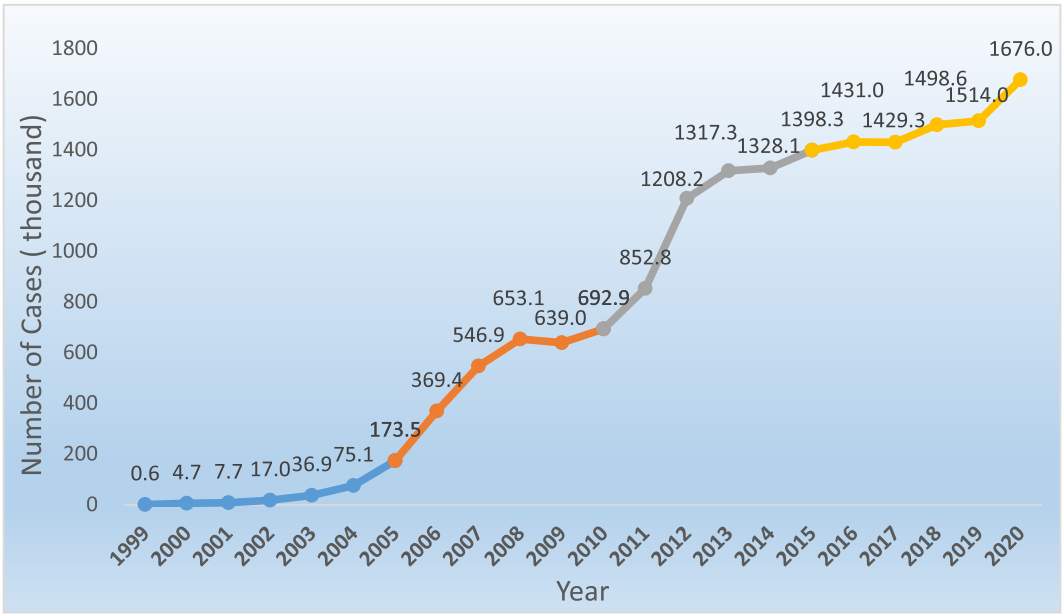

FIGURE 1 Spontaneous reporting on adverse drug reactions in China

CADRMS between 2010 and 2012.[36] At present, CADRMS incorporates a direct reporting system for ADRs for MAHs, a reporting system for ADRs for medical institutions and enterprises, a monitoring system for medical device-related adverse events, a monitoring system for adverse cosmetic reactions and a reporting system for drug abuse.[37] In addition, CADRMS has functional modules for data analyses, signal detection, potential alert management and periodic safety update report management. In recent years, CDR has explored and constructed an active monitoring system for drug safety based on electronic medical records from medical institutions.[38]

CADRMS received a total of 1.676 million ADR reports in 2020. Among these, 506 000 (30.2%) were reports of new or serious ADRs.[39] The average number of reports per million population is an important indicator to evaluate the status of adverse-reaction monitoring. In 2020, the average number of reports per million people in China was 1251,[39] close to or at the level of many developed countries. The cumulative number of ADR reports received by CADRMS from 1999 to 2020 reached 16.9 million.[39] ADRs and risks related to intrinsic toxicity, quality defects and irrational use of drugs can be identified according to the detection signals based on these data.[40,41]

The source composition of ADR reports in China is quite different from that of ADRs in the United States, Japan, the United Kingdom, and other countries. In 2020, the majority of China's reports came from professionals (85.4%), with 3.9% from MAHs,[39] while reports from MAHs accounted for only 1.4% 5 years ago.[42] This shows that in recent years China's MAHs have made progress in improving its pharmacovigilance capacity. NMPA, making reference to the practices of other countries,[43,44] created provisions for entrusting the management of pharmacovigilance in the GVP and organized inspections to ensure that MAHs' pharmacovigilance is compliant with the applicable regulations. In addition, CDR feeds ADR report data back to MAH through CADRMS as an important data source for MAH to evaluate drug safety and identify potential risks.[26]

In 2010, the former Ministry of Health and the National Medical Products Administration jointly formulated the National Guideline for the Surveillance of Suspected Adverse Events following Immunization, which clearly defined the reporting requirements for Adverse Events Following Immunization (AEFI) of post-approval vaccines. In accordance with the guideline's requirements, responsible reporting units and reporters should report suspected AEFI to their county-level Center for Diseases Control and Prevention agency, where the recipients are located.[45] China has gradually established and improved its AEFI monitoring information management system. In 2008, the AEFI case reporting network was complete on a national level.[46] The AEFI Monitoring System was established by the Chinese Centers for Disease Control and Prevention, and it shares information with Drug Adverse Reaction Monitoring Agency.[47]

In 2019, 536 million doses of vaccines were injected, and 16 298 cases of abnormal reactions to vaccination were reported, with a total reporting rate of 3.04/100000 doses. In 2020, 553 million doses of vaccine were injected and 13 342 cases of abnormal reactions to vaccination were reported, with a total reported rate of 2.41/100000 doses. Compared with the expected incidence of abnormal vaccine reactions published by the World Health Organization, the reported incidence of abnormal vaccine reactions in China was acceptable.

2.5.5 | Pharmacovigilance communication

Effective communication with stakeholders is an important part of drug risk management. Regulatory agencies usually issue drug safety warnings to alert the public through public channels such as the National ADR Monitoring Annual Report, the Pharmacovigilance Newsletter[48] (with 220 issues to date), the ADRs Information Bulletins[49] (with 77 issues to date) and Announcements, or they alert MAHs of suspicious safety signals through internal meetings, official documents and correspondence through nonpublic channels. In addition, the NMPA solicits input from stakeholders in the development of pharmacovigilance regulations or in important decision-making processes.

MAHs usually offer drug safety information to healthcare professionals (HCPs), patients and the public with methods that include the distribution of DHCP letters, patient safety medication reminders, announcements and press release conferences.[28]

Medical institutions usually conduct education and publicity activities for patients, as well as publishing cartoons, videos and other materials through the internet or in new media to guide patients on the safe use of medication.

Relevant information is also shared via academic conferences. Risk communication is an important theme of some regular academic conferences, such as the Chinese Pharmacovigilance Conference, a conference on risk assessment and risk management of post-marketing drugs. Participants in these meetings include HCPs, regulatory personnel, pharmaceutical researchers, MAHs and other stakeholders.

2.5.6 | International cooperation in pharmacovigilance

China attaches great importance to communication and cooperation with the WHO, the Uppsala Monitoring Centre (UMC) and regulatory agencies in other countries in the field of pharmacovigilance.[35] The CDR sends experts to participate in relevant working groups or academic meetings of the International Council for Harmonization of Technical Requirements for Registration for Pharmaceuticals for Human Use (ICH), the CIOMS, the International Society of Pharmacovigilance and other institutions. Experts from the UMC, Food and Drug Administration (FDA), European Medicines Agency (EMA), Medicines and healthcare products regulatory agency (MHRA) and Pharmaceuticals and Medical Devices Agency (PMDA) also participate in many pharmacovigilance exchange activities held in China. China has been an important participant in the International ADR Surveillance Cooperation Program since 1998. During the 12-month period ending on June 30, 2020, 15% of ICSRs in VigiBase were provided by China, second only to the rate in the United States, at 36%[50] (Table 2).

TABLE 2 China's international cooperation in pharmacovigilance

Year	Content of collaboration
1998	Joined the international cooperation program for adverse drug reaction monitoring
2013	Joined the international medical device regulators forum
2017	Joined ICH as the 8th regulatory body member in the world
2018	Became a member of the ICH management committee
2019	CDR and UMC signed a draft on their intention to cooperate in the monitoring of adverse drug reactions
2020	CDR experts participate in the drafting of the CIOMS expert consensus "Drug-induced liver injury (DILI): Current status and future directions for drug development and post-approval setting."

3 | PROBLEMS AND COUNTERMEASURES

Pharmacovigilance focuses on all harmful reactions related to drug use, including ADRs, product quality defects, medication errors and lack of efficacy. The Chinese pharmacovigilance system covers the whole life cycle of a product, from pre-approval to post-marketing. The planning of pharmacovigilance throughout a product's life cycle is a basic principle of ICH E2E.[51] China has established a drug priority review and approval process, allowing more and more innovative drugs to be marketed in China after passing through a rapid review and approval channel, which may involve many potential unknown risks. The development of children's medicine cannot meet clinical needs. Potential off-label drug use may occur in children, and this risk should not be ignored.[52] Drug safety problems in the elderly should be addressed with increased attention, as China has begun to be an aging society, and adverse drug events related to the elder population have been increasing over the past 12 years.[39,53,54] In addition, TCM is in widespread use in China. Because of the quality of TCM and the complexity of its usage, the signal detection and risk evaluation methods of TCM need to be combined with the characteristics of TCM.[55] China faces many problems and challenges in achieving the ideal goal of good pharmacovigilance practices.[56]

Key measures for addressing these issues and challenges include obtaining high-quality data from multiple sources to assess product risks more comprehensively and scientifically, strengthening the application of new technologies in pharmacovigilance practices, improving the pharmacovigilance practice for TCM in response to the characteristics of TCM and strengthening cooperation among stakeholders.

3.1 | Access to high-quality data from multiple sources

Having higher-quality data will lead to more comprehensive and scientific risk assessment, and the generation of reliable scientific evidence for drug safety regulatory decisions. China will address this problem by improving its spontaneous reporting system, conducting active surveillance based on real-world data and establishing new channels for patient reporting.[35]

3.1.1 | Improvement of the spontaneous reporting system

The number of spontaneous ADR reports in China was 1.7 million in 2020,[39] lower than the United States' 2.218 million reports over the same period.[57] In terms of Chinese Mainland's large population of 1412 million,[58] and the annual diagnosis and treatment data for up to 7.7 billion people,[59] China is making an effort to increase the number of such spontaneous reports.

Chinese ADR report data come largely from professionals. However, HCPs are busy with a large number of patient consultations and often do not have enough time to collect PV data and complete the ADR report, which has more than 50 fillable fields. Additionally, there is a lack of specific standards or training to instruct HCPs to report ADRs.[60] All of these factors may lead to underreporting or affect the quality of ADR reports.[11]

CDR launched the pilot program of National Adverse Drug Reaction Monitoring Sentinel Hospital Construction in 2017, which may help address ADR underreporting or reporting quality issues.[61] The program is aimed at tertiary hospitals across the country, and hospitals identified as sentinel sites have installed the China Hospital Pharmacovigilance System (CHPS) module in their Hospital Information System (HIS) systems. The main function of this module is to automatically capture most of the information needed for the ADR report form from the hospital's HIS system, which will lead to significant time savings for HCPs completing ADR reports and reduce the omission of important information during the filing process.[62] By the end of 2020, CDR had completed the construction of 366 national drug adverse reaction monitoring sentinel hospitals.

3.1.2 | Active surveillance of drug safety based on real-world data

Bringing together a wealth of real-world data to build new pharmacovigilance systems, such as Sentinel in the United States, the Medical Information Database Network in Japan, and the Drug Safety and Effectiveness Network in Canada, has proven the possibility of successfully detecting and assessing safety signals and effectively enhancing pharmacovigilance capabilities.[63,64] In 2020, the number of people covered by basic medical insurance in China reached 1361 million, or 96.4% of the country's population.[65] During the same period, the total number of medical consultations in medical institutions in China reached about 7.7 billion and the number of hospital discharges reached 230 million.[59] These transactions generate a large amount of health insurance claims data and electronic medical records (EMRs). Active surveillance using these data will help improve drug risk detection and evaluation capabilities, and provide reliable evidence to support regulatory decision-making. In addition, real-world data can be

used to promote the development of children's medicines and to improve the safety of medicines for the elderly. All in all, pharmacoepidemiology is a huge part of pharmacovigilance.

Since 2017, CDR has carried out active monitoring and evaluation studies on drug safety based on electronic medical record data. More than 40 institutions, including medical institutions, medical colleges and universities, academic societies and so on, have formed collaborative groups and created the Interface Specification for Active Surveillance Platform (V1.0) and the key points of active monitoring (for trial implementation). More than 10 million electronic medical records were screened in nearly 100 million visits to create a big data platform for active drug safety monitoring. The risk that medicinal and biological products, such as statins, nonsteroidal anti-inflammatory drugs, contrast agents, antitumor drugs and COVID-19 treatments could induce liver injury, kidney injury, allergic reactions or neutropenia was evaluated, and the results of these evaluations were explored to support drug safety regulatory decisions.[38] In addition, the analysis of these data has produced some valuable information, such as Hepatitis B Virus (HBV) and Epstein-Barr virus (EBV) infection as the main cause of abnormal results of on liver function tests in hospitalized Chinese patients.[38]

Active surveillance also faces many challenges. First, ensuring that research meets ethical requirements and protecting patient data privacy are the main priorities. Second, hospital electronic data systems are often built by different vendors and feature interoperability problems between different data standards and systems.[66] Third, study subjects must meet certain requirements, the ADR must have identifiable characteristics or clear diagnostic criteria, and the drugs involved must have distinguishable identifications or coding. Finally, the sample size and data quality also need to research requirements, which requires that the clinical use of the drugs meets a certain scale and that the information required for the research is recorded in the data system. Over-the-counter drugs (OTCs) or drugs primarily used in outpatient clinics are often lacking records for analyses in hospital information systems and are generally not suitable for safety evaluation using EMR data.[67,68]

3.1.3 | Explore new channels for patient reporting

Patients who are directly exposed to the drugs, while they may not be able to describe ADRs professionally, they can provide more direct information on the occurrence of ADRs and its impact on their quality of life.[67] Patient reports are a useful complementary to the spontaneous reporting system, reducing the difficulty of monitoring the ADRs of OTCs.[68] Patient self-reports, when analysed in combination with ADR data reported by professionals, aid in the early detection of safety signals.[69,70]

Many countries have specific patient reporting systems (such as the FDA's MedWatch, the MHRA's Yellow Card Scheme, and so forth) to enable patients to report their self-observed suspected adverse events of medical products. There is currently no dedicated patient reporting system in China and patients report ADRs mainly through medical institutions, production enterprises or operating enterprises. This may be a reason why the proportion of individual patients reporting is less than 0.1%.[39] China has recognized the importance of patient reporting and is considering the establishment of a dedicated patient reporting system.[35] In addition, China's MAH and Contract Research Organizations (CRO) organizations also seek to use social media tools such as mobile apps and WeChat applets to collect patient reports, but attention should be paid to patient data privacy protection and ethical issues as well.[71]

3.2 | Strengthen the application of new technologies in pharmacovigilance practice

The WHO defines pharmacovigilance as "the science and activities related to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems." As a field related to public health, pharmacovigilance deserves sufficient research resources, and the application of advanced technology is critical to improving pharmacovigilance capabilities.[72,73]

Because spontaneous data reporting does not include the number of drug users as a whole or accurately quantify risks, data from other sources are needed to evaluate risk. For rare or very rare severe adverse reactions, with an incidence rate <1/1000, if the large number of medicinal product exposures in China are taken into account, a certain number of patients may still suffer serious injuries each year. Evaluations of severe adverse reactions that are rare or have a low incidence often require the compilation of patient data from tens of thousands or more cases. Analysis of such massive amounts of data requires the help of big data and artificial intelligence technology.[74–77]

Machine learning and other artificial intelligence methods have proven to be useful for ADR evaluation.[78] CDR has also carried out useful explorations in this regard. Statistical modelling and artificial intelligence technology have been used to assess the correlation between liver injury and drug use as well as the quality of MAH pharmacovigilance practices. However, machine learning and other AI methods can lead to errors or biases, resulting in serious consequences,[79] and the application of these new technologies should consider the corresponding management measures.[78]

NMPA has implemented the Chinese Drug Regulatory Scientific Action Plan to carry out regulatory scientific research in the fields of medicinal products, medical devices and cosmetics, and it prioritizes pharmacovigilance technology and methodological research as a key project.[80] CDR attaches great importance to the study of advanced technology and in the field of pharmacovigilance through the establishment of key laboratories for pharmacovigilance research and evaluation with Peking University Health Science Center and the Chinese Academy of Medical Sciences, the establishment of a pharmacovigilance research institute at Nanjing Medical University and Chongqing Medical University, and the establishment of the Center of Pharmacovigilance Information Technology and Data Science Innovation at Tsinghua University. Beyond that, NMPA has set up the Active Surveillance Collaboration Group on Drug Safety and built the

National Alliance platform for Drug Adverse Reaction Monitoring Sentinel Hospitals, along with taking other measures to continuously promote technological innovation in pharmacovigilance.

3.3 | Improving the pharmacovigilance practice of traditional Chinese medicine based on its characteristics

TCM has a long history of application in China. During the COVID-19 pandemic, Chinese medicine has also had unique therapeutic value.[81,82]

According to the 2020 statistical analysis report on the drug circulation industry released by the Ministry of Commerce of China, TCM accounted for 16.4% of whole market share, chemical drugs accounted for 71.5%, and medical equipment and other products accounted for 12.1%. During the same period, according to the national Annual Report on ADR monitoring released by the NMPA, the number of ADR reports suspected related to TCM accounted for 13.4% of the total spontaneous reports, cases suspected related to chemical drugs accounted for 83.0%, and cases suspected related to biological products and unclassified drugs accounted for 3.6% (Figure 2). The number of serious ADR cases suspected related to TCM accounted for 6.3% of the total serious ADR cases reported, cases suspected related to chemical drugs accounted for 90.3%, and cases suspected related to biological products and unclassified drugs accounted for 3.4%. The above data suggested that many TCM had quite low proportion of serious ADRs, but there were still some TCM that led to considerable serious ADR cases, so the timely detection and evaluation of the safety signals of TCMs is very important.[83]

At present, commonly used signal detection methods are based on the theory of nonequilibrium measurement, which identifies signals of concern (drug-event combinations) by looking for an unbalanced distribution of drug-event combinations.[84] These signal detection methods are based on the characteristics of chemical drugs with a single active ingredient and are not suitable for compound preparations (a small number of chemicals and the vast majority of TCMs). CDR has improved the signal detection method[85] and found that some safety signals deserve attention.[41,55] Pharmaco-epidemiology, metabolomics, high-intensity screening, computational chemistry and other methods are also widely used in the study of the suspected risk for TCM.[86] These studies have played an important role in risk prevention and control for some TCMs.[55]

For TCMs with risk signals, Chinese drug regulatory authorities usually use a variety of data and materials, including self-reported data and post-market clinical research data, to evaluate the safety of these drugs. According to the evaluation results, measures such as withdrawal from the market, suspension of sales, product recall, announcement of ADR information, modification of the safety information in the instruction manual and restriction of drug use were taken to control the risk of drugs, which is basically similar to the regulatory measures for chemical drugs. In addition, NMPA also formulated some technical documents specially for guiding the risk management of TCMs, such as the Technical Guidelines for Revising the Contents of Safety Information items in The Instructions of Marketed TCMs, which is currently in the stage of soliciting opinions. These technical documents will boost the effective management of TCMs.

TCMs often contain a variety of chemical components, and patients often use them in combination with other TCMs or chemical drugs. These drug components may lead to uncertain interactions, so

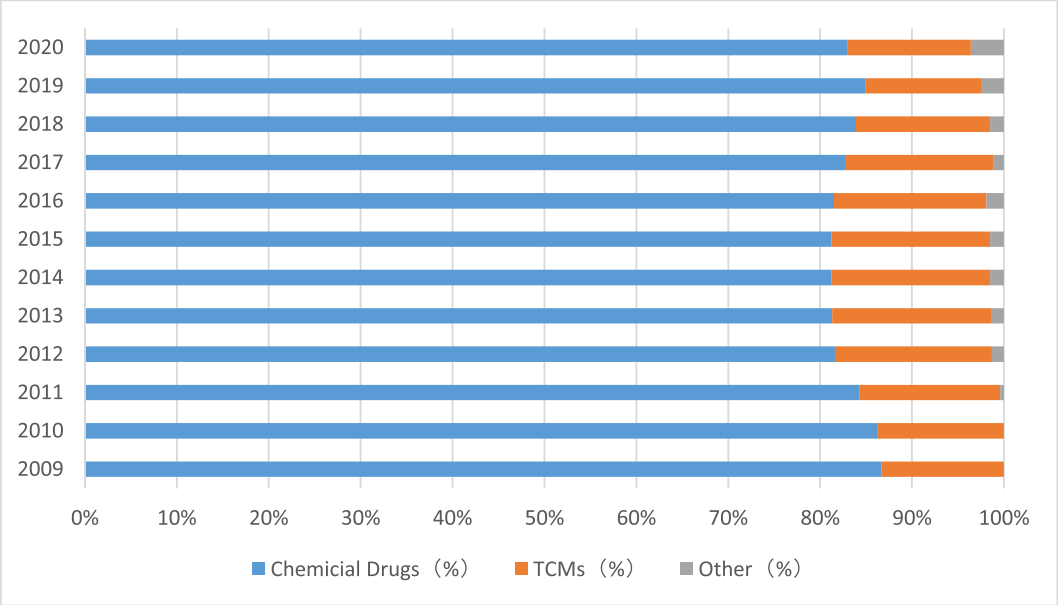

FIGURE 2 Proportions of suspected adverse reaction reports of different sorts of medicines. TCMs, traditional Chinese medicines

it is difficult to distinguish the exact component leading to ADRs. Chinese researchers have applied a variety of techniques, such as metabolomics, high-intentional screening and computational chemistry, to explore the potential risks of TCM.[86] The application of new technologies will help us to understand better the characteristics for the ADR occurrence and the genetic metabolic mechanisms that may be involved, so that we can develop more effective measures of risk management.[55]

Chinese scholars have also carried out extensive work in cooperation with their international counterparts in related fields, and Chinese scholars participated in CIMOS's 2020 International Consensus on Drug Liver Injury,[87] as well as sharing their latest research output on Causality assessment strategies and methods for TCM-induced liver injury in a chapter of the book *Liver Injury To Herbal and Dietary Supplements*.[88] The safety of TCMs is a global concern in the field of medication safety, so these collaborations are of great benefit to both sides.

3.4 | Strengthening stakeholder cooperation

Social co-governance is the basic principle of the regulation of drug administration regulation in China.[25] The WHO document The Importance of Pharmacovigilance states[3]: "A complex and vital relationship exists between a wide range of partners in the practice of drug safety monitoring. Sustained collaboration and commitment are vital if the future challenges in pharmacovigilance are to be met and the discipline is to continue to develop and flourish." Pharmacovigilance focuses on the risks of ADRs and other harms associated with drug use. Patients and HCPs, as key participants in drug treatment, are critical to identifying, assessing and preventing risks in drug use.[73] Such risks may stem from problems in product research, production or sales. The prevention and control of risks in drug use therefore requires the participation of other stakeholders. China's GVP requires MAHs and sponsors to strengthen their cooperation with medical institutions, pharmaceutical manufacturers, pharmaceutical enterprises, drug clinical trial institutions and scientific research institutes, industry associations, and other relevant parties to ensure the quality of pharmacovigilance activities.[28] At present, China is in a transition period from the CADRMS to a pharmacovigilance system, and the key to speed up this process lies in the extensive participation of stakeholders, which is crucial to achieving the goal of good pharmacovigilance practice.

4 | OUTLOOK

The implementation of the Chinese pharmacovigilance system will help advance the WHO's global goal of Medication Without Harm,[89] but it faces huge challenges. At present, the allocation of pharmacovigilance institutions and professionals is insufficient, and the technical research ability in related PV fields is relatively weak. Universities generally lack pharmacovigilance courses for undergraduate and postgraduate students. All of the above pose challenges to the implementation of pharmacovigilance in China.[90]

Chinese regulatory authorities and experts in the field of pharmacovigilance have recognized these problems and put forward a series of measures and plans to meet these challenges, including strengthening academic education and professional training in pharmacovigilance, as well as developing science popularization and education for the public on the safe use of medicines, building a standardized, structured and highly interoperable pharmacovigilance data-sharing platform, promoting the application of advanced technologies such as natural language processing, image recognition, multisource data fusion, intelligent decision-making analysis, and so on, building a sustainable collaborative model of proactive drug risk prevention and control with broad stakeholder participation,[35,91] and strengthening international cooperation as an aspect of pharmacovigilance. All these initiatives will help China move towards the ideal goal of good pharmacovigilance practices.

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COMPETING INTERESTS

The authors declare that they have no conflict of interest.

CONTRIBUTIONS

Conception and design: H.B.S., F.S. and X.H.X. Collection and assembly of data: H.B.S., X.J.P. and Z.X.L. Data analyses and interpretation: F.S. and Z.X.L. Manuscript writing and revision: all authors. Final approval of manuscript: all authors.

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