Research on the Optimization of Pharmacovigilance Laws and Regulations in China

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Abstract

Objective To analyze the problems of China's pharmacovigilance legislation, and to provide some suggestions for improving it. **Methods** Relevant literature at home and abroad were studied to compare the laws and regulations of the United States, the European Union, Japan and China. Then, the problems of China's pharmacovigilance legislation were analyzed. **Results and Conclusion** The Chinese pharmacovigilance legislation has such problems as nontransparent formulation process, poor dynamic adaptability, insufficient use of the attention mechanism, fragmentation of laws and regulations, and poor connection of laws and regulations, which should be optimized. It is recommended to carry out theoretical and methodological research on pharmacovigilance legislation to provide practical guidance for optimizing pharmacovigilance legislation with Chinese characteristics.

Keywords: pharmacovigilance laws and regulations; system optimization; policy recommendations

In contemporary countries ruled by law, the scientific practice of drug management needs to be fulfilled according to detailed and specific laws and regulations. The potential and benefits of regulatory science can be optimized in practice only when it is ultimately fully reflected at the level of laws and regulations. In terms of drug safety supervision, countries around the world face a common challenge of ensuring that pharmacovigilance legislation is structurally rigorous and complete, meanwhile, maintaining the openness and inclusiveness of regulatory science, which can facilitate the introduction of new tools, standards, and methodologies useful for supervision into pharmacovigilance practice. China's pharmacovigilance legislation was compared with the mature pharmacovigilance practice in foreign countries to find the weaknesses in China's pharmacovigilance practice. Then, the reasons were analyzed to put forward corresponding policy recommendations, which could improve the construction of the legal and regulatory system.

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1 Comparison of different pharmacovigilance legislations

1.1 Guideline of U.S. pharmacovigilance act regulations

U.S. federal laws are drafted by members of Congress, passed by Congress, and submitted to the president for approval and enactment. Section 505 § 355 of the "Federal Food, Drug, and Cosmetic Act" (FDCA) is closely related to pharmacovigilance, stating that companies should implement a

pharmacovigilance program to report ADRs [1]. "Code of Federal Regulations" (CFR) are published in the Federal Register by the executive agencies and departments of the U.S. federal government and have general applicability and mandatory legal effect. At the regulatory level, title 21 of the CFR provides for the implementation of pharmacovigilance, and the corresponding regulations for safety reporting of pre-market investigational drugs are included in 21CFR312, and the requirements for post-market drug safety reporting are included in 21CFR314. At the guidance document level, FDA has issued nearly 40 guidelines on post-market safety efforts [2]. Guidance documents such as the "Guidelines for Reporting Post-Marketing Adverse Drug Events", published in 1992, the "Guidelines for Pharmacovigilance Management Practices and Pharmacoepidemiologic Evaluation", published in 2005, and the "Guidelines for Planning and Reporting of REMS", published in the year 2019, provide guidance for the conduct of pharmacovigilance activities.

The sections and contents of U.S. laws and regulations that address pharmacovigilance are primarily shown in Table 1. Table 2 lists some of the key guidelines and content relevant to pharmacovigilance efforts.

Table 1 Sections of U.S. pharmacovigilance laws and regulations addressing pharmacovigilance

Acts/Regulations	Chapters	Content
FDCA	355(i)	Grants that FDA must require a drug company or drug study sponsor to develop and maintain records related to clinical studies of new drugs
	355(k)	Require MAHs to develop and maintain records for post-market drugs, and require FDA to conduct post-market risk identification for drugs
	355(r)	Require FDA to establish a web site to provide the public with post-market drug safety information
	355(o)	Provisions relating to the conduct of post-marketing studies on pharmaceutical products
	355-1	Provisions for the implementation of risk assessment and mitigation strategies
2007 FDAAA	Chapter 9	Strengthening of post-market safety monitoring of medicines, with provisions on risk/benefit assessment, risk assessment and reduction strategies, adverse drug reaction reporting, risk communication, etc.
PDUFA VI		User fees will be used to expedite post-marketing safety evaluations of pharmacovigilance activities and the effective assessment of their results
	310.305	Provides for the scope of adverse reaction reporting, reporting requirements, reporting forms, patient privacy, record keeping and disclaimers for new drugs
	312.32	Establishes requirements for the content and reporting channels of investigational new drug (IND) safety reports
CFR	314.80	Requirements for post-market adverse event reporting for new drugs
	314.98	Requirements for reporting of postmarketing adverse reaction events for generic drugs
	329.100	Requirements for postmarketing adverse event reporting for over-the-counter drugs
	600.80	Requirements for reporting of postmarketing adverse reaction events for biological products

Table 2 Key guidelines for pharmacovigilance in the United States

Guidance	Content
Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment	Guidance is provided on safety signal identification, pharmacoepidemiologic assessment and interpretation of safety signals, and pharmacovigilance program development
Development and Use of Risk Minimization Action Plans March 2005	Guidance to industry on the development, implementation and evaluation of risk minimization action plans for prescription drug products, including biologics
Guidance for Industry Postmarketing Studies and Clinical Trials	Provides information on the requirements for post-marketing studies and clinical trials under section 505(O)(3) of the Act Information on the requirements for post-marketing studies and clinical trials; describes the types of post-marketing studies and clinical trials
Guideline for Postmarketing Reporting of Adverse Drug Experiences	Guidance on ADE reporting requirements provided to applicants
Premarketing Risk Assessment	Provided guidance to industry on good risk assessment practices during the development of prescription drug products, including biologics; discussed the generation, acquisition, analysis and presentation of pre-market safety data
Drug safety information − FDA's Communication to the Public	Provides a description of how FDA communicates drug safety information to the public
Postmarket Adverse Event Reporting for Human Drugs and Licensed Biologics: Description of What Needs to be Reported	Specific instructions were provided on the content of adverse events to be reported
Post-market safety reports on human drugs and biological products, including vaccines	Some specific FDA thoughts and requirements for safety reporting
Format and content of risk assessment and mitigation strategies and their evaluation and modification	Provide guidance to organizations on how to establish risk assessment and mitigation strategies, and suggest standards for format and content

1.2 Guidelines of the EU pharmacovigilance regulation directive

Directive 201084/EU and Regulation (EU) No. 1235/2010 of the European Parliament and of the Council of Ministers, enacted in December 2010, which brought about significant changes in the monitoring of the safety of medicines across the EU [3]. The legislation amended existing pharmacovigilance legislation contained in Directive 2001/83/EC and Regulation (EC) No. 726/2004. Commission implementing Regulation (EU) No. 520/2012 accompanying the legislation provided comprehensive information on the operational aspects of the legislation. Good Pharmacovigilance Practices (GVP) issued by the EU provided advice for companies on pharmacovigilance implementation [4]. The EU GVP guidance is divided into two main blocks, chapters covering the main processes of pharmacovigilance (Chapters I-XVI) and product- or population-specific considerations (Chapter XVII). Chapters XI, XII, XIII and XIV of the guidance are left blank and they are replaced by other guidance documents available on the EMA website. The relevant regulatory directives and main contents are shown in Table 3, and the guidance documents are shown in Table 4.

Table 3 Main regulatory directives for pharmacovigilance in the EU

Name of regulation/directive	Content
Directive 2010/84/EU, Regulation (EU) No. 1235/2010	It sets out the legal requirements for the quality system established to strengthen pharmacovigilance in the EU; The requirement for marketing authorization holders to maintain and make available on request the pharmacovigilance system master file (PSMF); The improvement of the procedures for the submission of risk management plans by pharmaceutical companies; Periodic safety update reports (PSURs); Post-marketing safety and efficacy studies (PASS/PAES); Electronic submission of core pharmaceutical information by pharmaceutical companies; Patient reporting; And the development of a system for the management of the safety and efficacy of medicines in the EU. Periodic safety update reports (PSURs); Post-marketing safety and efficacy studies (PASS/PAES); Electronic submission of core drug information by pharmaceutical companies; Patient reports; EudraVigilace and data mining; Additional monitoring; Clarification of Pharmacovigilance Risk Assessment Committee (PRAC) responsibilities; Enhanced the openness and transparency of ferral procedure; Openness and transparency, etc.
Commission Implementing Regulation (EU) No. 520/2012	Structure, content, contents of annexes, maintenance, etc. of the main document of the pharmacovigilance system; Minimum requirements for the quality system of pharmacovigilance activities; Minimum requirements for the monitoring of data in the EudraViqilance database; Use of terminology, formats and standards; transmission of reports of suspected adverse reactions; Risk management plans; Periodic safety update reports; Post-marketing safety studies, etc.
Regulation (EU) No. 1027/2012, Directive 2012./26/EU	Timely notification and assessment of security issues

Table 4 Contents of the EU GVP guidelines

Modular	Chapters	Content
Module1: Main processes of pharmacovigilance	Chapter 1	Pharmacovigilance system and its quality system
	Chapter 2	Pharmacovigilance system master file
	Chapter 3	Pharmacovigilance screening
	Chapter 4	Audit of pharmacovigilance
	Chapter 5	Risk management system
	Chapter 6	Collection, management and submission of suspected adverse drug reaction reports
	Chapter 7	Regular security update reports
	Chapter 8	Post-marketing safety studies
	Chapter 9	Signal management
	Chapter 10	Additional monitoring
	Chapter 11	Security information communication
	Chapter 12	Risk minimization measures: Selection of tools and indicators of effectiveness
Module II: Specificity considerations related to products or populations		Vaccines against infectious diseases

1.3 Guidelines of pharmacovigilance laws and regulations in Japan

Japan's pharmacovigilance laws and regulations are centered on the "Pharmaceuticals and Medical Devices Law" (PMDL), and related laws and regulations are supplemented or extended by the PMDL, creating a tightly integrated system of laws and regulations [5]. The PMDL formally replaced the previously implemented "Pharmaceutical Affairs Law" in November 2014 and has become the highest level in Japan's pharmacovigilance legislation. Besides, relevant regulations were formulated on the basis of the PMDL [6]. The PMDL specifies pre-market and post-market vigilance requirements for drugs, as well as the need for ADR reporting for healthcare organizations and medical personnel.

Japanese Good Vigilance Practice [7] stipulated that MAHs should establish a pharmacovigilance system to convey drug safety information in a scientific and rational manner. Japan's GVP has 5 chapters and 17 articles, mainly covering the pharmacovigilance system (personnel, organization, and standard operating procedures), the allocation of duties within the MAH (duties of the general manager of manufacturing and sales, the person in charge of safety management, and the person in charge of implementation of safety management, etc.), the routine pharmacovigilance activity processes (collection of safety information, drafting and implementation of safety and security measures, risk management program, early post-marketing monitoring program), education and training requirements.

"Good Post-Marketing Surveillance Practice" [8] made clear that the MAH is the first responsible party for drug safety monitoring and must provide follow-up and feedback on drug safety.

"Guidelines for Reporting Adverse Reactions in Patients" [9] stipulated that patients suspected of ADR should have a clear process to guide them to report information to the drug regulatory authority.

1.4 Guidelines of pharmacovigilance laws and regulations in China

The "Administrative Measures for Reporting and Monitoring of Adverse Drug Reactions", which came into effect on July 1, 2011, played a driving role in establishing and improving the function of China's ADR monitoring system, and provided the direction for ADR monitoring in the following decade. With the development of the industry and the continuous change of the situation at home and abroad, a series of related policy documents and guidelines have been issued to further improve the ADR monitoring in pharmacovigilance practice.

At the 12th meeting of the Standing Committee of the 13th National People's Congress on August 26, 2019, the "Drug Administration Law of the People's Republic of China" was amended for the second time. The newly amended "Drug Administration Law" centers on the supervision and management of drugs, and unifies all aspects of the listing, production, operation, circulation, and use of drugs. Therefore, it is the guiding principle for guaranteeing the quality and safety of drugs, and it also is the programmatic law for pharmacovigilance legislation. The newly revised "Drug Administration Law" proposed in the general provisions that the state shall establish a pharmacovigilance system to monitor, identify, evaluate and control adverse drug reactions and other harmful reactions related to the use of drugs, which, for the first time, explicitly mentioned the concept of pharmacovigilance in Chinese laws and regulations.

On May 13, 2021, the announcement of the National Medical Products Administration (NMPA) on the GVP (No. 65 of 2021) was issued and came into force from December 1, 2021. The announcement specified that the purpose of the NMPA to organize and develop the GVP was to regulate and guide the pharmacovigilance activities of drug marketing license holders and drug registration applicants. Table 5 shows the framework of the guidelines for China's pharmacovigilance laws and regulations.

Table 5 Summary of Chinese pharmacovigilance laws and regulations guidance documents

Title	Publishing time	Level
Measures for the Administration of Adverse Drug Reaction Reporting and Monitoring (Ministry of Health Decree No. 81)	May 4, 2011	Departmental regulation
Code of Practice for the Writing of Periodic Safety Updates on Medicines	September 6, 2012	Sectoral normative documents
Guidelines for Adverse Drug Reaction Reporting and Monitoring and Inspection (Trial)	July 2, 2015	Sectoral normative documents
Announcement on Direct Reporting of Adverse Reactions by Marketing Authorization Holders of Medicines (Announcement No. 66)	September 30, 2018	Sectoral normative documents
Guidelines for the Collection and Reporting of Individual Adverse Drug Reactions (Circular 131)	December 21, 2018	Sectoral normative documents
Drug Administration Act	August 26, 2019	Law
Measures for the Administration of Drug Registration	March 30, 2020	Departmental regulation
Measures for the Supervision and Management of Pharmaceutical Production	March 30, 2020	Departmental regulation
Announcement of the State Drug Administration on the Publication of Pharmacovigilance Quality Management Standards (No. 65 of 2021)	May 13, 2021	Sectoral normative documents

Compared with the Europe Union and the United States, China has basically formed a system of laws and regulations on pharmacovigilance and is becoming more mature. But from the content and the formulation process, China's pharmacovigilance laws and regulations still have certain problems.

2 Problems in pharmacovigilance laws and regulations

2.1 Nontransparent formulation process

An analysis of the formulation process of China's "Drug Administration Law" and the GVP revealed that laws and regulations were formulated in accordance with China's tradition of policymaking, i.e., two-way interactions of top-down and bottom-up that formed specific policies and regulations.

In the United States, the European Union, and Japan, during the long process of formulating pharmacovigilance laws and regulations, the regulatory agencies were able to listen to the demands of various stakeholders in the broadest sense and formed the laws. The maintenance and further revision of the EU GVP can be proposed by any member of the EU regulatory network and any other stakeholder to amend or add chapters to the GVP. Besides, members of the public and non-regulatory stakeholder organizations can send their proposals through the relevant websites. The development of China's pharmacovigilance laws and regulations, from the outset, is from the top. It means the State Drug Administration proposed and drafted the laws, and then it went down with the problem to do some research. After several iterations, the laws were finally formed. In this process, it was not transparent since the whole society did not participate, which cannot fully reflect the essence of the drug safety incident requirements. Therefore, the administrative implication was over the professional implication.

2.2 Poor dynamic adaptability

As the construction of laws and regulations is actually administratively led, coupled with the long-established sense of bureaucratic mindset and its

corresponding mode of operation, the formulation and implementation of legal norms in the area of pharmacovigilance tend to lag behind the real needs of society, results in poor dynamic adaptability.

The formulation of pharmacovigilance laws and regulations in the United States, the European Union, Japan and other countries is more closely linked to the social needs, and can adapt to the development of the society. Meanwhile, new tools, new standards, and new methods of supervision can also be applied to pharmacovigilance practice.

However, some China's laws and regulations, such as the "Measures for the Administration of Adverse Drug Reaction Reporting and Monitoring", have not been revised for nearly 10 years. Both the original intent of the legislation and regulations, as well as the process of their enactment and the status of their promulgation and implementation, has a considerable time lag in relation to the ever-changing situation of drug production, operation and use, and the people's demand for medication. The formulation, amendment and implementation of other corresponding legal norms on pharmacovigilance are also quite similar. This situation shows that the dynamic

2.3 Insufficient use of attention mechanisms

From the practice of pharmacovigilance, whether in developed countries (such as the United States) or in developing countries (such as China), the attention mechanism is of great significance to the formulation and implementation of legal norms on pharmacovigilance. Regulatory agencies use sudden drug events to attract social forces, including the public, the official and the media. This cannot adjust, improve or even create new legal norms by paying great attention to the safety of medicines and the related regulatory policies of the whole society. The U.S. FDA analyzed the reasons for the regulatory lag in the Rofecoxib withdrawal incident, and promulgated the "Food and Drug Administration Amendments Act". It also reorganized the Center for Drug Evaluation and Research (CDER) and conducted regulatory scientific research to optimize its pharmacovigilance system. China has not utilized the attention mechanism in the formulation of pharmacovigilance laws and regulations, resulting in the phenomenon that the laws and regulations were out of touch with the reality of pharmacovigilance practice.

To make drug safety regulation highly adaptable, the attention mechanism of drug regulatory laws and norms should be established. It is only through the transmission of the attention mechanism that information on major issues related to the drug industry and drug control can be introduced into the agenda of pharmacovigilance policy in a timely and effective manner, thus promoting the construction and adjustment of pharmacovigilance policy in a timely manner.

2.4 Fragmentation of the guide to laws and regulations

From a systemic perspective, China's policies, laws and regulations relating to pharmacovigilance have not been systematic enough, and there is a lack of rigorous supporting guidance documents. There are conflicts in the current laws and regulations, and their functions cannot be fulfilled. Some laws and regulations are no longer able to meet the needs of the society and should be repealed or amended. Other laws should be set up on time. All of these require further efforts by the relevant departments. For example, in terms of the time limit for reporting individual ADRs, according to the GVP issued and implemented in 2021, serious ADRs should be reported as soon as possible, not later than 15 days after the information is known, and non-serious ADRs not later than 30 days after the information is known. However, the "Measures for the Administration of Reporting and Monitoring of Adverse Drug Reactions", which was released and implemented in 2011, stipulates that drug manufacturers, business enterprises and medical institutions should report new and serious adverse drug reactions within 15 days, but ADR with deaths should be reported immediately. Other adverse drug

reactions should be reported within 30 days. The time limit for reporting new and general cases in the above two documents is not consistent.

To ensure the smooth implementation of pharmacovigilance activities, the U.S. FDA has issued nearly 40 documents to guide enterprises in post-marketing pharmacovigilance, which elaborates on the details and methods of safety identification, risk minimization plan, post-marketing study, adverse reaction report, risk communication and other processes in pharmacovigilance. The European Union has also developed a detailed document to guide member states in their pharmacovigilance activities. Each chapter of the EU GVP provides the legal, technical, and scientific background in Section A. Section B gives operational guidance that is based on EU regulations and reflects the various international scientific and regulatory approaches, formats, and standards for Section A. If there is no such formal agreement or expert consensus, Section B describes the approach considered in light of current general thinking in the field. Section C focuses on the details of applying the methods, formats and standards in the EU, as well as other aspects of operating the corresponding processes in the EU. China has established a pharmacovigilance system and promulgated the GVP to define the scope of responsibilities and behaviors of MAHs in pharmacovigilance activities. However, the lack of technical documents on guidelines for regulators, healthcare institutions, drug manufacturers, drug distributors, drug dealers, patients, and other stakeholders constrains the construction of a legal system for pharmacovigilance.

China is currently in a transitional stage from ADR monitoring to pharmacovigilance, the content of which still focuses on ADR monitoring, and the relevant provisions lack systematic and in-depth research. Therefore, China can accelerate the establishment and improvement of China's pharmacovigilance legislation by strengthening the concept of pharmacovigilance, clarifying its contents and procedures, integrating scattered legal provisions, adjusting inapplicable legal provisions, and supplementing new requirements, and methods, so as to lay the foundation for carrying out pharmacovigilance work as soon as possible.

2.5 Poor articulation of laws, regulations and institutional guidelines

The laws and regulations in the United States not only stipulate the basic principles and requirements of pharmacovigilance, but also provide in detail the specific operational procedures and methods, including the monitoring, reporting, assessment and control of adverse drug reactions. In addition, U.S. pharmacovigilance laws and regulations are also linked to laws in other related fields, such as medical devices and cosmetics, which can ensure the safety and efficacy of the entire drug, cosmetic and medical devices.

A series of relevant laws and regulations have also been introduced to further refine and standardize the specific operation of pharmacovigilance in China. For example, there are clear legal provisions on the duties and obligations of all parties in pharmacovigilance, including drug marketing license holders, medical institutions and drug manufacturers. However, after the introduction of laws and regulations, the connection between laws and regulations is weak. Taking the system and guidelines of pharmacovigilance as an example, the "Measures for the Administration of Adverse Drug Reaction Reporting and Monitoring" was released in May 2011 and implemented in July, the "Drug Administration Law" was released on August 26, 2019, and implemented in December, and the GVP was released on May 7, 2021, and implemented in December. For MAHs, it is inevitable that there will be a situation of non-adaptation in a short period of time when they change from the adverse drug reaction reporting system, which has been in force for more than 10 years. For the pharmacovigilance system, which has a wider scope of monitoring and more targets, has a great impact on pharmacovigilance practice. It is suggested that China's health administration should work with the drug supervision and management

departments to make the connection among the "Measures for the Administration of Adverse Drug Reaction Reporting and Monitoring", the "Drug Administration Law" and the "GVP" closely. Besides, they should make it clear that different main bodies should bear corresponding responsibilities under the concept of the full-life-cycle supervision of pharmacovigilance.

3 Recommendations for optimizing pharmacovigilance laws and regulations

(1) We should enhance the openness and transparency in formulating laws and regulations. When formulating laws and regulations on pharmacovigilance, the regulatory authorities should fully solicit opinions from all sectors of the society, especially the MAHs, drug manufacturers, drug sales enterprises, medical institutions and patient groups. Through public consultation, symposiums, hearings, surveys and questionnaires, opinions from all parties will be widely collected to ensure that the process of formulating laws and regulations is more open, so that the guideline documents for laws and regulations can reflect the will of the majority of stakeholders. The above measures can solve the problems of a closed formulation process and poor dynamic adaptability.

(2) We should establish a rapid response mechanism. The mechanism of attention should be utilized to pay attention to the problems and risks of drugs. Government departments can collect and analyze information on a variety of aspects in the field of pharmacovigilance, such as major events, controversial cases, and domestic and international research progress, to identify problems and potential risks. Then, corresponding pharmacovigilance laws and regulations can be formulated. At the same time, it is necessary to respond to emerging problems in a timely manner, including new serious adverse drug reactions, drug interactions, medication errors and so on. The above measures can address the problem of underutilization of attention mechanisms.

(3) We should continuously update and revise laws and regulations. A mechanism can be established for the regular review and revision of legal norms on pharmacovigilance, keeping abreast of new changes and technological development trends in international drug research and development, production, circulation and use. The above measures can solve the problem of poor dynamic adaptability of laws and regulations.

(4) We should systematically integrate and clarify these regulations and laws at the legislative level. It is recommended that existing pharmacovigilance-related laws, regulations, systems, guidelines, norms and other documents should be sorted out. Then we can identify provisions that are in conflict, overlap or ambiguous. By revising or formulating new laws and regulations, the scope of application, targets, procedures, responsibilities and other elements should be clarified to ensure coordination and consistency among the systems. The above measures can solve the problem of fragmentation of the guidelines on laws and regulations.

(5) We should strengthen interdepartmental coordination among regulatory agencies. An interdepartmental coordination mechanism should be stablished for pharmacovigilance, which will promote information-sharing, communication and cooperation among various departments. Besides, we should clarify the responsibilities and authority of each department to avoid regulatory duplication and gaps and ensure smooth articulation between systems. The above measures can solve the problem of poor convergence between the guidelines of laws and regulations.

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