Research on the Optimization of China's Pharmacovigilance Organization Management

Zhang Zhi, Sun Lihua*

(School of Business Administration, Shenyang Pharmaceutical University, Shenyang 110016, China)

Abstract

Objective To analyze the problems of China's pharmacovigilance organization system, and to provide targeted suggestions for improving it. **Methods** The relevant literature at home and abroad was reviewed to compared the differences in pharmacovigilance organizations in the United States, the European Union, Japan and China. Then, the problems of China's pharmacovigilance organization management were found out. **Results and Conclusion** China's pharmacovigilance organizational system has problems such as inadequate organizational setup, immature institutional construction, no coordination mechanism for pharmacovigilance practice, and industry associations of third-party organizations having no role to play. It is recommended to carry out theoretical and methodological research on the pharmacovigilance organizational system to provide practical guidance for optimizing the system with Chinese characteristics.

Keywords: pharmacovigilance organization; system optimization; policy suggestion

Pharmaceutical regulatory agencies in Europe, the United States and Japan have long been committed to the practice of safety regulation, and the scientific concept of drugs has penetrated into all aspects of these regulatory agencies. Therefore, experience in scientific practice has been gradually accumulated and enriched. These experiences have been solidified and continuously improved through the establishment of specialized institutions, clear division of labor and close cooperation among institutions, and the standardization of specific operational and practical procedures. In contrast, China's pharmacovigilance practice started relatively late, we had to learn from foreign experience in the establishment of institutions, division of labor and coordination mechanisms, as well as specific operational practices. Based on China's actual conditions, the localization and improvement of these experience is of great significance to the smooth development of China's pharmacovigilance practice.

1 Comparison of national pharmacovigilance organizations

1.1 Establishment and functions of pharmacovigilance organizations in the United States

The U.S. Food and Drug Administration (FDA), the primary regulatory agency for pharmacovigilance, has been part of the department of human health and sanitation services since its establishment in 1906 and is authorized by congress to assume the highest law enforcement responsibility for food and drug supervision and management. The FDA's regulatory

* Corresponding author: Sun Lihua, professor. Major research area: Pharmacoeconomics, medical investment performance and management, etc. Tel: 024-23986553, E-mail: slh-3632@163.com.

team brings together a diversity of professionals, including physicians, attorneys, microbiologists, chemists, and statisticians, to form a government regulatory agency dedicated to protecting and enhancing the quality of food and drugs. These experts ensure that FDA plays a vital role in pharmacovigilance through their in-depth expertise and rigorous work ethic [1]. The FDA has a hierarchical internal structure with scientific and rational departmental settings, among which the Center for Drug Evaluation and Research (CDER) is the department specifically responsible for pharmacovigilance [2]. In addition, the Office of New Drugs, the Office of Compliance, and the Office of Pharmaceutical Quality are closely related to pharmacovigilance, which work together to ensure comprehensive coverage and efficient implementation of pharmacovigilance efforts [3]. FDA's organizational structure is shown in Fig. 1.

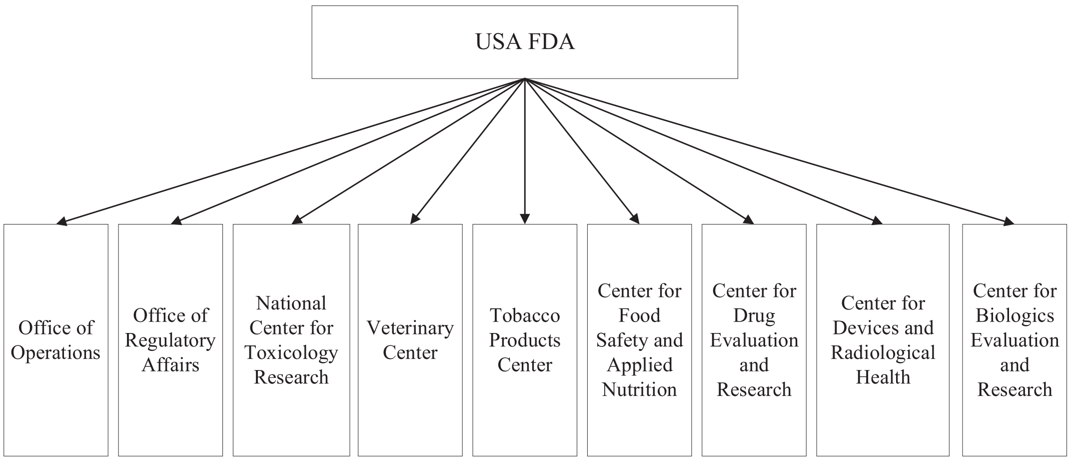

Fig. 1 FDA's organizational structure

Founded in 1988 and headquartered in Washington, D.C., the CDER has more than 1 800 employees, about half of whom are food and drug evaluation staff. The CDER is the largest secondary organization and division of the FDA, which is responsible for evaluating and conducting research on the safety and efficacy of prescription, OTC, and generic drugs, as well as biologic therapies, medical devices, and other drugs. The organizational structure of the CDER is shown in Fig. 2.

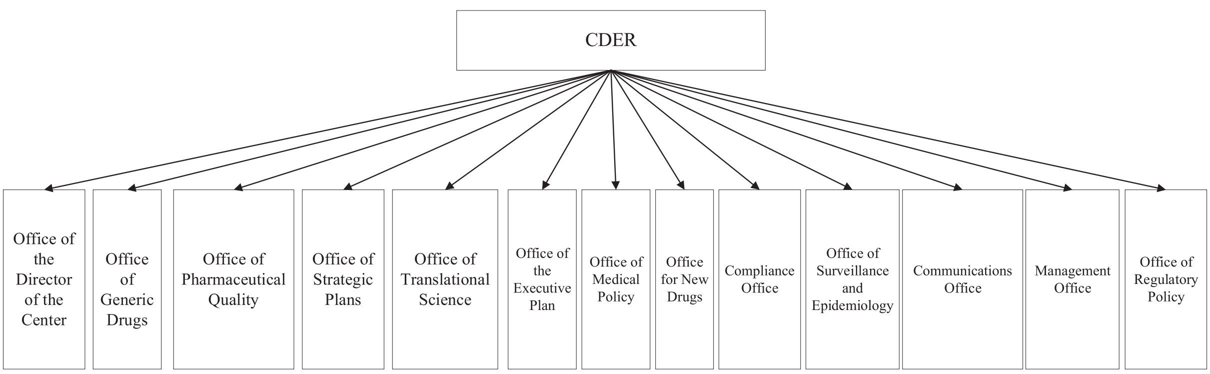

Fig. 2 Organizational structure of the Center for Drug Evaluation and Research (CDER)

The primary department responsible for pharmacovigilance in the CDER is the Office of Surveillance and Epidemiology (OSE). The OSE is responsible for evaluating the safety of medicines throughout their life cycle, including Adverse Drug Reaction (ADR) reporting, safety information dissemination (MedWatch), and risk information management. Its organization chart is shown in Fig. 3.

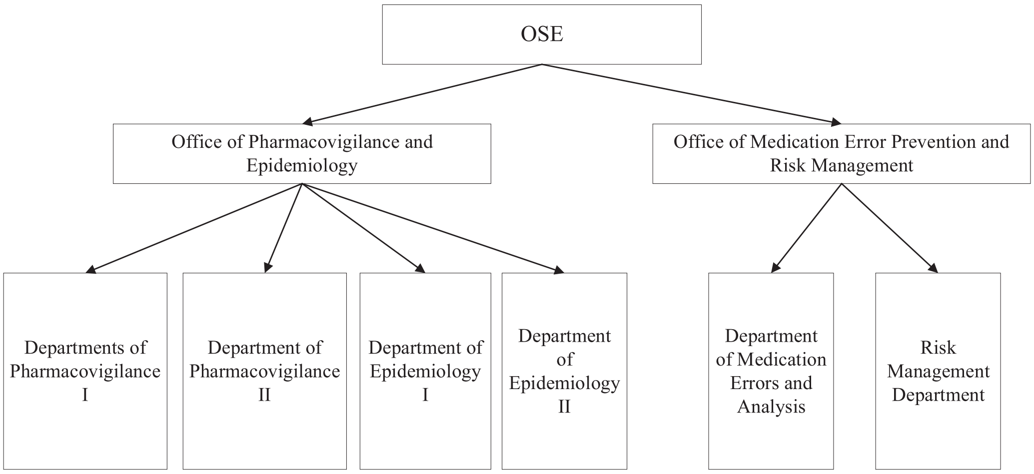

Fig. 3 Organizational structure of the Office of Surveillance and Epidemiology (OSE)

There are multiple levels of OSE, with 2 main divisions under its direct management responsible for pharmacovigilance: The Office of Pharmacovigilance and Epidemiology (OPE) and the Office of Medication Error Prevention and Risk Management (OMEPRM) [4].

The OPE is divided into Departments of Pharmacovigilance I and II, and Departments of Epidemiology I and II. Pharmacovigilance I and II are mainly responsible for monitoring the safety and safety alert signals of marketed drugs and therapeutic biologics, as well as evaluating their related safety issues. Epidemiology I and II are mainly responsible for reviewing whether manufacturers have fulfilled the requirements and commitments for post-marketing pharmacovigilance, and for reviewing the epidemiological research programs and reports related to drug safety proposed by them.

OMEPRM consists of the Department of Medication Error Prevention and Analysis (DEPA) and the Department of Risk Management (DRM). The DEPA's main responsibility is to conduct pre-market evaluation of the name, packaging, labeling or design of drugs regulated by CDER. The DRM is responsible for providing risk management expertise for better supervision and management, which is the core department of CDER for carrying out risk management and supervisory activities. FDA has the highest enforcement responsibilities for food and drug supervision and management. The CDER is the largest secondary organization and department of FDA, which is mainly responsible for safety and efficacy evaluation and research of prescription drugs, over-the-counter drugs, generics and other drugs, as well as biologic therapies, and medical devices. The OSE's main responsibilities are to assess the safety of the entire life cycle of pharmaceuticals, including ADR reporting, MedWatch, and risk information management. There are multiple levels of departments under the OSE, with two major departments under its direct management responsible for pharmacovigilance, of which OPE is responsible for post-marketing pharmacovigilance, and OMEPRM, which is responsible for the DEPA and the risk management of medicines.

The United States pharmacovigilance organizational system has the following characteristics.

(1) Centralization and specialization. The United States pharmacovigilance organization is a centralized system with a separate national center and no local pharmacovigilance organizations. The main undertaker of pharmacovigilance practice is the CDER, which is a highly specialized agency responsible for pre-market evaluation of new drugs and supervision of drugs sold on the market.

(2) Hierarchical organizational structure. CDER has a number of offices, such as Office of New Drugs (OND), OSE, Office of Compliance (OC), etc., each of which is responsible for different pharmacovigilance-related issues. The OSE, as the main department in charge of pharmacovigilance within the center, has further set up the OPE and OMEPRM, which ensures the

detailed implementation of pharmacovigilance practice.

(3) Clearly defined responsibilities. The CDER and its subordinate offices have clearly defined responsibilities, such as the OND is responsible for providing supervision and management of the research process during the drug development phase, and the OSE is responsible for post-marketing safety, etc. OPE and OMEPRM under OSE also have their own responsibilities.

(4) Professional and large staffing. The CDER, as the largest second-tier organization and department of the FDA, has more than 1 800 staff members, and about half of the staff members are FDA evaluation members. These employees come from a wide range of fields, including medicine, law, microbiology, chemistry, and statistics, ensuring that pharmacovigilance efforts are comprehensive and specialized.

1.2 Establishment and functions of pharmacovigilance organizations in the EU

The European Medicines Agency (EMA) is the main review body for medicines and related products in the European Union [5]. It is responsible for public health issues in the EU Member States and serves the EU regional market of over 500 million people. The goals, objectives and focus of its work are to promote the development and innovation of medicines in compliance with standards and requirements, so that patients have faster access to safe and effective medicines.

The supreme body of EMA is the Management Board, which appoints the executive director, who is usually underpinned by departments such as the executive deputy director and the advisory department, and then 7 departments responsible for the supervision and management of the fields of research and development of medicines for human use, veterinary medicines, rare disease medicines, herbal medicines, advanced therapeutic products, pediatric medicines, and pharmacovigilance, respectively. To carry out the above functions, 7 professional committees have been formed, and the basic organizational structure of EMA is shown in Fig. 4.

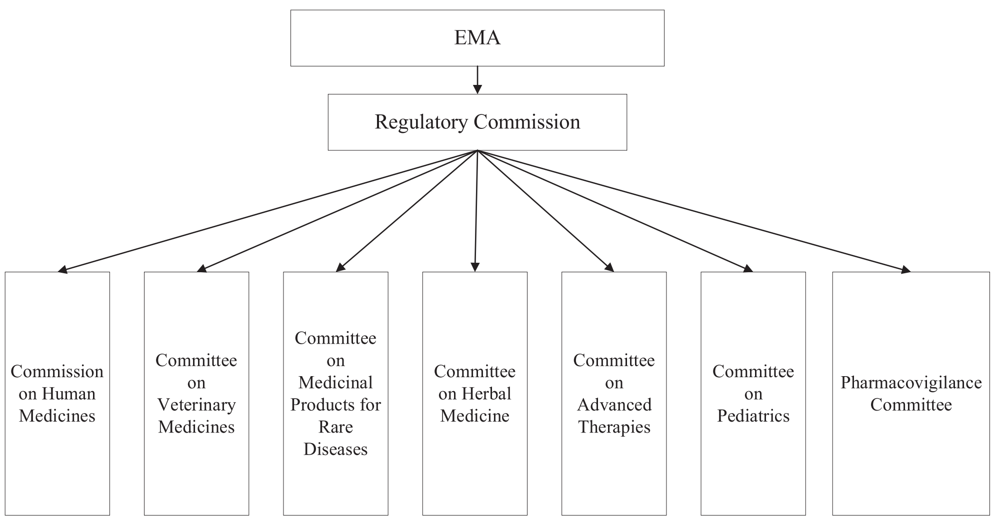

Fig. 4 Organizational structure of the European Medicines Agency (EMA)

To strengthen the monitoring of the safety of medicines in Europe, the EMA established the Pharmacovigilance Risk Assessment Committee (PRAC) in 2010 in accordance with the pharmacovigilance legislation, which is the EMA's scientific committee in charge of assessing and monitoring the safety of medicines for human use.

The EMA is the main accreditation body for medicines and related products in the EU, with the PRAC being the body responsible for assessing and monitoring the safety of medicines for human use.

The following characteristics exist in the EU pharmacovigilance organizational and institutional system. (1) Clear core roles and responsibilities: The EMA plays a core role in the pharmacovigilance system, with the functions of coordination and supervision. The Executive Director of the EMA bears the legal responsibility for the whole organization and is the supreme person in charge, while the Heads of Division implement and manage pharmacovigilance practice and monitor the operation of the pharmacovigilance system. (2) Focus on communication and collaboration: Pharmacovigilance has a variety of communication methods, including direct medical professional communication, plain language documents, and newsletters to ensure accurate transmission of information and public understanding. The EMA has a central role in coordinating the work of the drug regulatory agencies of the member states, drug manufacturers, etc., so as to make the whole pharmacovigilance system more flow and standardized. (3) Emphasis on continuity and process: Pharmacovigilance practice focuses on continuity and benefit-risk assessment, which requires all parties, including drug manufacturers, drug regulatory authorities of member states and EMA, to pay continuous attention to the safety issues of drugs and take necessary measures to manage and control them. Pharmacovigilance is integrated into the European Medicines Quality Management System (EMQMS), forming a complete scientific monitoring system with complementary, mutually supportive and linked components.

1.3 Establishment and functions of pharmacovigilance organizations in Japan

In Japan, the agencies responsible for pharmacovigilance include the Ministry of Health, Labor and Welfare (MHLW) [6]. The MHLW [7] consists of two sub-agencies, the Pharmaceutical Safety and Environmental Health Bureau (PSEHB), which is responsible for the safety and health of the public, and the Pharmaceuticals and Medical Devices Agency (PMDA) [8].

The central body of the drug regulatory organization is the MHLW, which is primarily responsible for drug policy matters and assumes the role of decision maker within the pharmacovigilance structure. In the work carried out by the pharmacovigilance system, the MHLW has the final and absolute authority to approve recommendations and regulatory findings on the safety of medicines originating from the PMDA or PSEHB [9].

The PSEHB is responsible for clinical research, marketing approval review and post-market safety management. The PSEHB, as one of the eleven directorates of the MHLW department, arranges for the management of the pre-market and post-market quality and safety of medicines, among other things.

The PMDA's core responsibility is to ensure the safety of medicines, which involves the collection and study of drug safety data from spontaneous reports and medical databases to respond rapidly to ADRs and minimize potential threats to public health from biological sources, drug infections, and other factors. By establishing a coherent data system, the PMDA is able to guide and review the quality, safety and efficacy of drugs and medical devices from pre-market to post-market approval. In addition, the PMDA is responsible for collecting, researching and providing information on the safety of medicines once they are on the market, and taking the necessary safety measures to safeguard the public's physical and mental health [10]. Besides, the PMDA, as an independent agency, provides MHLW with review of post-marketing applications and safety monitoring, as well as research on drug safety strategies, primarily to provide compensatory relief to patients suffering from ADRs [11].

The MHLW consists of two subordinate organizations, of which PSEHB is responsible for clinical research, marketing approval review, and post-market safety management, and the PMDA is responsible to ensure the safety of drugs.

The following features exist in Japan's pharmacovigilance organizational system. (1) Clearly defined regulatory agencies and their responsibilities: The MHLW and the PMDA share the responsibility for drug safety regulation in Japan. the PSEHB under the MHLW ensures the efficacy and safety of pharmaceuticals, quasi-drugs, cosmetics, and medical devices, etc. The PMDA is responsible for three major areas of business: review, safety countermeasures, health and injury relief, and safety management throughout the life cycle of pharmaceuticals, medical devices, and health and safety management. (2) Comprehensive pharmacovigilance activities: Pharmaceutical companies have established a spontaneous safety reporting system, and in addition to collecting and reporting suspected ADRs to the regulatory agency, they also undertake the legal obligation of drug use investigation (DUI), requiring doctors to register newly marketed products and to report suspected ADRs to the regulatory agency. Meanwhile, it introduces early post-marketing surveillance (PPV) as an additional requirement for pharmacovigilance. The Risk Management Plan (RMP) is implemented, which incorporates the Risk Minimization Action Plan (MAP). (3) Emphasis on international cooperation: As one of the founding members of the ICH, Japan actively participates in international cooperation on pharmacovigilance to ensure that pharmacovigilance activities are in line with international standards.

1.4 Establishment and functions of pharmacovigilance organizations in China

Within National Medical Product Administration (NMPA), there is the pharmacovigilance Division of Drug Supervision and Administration (DDSA) [12], which is responsible for developing and supervising the implementation of the ADR monitoring and pharmacovigilance system. The division is also responsible for formulating and organizing the implementation of the drug sampling system and annual plan, issuing regular quality bulletins, and organizing the re-evaluation of drugs.

As the main executive body of pharmacovigilance, the Center for Drug Reevaluation of NMPA, or the National Center for ADR Monitoring, is responsible for carrying out work including ADR monitoring, drug abuse monitoring, and post-marketing safety evaluation, as well as building and maintaining the national ADR monitoring information network. The Center is also required to report the results of the comprehensive analysis of serious ADR to the NMPA's Comprehensive Business Division in a timely manner, organize and carry out methodological research on relevant monitoring and post-marketing safety evaluation, and provide guidance to localities in carrying out relevant monitoring and post-marketing safety evaluation work.

In addition, provincial ADR monitoring centers have been established nationwide, responsible for ADR reporting and monitoring in their respective administrative regions, formulating annual supervision and inspection plans, analyzing ADR reports received, and reporting them to the provincial drug administration and the National Center for ADR Monitoring in time.

The Clinical Trial Management Division under the Drug Evaluation Center is responsible for receiving, analyzing and evaluating reports of unexpected serious ADRs during drug clinical trials and safety updates during drug research and development, and for timely monitoring of safety issues in drug clinical trials.

Currently, China practices the mode of reporting ADRs at different levels, with each province responsible for ADR monitoring in its own region, which helps to improve the efficiency of handling ADR reports.

2 Problems with the organizational structure of pharmacovigilance in China

China and the United States, the European Union and Japan have adopted a centralized drug safety regulatory model, supplemented by regional centers, but there are some differences in their specific functional management.

The power of the U.S. FDA is more centralized than that of other regions, and all related administrative and operational work is done in the FDA, with regional centers only involved in vertical support work. The 16 external advisory committees formed by the FDA are mainly involved in safety monitoring work.

The European Union, as a close-knit collection of countries, has a certain national character of its own. If it is viewed as a country, its member states are the regions within it. The EU regulatory model is therefore a combination of a centralized and multi-regional pharmacovigilance system. In the pharmacovigilance practice, each member state follows the guidance of EMA to supervise the safety of medicines in their own countries. They can also set up their drug safety supervision system according to their realities. For example, the United Kingdom, which was originally a member state of the European Union, had used central management, and its five regional centers only completed part of the research tasks of the MHRA.

China's pharmacovigilance system differs from that of the above-mentioned countries. From the national point of view, NMPA is the highest drug safety supervision and management administrative organization, including the Drug Supervision and Management Division and Pharmacovigilance Division as the administrative and management executive body, which is specifically responsible for setting up and implementing the ADR monitoring system, investigating the problems of drug safety supervision and putting forward the corresponding treatment recommendations. The National Center for ADR Monitoring undertakes technical support, and the provincial food and drug administrations are responsible for administrative management in their respective regions. Under the command of the State Bureau, they have the relatively independent function of drug supervision.

2.1 Inadequate organizational set-up for pharmacovigilance

In terms of specific institutional settings, the European Union and the United States attach great importance to the safety of drugs and have risk management departments specifically responsible for pharmacovigilance. The European Union has set up a PRAC, and the U.S. FDA's CDER agency has set up a special department for PRAC. The tasks of the above departments in the European Union and the U.S. cover all areas of drug risk management, including the provision of expertise and the provision of training. However, there is no specialized risk management department in China.

2.2 Immature institutionalization of pharmacovigilance

The European Union, the United States, Japan and other countries have set up special organizations for pharmacovigilance since they pay more attention the safety of drugs. For example, the United States set up a drug epidemiology department to trace cause of ADRs. The European Union Pharmacovigilance Supervision and Administration Department is divided into drug research and development, veterinary drugs, rare disease medicines, herbs, advanced therapies, pediatrics to carry out the supervision in the field of pharmacovigilance. The Japanese drug supervision and management set up the relevant departments to supervise the whole life cycle of the drugs by establishing a coherent data system to ensure the safety of the public medicines and compensate for the damage caused by drug-related incidents.

China's pharmacovigilance organization has two organizational structures, the administrative organizational structure and the technical organizational structure. China's current pharmacovigilance system, with its own advantages suited to the national conditions, can give full play to the enthusiasm of the central and local (especially the local) governments. In terms of institutional setup, staffing, financial support and other aspects, the local governments is able to provide great support, which can not only reduce the central government's corresponding pressures, but also ensure that the regulatory work is more diverse and in line with the realities of different provinces. Due to the intervention of local governments, the strength and effectiveness of drug supervision is much better and greater, thus also further motivating local governments to take the initiative and creativity. At the same time, for the sake of the harmonious development of different provinces' respective socio-economies and their achievements in drug control, provinces can consciously strive to be the front-runner in drug regulation, endeavoring to improve their regulatory methods and approaches, as well as their regulatory efficiency. However, there are unavoidable problems with this system in the following ways. Firstly, local governments may use drug regulation as a tool for local protectionism. Since the capacity and authority of local regulation is limited, it is beyond the power of local governments to deal with certain illegal and disciplinary behaviors. These problems should be solved in tandem with China's reforms, so that they can be fundamentally addressed while achieving progress in the overall reform of society. Second, the technical organizational structure manifests itself in the insufficient monitoring capacity of the grass-roots ADR monitoring agencies, which are unable to transform the occurrence of ADR events into a usable data source, resulting in the low efficiency of the monitoring.

2.3 No coordinated mechanism for pharmacovigilance practices throughout the life cycle of medicines

In China's current drug safety regulatory system, the key aspect of pharmacovigilance encompasses a wide range of functions, including pre-market approval, post-market monitoring and evaluation, and auditing and testing, which are effectively decentralized and synergized across a number of different departments. Specifically, the ADR monitoring department is committed to in-depth assessment of the safety of medicines after marketing to ensure the safety of public medication. Meanwhile, the drug review and approval department focuses on the safety and efficacy assessment of medicines before marketing to provide scientific and rigorous safeguards for the smooth entry of medicines into the market. This division of labor and collaborative regulatory model helps to realize the safety regulation of the whole life cycle of drugs and ensure the quality and safety of drugs. The Pharmacovigilance Division of the Department of Drug Supervision and Administration of the NMPA is responsible for formulating and supervising the implementation of the Adverse Drug Reaction Monitoring and Pharmacovigilance System. However, these agencies have not yet established an effective communication and coordination mechanism among them. Table 1 shows a comparison of the functions of regulatory agencies at different stages.

Table 1 Summary of functions of pharmacovigilance regulatory agencies

Regulatory agency	Role
The Clinical Trial Management Division of the Center for Drug Evaluation (CDE) is responsible for pre-market	Responsible for information review and other related work on the drug clinical trial registration and information disclosure platform. Responsible for organizing the reception, analysis and assessment of unanticipated serious adverse reactions during drug clinical trials and safety update reports during drug research and development related to drug review. Responsible for the formulation and implementation of relevant technical documents. Undertake other matters assigned by the Center
The Center for Drug Evaluation (CDR) is responsible for post-marketing	(A) To organize the formulation and revision of technical standards and norms for the monitoring of adverse drug reactions, adverse medical device events, adverse cosmetic reactions and post-marketing safety evaluation, as well as drug abuse monitoring; (B) Organize and carry out the monitoring of adverse drug reactions, adverse events of medical devices, adverse reactions of cosmetics and drug abuse; (C) To carry out post-marketing safety evaluation of drugs, medical devices and cosmetics; (D) Guiding local monitoring and post-marketing safety evaluation work. It also organizes and carries out methodological research, technical consultation and international (regional) exchanges and cooperation on relevant monitoring and post-marketing safety evaluation
NMPA and its internal agency, the Pharmacovigilance Branch of the Division of Drug Oversight and Management, are responsible for reviewing and verifying	It is responsible for formulating the system of monitoring adverse drug reactions and pharmacovigilance and supervising its implementation. It formulates drug sampling system and annual plan and organizes its implementation, and issues quality bulletins on a regular basis. It organizes and carries out drug re-evaluation

2.4 Failure of third-party institutions, experts, and industry associations to play their roles

In the process of improving related to pharmacovigilance practices, the drug regulatory authorities of the United States, the European Union and Japan fully adopt the recommendations of third-party organizations, experts and industry associations, which can guide the practice of pharmacovigilance. Every year, the WHO Uppsala Monitoring Center cooperates with ISOP, ICH and other international organizations to hold pharmacovigilance training courses, and provides a series of online learning courses for pharmacovigilance and health professionals. It greatly strengthens the awareness of professionals and the public on the practice of pharmacovigilance and risk communication. Besides, it can strengthen the foundation of their pharmacovigilance research, and actively obtain information on drug safety for analysis and dissemination. It promote communication with the public, and gives full play to the role of professional organizations in pharmacovigilance practice.

The administrative department for pharmacovigilance in China is the NMPA, while the technical management department is the Center for Drug Evaluation (CDR). The former is mainly responsible for drafting and formulating laws and regulations related to pharmacovigilance and managing the implementation of policies by the NMPA, while the latter is responsible for nationwide monitoring of ADRs and guiding ADR monitoring centers in provincial-level administrations in the collection and reporting of ADR information. Despite the collaborative relationship between the two, administrative and technical management, there are few reports of experts, third-party organizations, and industry associations participating in the development of relevant processes. The training system for pharmacovigilance personnel exists, but it is not systematic, and the relevant training courses are expensive, which discourages the participation and enthusiasm of pharmacovigilance practitioners from medical institutions, drug manufacturers, drug distributors, and drug dealers. Therefore, we can explore the application of the power of industry associations to train pharmacovigilance practitioners, and give full play to the role of industry organizations in pharmacovigilance activities.

3 Recommendations for optimizing the organizational structure of pharmacovigilance

3.1 Strengthening top-level design and overall planning

A comprehensive strategy and plan should be developed for pharmacovigilance, with clear objectives, principles and key tasks for its construction. Then, all efforts should be coordinated to promote pharmacovigilance and ensure the effective implementation of policies and measures. Finally, the objective laws of pharmacovigilance should be respected by setting up pharmacovigilance regulatory science organizations, and strengthening the application of new tools, methods and technologies of regulatory science in pharmacovigilance.

3.2 Establishing a multi-level coordination mechanism

A collaborative mechanism between central and local regulatory agencies should be established to strengthen information sharing and communication and ensure the smooth implementation of regulatory policies. Pre-market and post-market review and verification agencies should strengthen communication and collaboration to jointly address challenges and problems in drug regulation. For example, joint meetings or working seminars can be held regularly to discuss difficult and hot issues in drug review and verification. At the same time, joint working groups or special working groups can be set up to collaborate and cooperate on specific issues or incidents, so as to form a synergy to solve problems.

3.3 Establishing a long-term mechanism

The pharmacovigilance management system should be regularly assessed to identify problems and rectify them in a timely manner. Besides, supervision and assessment should be strengthened to ensure that policies and measures are effectively implemented. A perfect reward and punishment mechanism should be established to recognize and reward units and individuals who have made outstanding contributions in their work, and severely punish violations of the law.

3.4 Enhancing interaction and cooperation

We should strengthen close contact and cooperation with government regulatory agencies, academic groups, medical institutions and enterprises, and regularly organize seminars, training and other activities to enhance consensus and collaboration among all parties in pharmacovigilance practice. Then, the establishment of an effective information-sharing mechanism should be promoted so that expert committees and industry associations can obtain and disseminate the latest pharmacovigilance research results and practical experience quickly.

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