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LEADING ARTICLE

Pharmacovigilance in China: Current Situation, Successes and Challenges

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Abstract With the integration of the global pharmaceutical economy and the gradual transformation of the healthcare insurance system in China, the legislative framework for a comprehensive regulatory system monitoring the whole process including drug development, manufacture, distribution and use has been established by the China Food and Drug Administration (CFDA) to ensure the safety and effectiveness of medication use. China has established a relatively comprehensive pharmacovigilance system covering regulation, organisation and technology from 1989 to 2014. As of 2013, one national centre, 34 provincial centres and more than 400 municipal centres for adverse drug reaction (ADR) monitoring were included in the four-level pharmacovigilance network (national, provincial, municipal and county) with more than 200,000 grassroot organisation users. The China Adverse Drug Reaction Monitoring System (CADRMS) is an online spontaneous reporting system which connects the four-level pharmacovigilance network. By 2013, CADRMS had received over 6.6 million ADR case reports. After integrating and analysing pharmacovigilance data, the National Centre for ADR Monitoring (NCADRM) publishes medication safety information by releasing ADR bulletins, National ADR Annual Reports and International Pharmacovigilance Newsletters. The NCADRM also routinely provides CADRMS data feedback to manufacturers. The CFDA implemented risk management through several approaches, including arranging 'manufacturer communication meetings', modification of medication package

Key Points

A relatively comprehensive pharmacovigilance system has gradually developed in China since 1989

As of 2013, one national centre, 34 provincial centres and more than 400 municipal centres for adverse drug reaction (ADR) monitoring were included in the four-level pharmacovigilance network (national, provincial, municipal and county), with more than 200,000 grassroot organisation users in China

The China Adverse Drug Reaction Monitoring System (CADRMS) had received more than 6.6 million ADR case reports by 2013

To offset the limitations of the CADRMS, the 2011 new *Adverse Drug Reaction Reporting and Monitoring Provision* presented the concept of a 'Key Monitoring Scheme', which requires pharmaceutical manufacturers to conduct active surveillance within a requested monitoring period for specific newly launched domestic drugs, 5 years for newly imported drugs, as well as for other specific drugs with suspected important safety signals

Seamless information exchange with overseas regulatory authorities and organisations remains an area for improvement. Further development of the China pharmacovigilance system in terms of signal generation and education is also needed

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inserts, and restriction, suspension or withdrawal of marketing authorisations. Seamless information exchange with overseas regulatory authorities and organisations remains an area for improvement. Further development of the China pharmacovigilance system in terms of signal generation, post-marketing pharmacoepidemiology research and education is also needed.

1 Introduction

With the integration of the global pharmaceutical economy and the gradual transformation of the healthcare insurance system in China, the rapid development of the pharmaceutical industry in China has impacted the national economy and employment. Over the last few years, the China Food and Drug Administration (CFDA) has emphasised the importance of innovative drug development, safety surveillance and risk management. Simultaneously, a regulatory system covering the process of drug development, production, distribution and use of medicinal products has gradually been established to ensure the safety and effectiveness of medication use. The aim of this paper is to provide a brief introduction of the current situation, successes and challenges of pharmacovigilance in China.

2 The Healthcare System in China

China has a population of about 1.35 billion [1] over 9.6 million square kilometres. Although economic development has been progressive, the pace of change differs in urban and rural areas. China's healthcare system restructure was launched in the 1980s to meet the needs of a rapidly changing country. The basic healthcare system covers both urban and rural populations, and comprises traditional Chinese medicine (TCM) and Western medicine (WM). As of 2011, a basic healthcare insurance system was established, including the Employee Basic Medical Insurance, the Urban Residences Basic Medical Insurance and the New Rural Cooperative Medical Care System. This insurance system covers more than 1.3 billion people, up to 95 % of the total Chinese population. Two major improvements resulted from the launch of this system [2]. First, the National Essential Drug System was initiated to achieve full coverage of the grassroots, thus improving the primary healthcare system and services between urban and rural areas. Second, the basic healthcare service system was further developed and is widely available to the urban and rural population. Breakthroughs were achieved at public hospitals where pilot schemes were implemented, significantly improving accessibility and availability to safe, effective and affordable basic healthcare services. This initiative laid the foundation for improving whole population health throughout China.

3 The Medicines Regulatory System and Pharmaceutical Industry

Restructuring China's healthcare system has opened doors to opportunities for the pharmaceutical industry. In recent years, the CFDA has highlighted the importance of innovative drug development and safety surveillance by establishing and improving regulatory systems covering pre-clinical and clinical research, registration, supply, adverse drug reaction (ADR) monitoring and medicine recalls. A relatively comprehensive system monitoring the whole drug production process from manufacturing and distribution to safety monitoring has gradually been established, including quality control of active pharmaceutical ingredients, post-marketing surveillance, and implementation of guidelines such as 'Good Manufacturing Practice for Drugs' (GMP), 'Good Clinical Practice' (GCP), and 'Good Pharmacovigilance Practices' (GVP). Other approaches to maximise public protection in terms of medication safety and effectiveness include upgrading standards of drug testing in the new version of the *Chinese Pharmacopoeia*, disseminating and implementing the newly revised GMP and 'Good Supply Practice for Drugs' (GSP) provisions, promoting the development of the national electronic drug regulatory system [3] to track the quality of pharmaceutical products, strengthening ADR monitoring and drug re-evaluation.

According to CFDA in-house information, there are more than 4,500 pharmaceutical manufacturers and about 180,000 approved products in China. Various pharmaceutical companies, including state-owned TCM/WM companies, small biotechnology firms, foreign-owned and joint ventures are involved in drug research, development and production. In the last few years, some multinational pharmaceutical companies have increased investment in drug development in China.

4 The Pharmacovigilance System

Development of the pharmacovigilance system in China can be described in four stages: the preparation period between 1989 and 1999; the initial development period between 1999 and 2004; the rapid development period between 2004 and 2011; and a period of stability following implementation of the revised version of the *Adverse Drug Reaction Reporting and Monitoring Provision* (hereafter referred to as the *Provision*). After more than 20 years of development, a relatively mature regulatory, management and technology system has been established.

4.1 Coordination of the Pharmacovigilance System

There are four administrative levels in the pharmacovigilance system—national, provincial, municipal and county—forming a technical support system to carry out ADR monitoring and assessment at each level. The Department of Drug and Cosmetics Surveillance (DDCS) of the CFDA takes full responsibility for the surveillance of the manufacturing, supply, distribution and utilisation of drugs, cosmetics and special drugs or formulations. The DDCS also supervises the implementation of GMP, GSP, 'Good Agricultural Practice' (GAP) and ADR monitoring regulations, and responds promptly to urgent safety issues. The National Centre for ADR Monitoring (NCADRM) (also known as the Centre for Drug Re-evaluation, which is affiliated with the CFDA) is the technical supporting institution for the DDCS, which monitors ADRs and re-evaluates marketed pharmaceutical products, thus providing evidence for risk-management decisions made by the CFDA. As of 2013, one national centre, 34 provincial centres and more than 400 municipal centres for ADR monitoring were included in the four-level pharmacovigilance network, with more than 200,000 grassroot organization users, forming the foundation for further development of pharmacovigilance in China. Figure 1 briefly illustrates the structure of the pharmacovigilance system in China.

4.2 Regulation of the Pharmacovigilance System

After initial promulgation of the *Provision* in 1999, two respective amendments in 2004 and 2011 effectively advanced pharmacovigilance development in China. In particular, the new 2011 *Provision* clarified municipal and provincial responsibilities for the first time, further regulating ADR reporting practices and setting ADR technical requirements for analyses. The 2011 *Provision* required the provincial centres to seasonally extract and analyse medication safety data, and to make recommendations for risk management. Moreover, the role of pharmaceutical manufacturers in pharmacovigilance was also emphasised. For instance, manufacturers are required to report serious ADRs incurred abroad within 30 days via the China Adverse Drug Reaction Monitoring System (CADRMS). The manufacturers are also required to submit written reports to the CFDA and NCADRM within 24 h if any overseas pharmaceutical products are suspended or withdrawn from the market. The *Provision* has also introduced the concept of the 'Key Monitoring Scheme' (KMS), which emphasises pharmaceutical manufacturers as the primary party responsible for intensive ADR monitoring of their own products. Pharmaceutical manufacturers are required to initiate ADR monitoring and research to complement the CADRMS. The provincial or above-mentioned regulatory agencies have the right to initiate a KMS where necessary. The *Provision* also emphasises the strengthening of information management and establishment of exchange and feedback mechanisms.

Other relevant requirements for ADR monitoring are addressed in the GMP, GSP, 'Provisions for Drug Registration' and 'Administrative Measures for Drug Recalls' regulations.

4.3 Technical Support of the Pharmacovigilance System

4.3.1 China Adverse Drug Reaction Monitoring System

Prior to 2003, ADR cases were reported to the provincial ADR centres in writing, by fax or telephone. These ADR cases were then conveyed to the NCADRM by the provincial centres using CD-ROM. In 2003, a nationwide CADRMS, an online spontaneous reporting system [4], was established. To adapt to the rapid development of pharmacovigilance in China, the national ADR monitoring and updating platform was officially launched online on 1 January 2012. Based on daily routine requirements, the new management modules on the CADRMS online platform included (1) individual ADR case reports; (2) 'group adverse event reports' (reports for mass incidents); (3) foreign ADR reports; (4) periodic safety update reports; (5) KMS; (6) quality evaluation; (7) early warning; (8) structured data; and (9) category analysis. There are two analysis functions in the 'Category Analysis Module' (CAM), which is able to perform ADR analysis based on (a) the different mechanisms of drug action or (b) different organ systems. The new ADR monitoring platform can offer various statistical functions and, more importantly, ensure effective management and data utilisation.

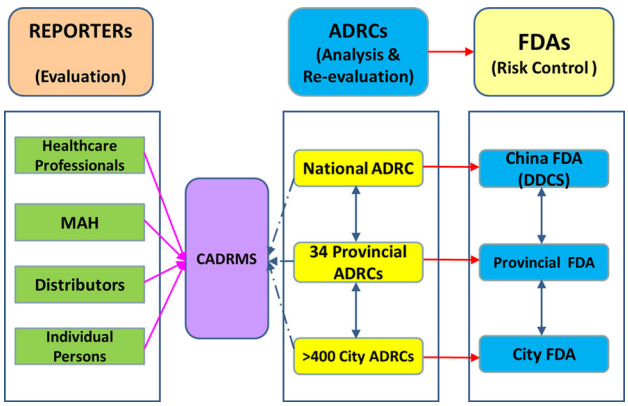

Fig. 1 Structure of the pharmacovigilance system in China. *ADRC* adverse drug reaction centre, *CADRMS* China Adverse Drug Reaction Monitoring System, *DDCS* Department of Drug and Cosmetics Surveillance, *FDA* Food and Drug Administration, *MAH* marketing authorisation holder

Currently, healthcare professionals and pharmaceutical companies mainly report ADRs online. Patients/consumers can request that their healthcare professionals, pharmaceutical companies or local centre staff submit the ADR reports. ADR case reports from rural areas can be submitted on paper or by telephone, and are then sent to regional or national centres by mail or fax. The information is subsequently entered into the CADRMS system electronically.

By the end of 2013, the NCADRM had received more than 6.6 million reports. In that year alone, 1,317,000 case reports were received, of which almost 291,000 (22.1 % of the total case reports) were unexpected and serious ADRs, an increase of 2.4 % compared with 2012, averaging 983 reports per million [5]. Of the total case reports in 2013, western drugs, TCM and biological products accounted for 81.3, 17.3 and 1.4 %, respectively, involving more than 2,300, 3,400 and 130 products, respectively [6]. The medical information in the CADRMS is reviewed and verified by staff from different levels of the pharmacovigilance centres for assessment of completeness and information accuracy. The original reporters as well as municipal, provincial and national centres review and assess the causality of those ADR case reports. CADRMS is able to select and delete duplicated ADR reports by identifying the same information regarding patient name, drug, hospital, name of ADR and time occurred.

4.3.2 Key Monitoring Scheme

As development continues, the focus of pharmacovigilance in China has shifted from collecting ADR case reports to the evaluation and research of ADRs. To compensate for limitations in the CADRMS, the concept of a KMS was included in the new 2011 *Provision*, in which it is defined as "a specific approach of pharmacovigilance, aiming to further understand the clinical use and ADR occurrence of post-marketing medication, to investigate the characteristics, severity and incidence of ADRs" [7].

Unlike passive monitoring through CADRMS, the KMS emphasises proactive monitoring and post-marketing research mainly carried out by pharmaceutical manufacturers. This active surveillance requires manufacturers to formulate and implement a scientific monitoring programme, and collect complete safety information for the listed drug to detect safety issues in clinical practice among the general population. According to the *Provision* [7], there are three conditions in which the KMS will be initiated: (1) domestic newly marketed drugs under the requested surveillance period; (2) newly imported drugs within 5 years since first importation; and (3) other specific drugs with suspected important safety signals. Drugs meeting condition (1) or (2) will be under mandatory KMS; while those meeting condition (3) will be under the mandatory KMS required by the provincial Food and Drug Administration or the CFDA, or manufacturers may initiate action in some circumstances. In short, the KMS of post-marketing pharmaceutical products led by pharmaceutical manufacturers is a new initiative to improve medication safety. To date, the development of the KMS is still at an early stage.

5 What are the Successes?

In the past decade, there has been significant improvement in the quantity and quality of ADR reports from the CADRMS. Social awareness and acceptance of ADR monitoring as well as the legislation of drug regulation have improved. Pharmacovigilance in China has moved rapidly onto a new stage. There are 6.6 million case reports in the CADRMS. Different techniques to enhance the CADRMS have been explored to enable it to play an important role in pharmacovigilance and risk management. Successful examples include early detection of drug safety risk [4, 8]; identification of majority risk signals such as puerarin-induced immune haemolytic anaemia [9] and early warning of drug quality issues such as armillarisin injection-induced acute renal failure [10] were all credited to the CADRMS. Besides the routine work, the NCADRM also enriches the CADRMS with a 'national/provincial synchronous precautionary function'. In general, provincial agencies and those under them are only able to access ADR reports from their own administrative area. Under specific circumstances, when ADRs occur in the same pharmaceutical products or batch number or products by the same manufacturer, the NCADRM and provincial centres can share ADR databases to allow nationwide information sharing and uniform risk management.

The CFDA launched the *ADR Information Bulletin* with the aim of informing patients, manufacturers and the public about ADRs and drug safety issues in an open, timely and efficient manner. By August of 2014, 62 issues of the *ADR Information Bulletin* had been published, listing 103 ADR alerts. The CFDA implemented risk management through several approaches, including arranging manufacturer communication meetings, modification of medication package inserts, and restriction, suspension or withdrawal of drugs [4]. To strengthen communication and information sharing, the CFDA will also publish the *International Pharmacovigilance Newsletter* based on risk-management information from overseas pharmacovigilance organisations. In 2009, the CFDA initiated the *National ADR Annual Report*. In summary, with the establishment and improvement of the pharmacovigilance system in China, there has been an increased effort in ADR detection, reporting, handling, information exchange, risk control and emergency management.

6 What are the Challenges?

6.1 Signal Detection

At present, attempts are being made to improve the capability of monitoring drug risk signals manually through strengthening daily monitoring, weekly summaries and seasonal reports. However, with a sharp increase in the amount of data, an increasingly prominent limitation is emerging regarding manual signal detection. There has been an urgent need to realise that computer-aided warnings and signal detection is required to effectively make use of the massive amount of data in the national database.

The proportional reporting ratio (PRR), reporting odds ratio (ROR) and Bayesian Confidence Propagation Neuron Network (BCPNN) are common methods for detecting ADE signals using spontaneous reporting data. However, due to the quality and methodology of case reports, as well as over-filtered signals, these computer-aided filtering systems are not officially applied in routine practice in China. In the past 2 years, the NCADRM has invested much manpower and resources in establishing drug and disease databases, structuring raw data and improving the quality of case reports in order to attain computer-aided warnings and signal detection. The NCADRM takes responsibility for collecting and analysing case reports via online CADRMS, and releasing the ADR bulletin on the related signal to the public. However, experience from the World Health Organization (WHO)–Uppsala Monitoring Centre (UMC) (WHO-UMC) and other collaborations from developed countries are still needed for techniques regarding signal detection and data mining.

6.2 Active Surveillance of Post-Marketing Pharmaceutical Products

Medical organisations, pharmaceutical enterprises and research institutions have already undertaken some KMS projects and post-marketing clinical studies. However, the validity, reliability and value of these studies are largely untested. Some of the challenging issues that require further development are how to draw on the experience of the *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)—ICH Harmonised Tripartite Guideline Pharmacovigilance Planning E2E* (in the European Union) [11], GVP guidelines [12] and GPP guidelines [13] by the International Society for Pharmacoepidemiology (ISPE); and how to implement monitoring requirements, achieve connection and integration with the hospital information system and medical insurance systems, as well as link to other large healthcare databases.

There is an urgent need to strengthen research on drug-induced diseases; effective approaches should be taken to integrate resources for cooperation between hospitals and research institutes. These approaches include jointly building nationwide research platforms for drug-induced diseases and separately establishing drug-induced disease research centres, particularly for the liver, kidney and heart, which will also further the development of pharmacovigilance research in China.

6.3 The Pharmacovigilance System for Traditional Chinese Medicines

China's healthcare system is unique in that TCM and WM exist simultaneously throughout the country. All marketed Chinese patented medicines undergo stringent pharmaceutical research, non-clinical and clinical studies, and are examined by the CFDA prior to marketing authorisation approval. To date, TCM and WM share the same spontaneous reporting system. However, TCM specificity and the risk factors influencing TCM safety, multi-ingredients, different plant origins and non-uniform drug names are typically great challenges for TCM pharmacovigilance. Furthermore, individualised treatment according to the system of 'TCM theory' rather than western medical knowledge makes the situation even more challenging. Development of a specific pharmacovigilance system for TCM based on its unique characteristics and designing suitable active surveillance and post-marketing research methods during the KMS process will need further research. Since TCM shares many common concerns with herbal medicine, this will also lay a solid foundation for developing a suitable and effective global pharmacovigilance system for herbal medicine [4].

6.4 Communication, Training and Information Sharing

With a vast territorial area and a large population, mutual communication and learning must be facilitated between monitoring institutions through training, experience sharing and research collaborations to improve the overall level of pharmacovigilance capability in China. The CFDA organises training and workshops in various ways, including training courses for staff at all levels, compiling pharmacovigilance manuals, organising nationwide pharmacovigilance seminars and meetings with directors from provincial and municipal ADR centres, and encouraging pharmacovigilance research. The national pharmacovigilance annual meeting has invited specialists from the US Food and Drug Administration, UK Medicines and Healthcare products Regulatory Agency and European Medicines Agency to present the pharmacovigilance systems in different countries and regions. Manufacturers, academic researchers, staff

from all levels of ADR centres and government officials also attend these events. Still, systematic training programmes are needed to help staff to better understand the methods and gain updates on international pharmacovigilance work. Therefore, it is important to fully engage with international and domestic resources, including the professional platform offered by the WHO-UMC, International Society of Pharmacovigilance (ISoP) and ISPE to establish a systematic pharmacovigilance training programme.

The CFDA also submits unexpected and serious ADR case reports to the UMC, which promotes the understanding of medication safety issues worldwide. Further exploration of information sharing is another important issue to consider in the future. Since the CADRMS was developed in Chinese, language may pose a challenge at different stages of pharmacovigilance in China in terms of global information communication. Nevertheless, there are solutions to this issue. The Chinese versions of the *WHO Adverse Reaction Terms* (WHO-ART) and *WHO-Drug Dictionary* are being developed by UMC, which might overcome the language challenge, and thus improve the exchange of information with other national and international institutions.

7 Conclusion

At present, a monitoring and regulatory system has been established covering drug development, manufacturing, distribution and utilisation. Meanwhile, pharmacovigilance has also developed and is continuously strengthened with an increasingly wide range of technical measures and matured risk control methods, which has pushed forward the development of drug surveillance in China. However, when compared with countries in the EU and USA, awareness among pharmaceutical companies and the general population still need to be strengthened. Integration of domestic and overseas research resources can potentially improve pharmacovigilance and risk management in China. Ultimately, the CFDA aims to develop a well-established pharmacovigilance system to ensure safe and effective medication use in China.

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