

Influence of Supply Chain on the Safety of Biomedicine: Case from Vaccine Cold Chain Logistics

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Abstract. Medicine, as a particular commodity, its numerous properties that determine the importance of its safety. The pharmaceutical supply chain is a crucial link to ensure it. China steps up late in the pharmaceutical industry, and there are still many problems to address in the supply chain that threaten the safety of medicines. This article first introduces the concept of biomedicine and its supply chain, and the particularity of pharmaceutical products. Then, through the case analysis, the lack of standardization and non-compliance with storage and transportation are the reasons for medicine accidents in the pharmaceutical supply chain. Finally, it puts forward suggestions for the future development of the pharmaceutical supply chain from two aspects: strengthening information management and improving rules and regulations.

Keywords: Pharmaceutical supply chain; Medicine safety; Logistics; Informatization.

1. Introduction

The bio-pharmaceutical supply chain is the supply chain system of the biopharmaceutical industry, whose main components include medicine developers, medicine manufacturers, medicine wholesalers, medicine retailers, and patients. As a particular product, medicine has many characteristics that other commodities do not have, such as strict timeliness, unique chemical properties, high-quality requirements, and high professionalism. The combination of these complex properties places high demands on the quality and safety assurance of every link in the pharmaceutical supply chain. The quality and safety assurance of any link in the bio-pharmaceutical supply chain will affect the quality of medicines and cause more serious social problems.

For many years, medication safety, especially bio-medicine safety, has been a common concern of society. Especially in recent years, medication safety incidents in bio-medicine have been repeatedly exposed, immediately becoming a hot spot of public opinion. In past cases, a large part of the problems occurred in the field of the bio-pharmaceutical supply chain or have a close connection with this field. One of the typical cases is the Shandong Vaccine Incident in March 2016. These events also prompted relevant state departments and legislatures to quickly issue laws and regulations to regulate medicines, especially in bio-medicine, mainly involving production, procurement, transportation, and other links in the bio-pharmaceutical supply chain. Based on the above phenomenon, this paper discusses the internal relationship between the bio-pharmaceutical supply chain and medication safety, clarifies the development context, current situation, and problems to be solved of the bio-pharmaceutical supply chain, and provides a reference for the healthy development of bio-pharmaceutical supply chain and its future guarantee for medication safety.

2. literature review

Safety has always been one of the most important topics in the pharmaceutical industry. Yan and Zhou summarized the particularity of medicines in terms of duality, exclusivity, importance of quality, defects and realization [1]. In general, the bio-pharmaceutical supply chain is a very complex structure, which is mainly divided into research and development, production, circulation and use, covering institutions including pharmaceutical material suppliers, pharmaceutical companies,

scientific research institutions, colleges and universities, medical equipment manufacturing merchants, distributors, hospitals, pharmacies, etc. Compared with the supply chains of other industries, the supply chain of the bio-pharmaceutical industry often has more possibility of problems in terms of security. Shen and Li respectively analyzed the complex structure of the supply chain and the production and circulation of related enterprises, and elaborated the reasons why the security problems in the pharmaceutical supply chain emerged [2]. Starting from the specific temperature requirements of biological products in transportation and storage, Li et al. took the temperature control, monitoring and management in cold chain logistics as an example to illustrate the strictness and refinement of the safety guarantee of biological products [3].

Issues in the pharmaceutical supply chain have long been a pain point in the industry. Because this not only involves traditional problems in inventory, procurement, and information exchange in the supply chain, but also social problems such as lack of professional knowledge, weak supervision, policy negligence, and even abuse of power. All problems will ultimately have serious implications for medication safety. Dheeraj and Kumar, using interpretive structural modelling (ISM) approach, find that the factors demand forecast, communication between the supply chain members and 'proper planning and scheduling' are three most critical factors of vaccine supply chain [4]. Liu et al. construct a vaccine traceability service platform based on blockchain technology, providing important support for enterprises to adopt blockchain technology and some guidance for decision makers to implement scientific and feasible vaccine supply chain management schemes [5]. Solving the problems of the pharmaceutical supply chain is a long-term and multi-faceted process. For example, Aren has proposed a new electronic information management method for medicine inspection and faster than the previous paper method [6]. Additionally, information cooperation between hospitals and commercial companies has been strengthened. Fatima Ouzayd et al. propose a model for instant cold chain monitoring using a colored Petri net (CPN), which focuses on the central storage of vaccines and takes into account certain WHO (World Health Organization) recommendations [7]. Qi et al. Lev develop a model to study the conditions under which the distributor will transport the vaccines via a cold chain or non-cold chain, emphasizing the retailer's role in improving the and cold chain transportation [8]. This method is more intelligent distributor's non-cold chain transportation behavior.

This article will use the method of typical medicine safety case analysis to clarify the typical problems in the current bio-pharmaceutical supply chain, and discuss the solutions to such problems and the development direction of the future pharmaceutical supply chain.

3. Bio-pharmaceutical Supply Chain

3.1 The Concept of Bio-medicine

Bio-medicine is modern medicine that integrates biotechnology and medical technology through the pharmaceutical and biomedical engineering industries. The biomedical sector is composed of the biotechnology industry and the pharmaceutical industry. Biomedical engineering is the comprehensive application of life science and engineering science principles and methods. It is the general term for understanding the structure, function, and other life phenomena of the human body from the perspective of engineering at multiple levels of molecules, cells, tissues, organs, and even the entire human body system, and studying artificial materials, products, devices, and system technologies, which are used for disease prevention, treatment, human function assistance, and health care.

The main subjects of the pharmaceutical supply chain include bio-pharmaceutical enterprises, financial institutions, and bio-pharmaceutical distribution enterprises [9]. Foreign research on the pharmaceutical supply chain mainly focuses on logistics. Most domestic investigations conduct on inventory costs from the perspective of hospital pharmacies. The pharmaceutical supply chain is a network structure in which pharmaceuticals are produced by pharmaceutical factories, distributed and sold by pharmaceutical companies, and used by hospitals for patients. As shown in figure 1, the five

prominent members of raw material suppliers, medicine manufacturers, medicine wholesalers, medicine retailers, and patients constitute a traditional pharmaceutical supply chain in a general sense.

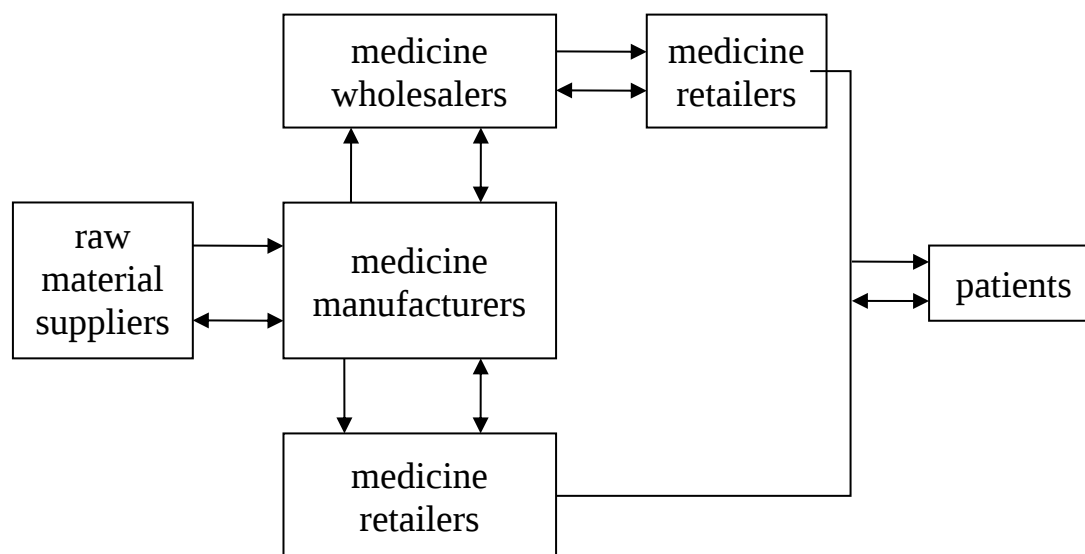


Fig. 1 Pharmaceutical supply chain structure model

3.2 The Particularity of Bio-pharmaceutical Supply Chain

Biological medicines generally have the following characteristics. They have Biological activities. The physical action of the natural medication is the pharmacodynamic effect, and the molecular structure of biological medicines has specific active sites [10]. They have complicated structures. They are biological macromolecules or organisms. In addition to the natural conformation, some are also artificially allosteric or modified. These active structure parts have a strict spatial arrangement. Once the functional structure is destroyed, its pharmaceutical effect will disappear. The production or preparation process requires complex, harsh conditions. They also have poor stability. The high nutritional value of biological medicines is easily contaminated by exogenous factors, resulting in failure and toxic side effects. Low temperature and sterile are required in the production process.

The characteristics of bio-medicine are closely related to the requirements of the corresponding supply chain. Because of the many attributes of biological medicines, such medicines are easily affected by environmental cleanliness, temperature, light, and even rays, which might change their safety and effectiveness. And these influencing factors are closely related to all aspects of the biological medicine supply chain. The supply of raw materials, production process, packaging materials, storage environment, transportation requirements, and usage methods of natural medicines, as well as the formulation and implementation of policies and regulations closely related to these links, will directly impact the safe use of biological medicines.

3.3 Inadequacy of Bio-pharmaceutical Supply Chain in Ensuring Medication Safety

With the development of science and technology and the continuous improvement of people's living standards, the masses have a higher demand for pharmaceutical products with good efficacy, while the competition among pharmaceutical distribution enterprises is also increasing. In our country, although significant progress has been made in the supply chain industry in recent years, there are still many defects in the supply chain in the pharmaceutical field. The more severe defects often lead to the quality of pharmaceutical products and medication safety, which need to attract the attention of relevant scholars and practitioners. These defects are mainly reflected in the following aspects:

Firstly, there is information asymmetry. In the entire medicine supply chain, medicine sales links, such as pharmacies, have more information on medicines than other links in the supply chain [11]. In addition to being more independent in choosing common treatments and drugs, the general public chooses appropriate medication according to the guidance of doctors in most cases. Doctors often

have absolute dominance over patients' medication choices, which results in information asymmetry between doctors and patients about medicines. Once a doctor without medical ethics prescribes indiscriminately and indiscriminately for personal gain, patients will become the most direct victims. Not only did they suffer property losses, but their health could not be effectively improved and, in severe cases, even life-threatening. This phenomenon is one of the reasons that the doctor-patient relationship is strained today.

Secondly, the level of each node in the supply chain is uneven, which might increase the risk of medication safety. Due to the particularity of pharmaceutical products and the complexity of the pharmaceutical supply chain, whether it is for the production, storage, and transportation of pharmaceutical enterprises or the manufacturers and wholesalers of related equipment and facilities, the safety requirements of every node of the supply chain are very high. However, it is tough to maintain a high degree of coordination among each enterprise in the pharmaceutical supply chain. Even some large enterprises will experience medicine injury incidents caused by the supply chain. Therefore, it isn't easy to ensure the quality of medicines in the whole process from manufacture to use.

Thirdly, there are irregularities in the circulation link. Many bio-pharmaceutical enterprises, poor management ability, and the disorder of medicine circulation have caused various counterfeit medicines and inferior medical devices to enter the market in our country. What is worse, to make huge profits, they collude with illegal medical practitioners or even legal practitioners to buy relevant medicines and equipment at low prices, dump them to various places at a higher price without adopting compliant transportation methods and conditions, in which situation medication safety is even more impossible to be guaranteed. This phenomenon is widespread in the second-class vaccine industry.

4. Case Analysis - Shandong Illegal Vaccine Case

4.1 Background

In March 2016, Shandong police cracked a criminal vaccine case worth 570 million yuan. Nearly 2 million doses of Class II vaccines for adults and children were shipped to 80 counties and cities in 24 provinces without strict cold chain storage and transportation. The perpetrators, Pang Hongwei and Sun Qi, mother, and daughter, contacted relevant legal or illegal vaccines sales persons through the Internet, purchased a total of 25 second-class vaccines such as rabies and influenza virus, and then sold them at a higher price to more than 300 illegal vaccine operators or CDC's grassroots inoculation points in 24 provinces across the country. In this case, Pang Hongwei and Sun Qi bought the vaccines for 260 million yuan and sold them for 310 million yuan, earning an illegal income of more than 50 million yuan.

In 2017, the Intermediate People's Court of Jinan City, Shandong Province, sentenced the defendant Pang Hongwei and Sun Qi in court. According to the court decision, defendant Pang Hongwei was convicted of illegal business operations and was sentenced to 15 years in prison and all personal property confiscated. Defendant Sun Qi was sentenced to six years in prison for the crime of illegal business operations and seized 7432859.40 yuan of private property and unlawful vaccines and other medicines according to law.

4.2 Related Information

Vaccines can be classified into many different categories according to their other effects and properties; first-class and second-class vaccines are the two basic types of vaccines in China, which are not distinguished by chemical properties and effects but by cost. The former is a state-paid vaccine, while the latter is an individual-paid vaccine. Generally speaking, Class I Vaccines are much more critical than Class II Vaccines because they usually involve safeguarding the health base of citizens and preventing the spread of epidemic diseases. The widely vaccinated Covid-19 Vaccines are a type of Class I Vaccines, and the vaccines, in this case, are all Class II Vaccines.

The storage and transportation requirements of vaccines are stringent. Slight negligence may lead to the inactivation of vaccines, which may cause many adverse effects on the human body. In mild cases, the vaccination will be ineffective, the timing of vaccination will be delayed, and in severe cases, it will endanger the life of the vaccinated, even leading to death.

4.3 Case Analysis

This case mainly reflects two significant problems in the current supply chain of bio-medicine, especially vaccines: one is the lack of standardization in circulation, the other is no strict storage and cold chain transportation requirements, and the third is the insufficiency of information sharing.

4.3.1 Lack of Standardization in Circulation

Generally speaking, the circulation process of Class II vaccines is shown in figure 2. The income composition of vaccine-related staff mainly includes three parts: basic salary, performance salary, and bonus. The prize is basically from the income of the second-class vaccine. As a result, it is no longer a secret that companies increase their sales prices when allocating Class II vaccines. To ensure expenses, companies focus on increasing sales prices. It isn't easy to strictly review business licenses and certificates of the enterprises in the distribution channels of Class II vaccines, and so does the quality assurance of vaccines. For further profit increase opportunities, as a means of competition, lower price advantage causes cost reduction, e.g., cheating on cold chain transportation. The quality of vaccines with unqualified storage will be significantly affected or even efficacy lost.

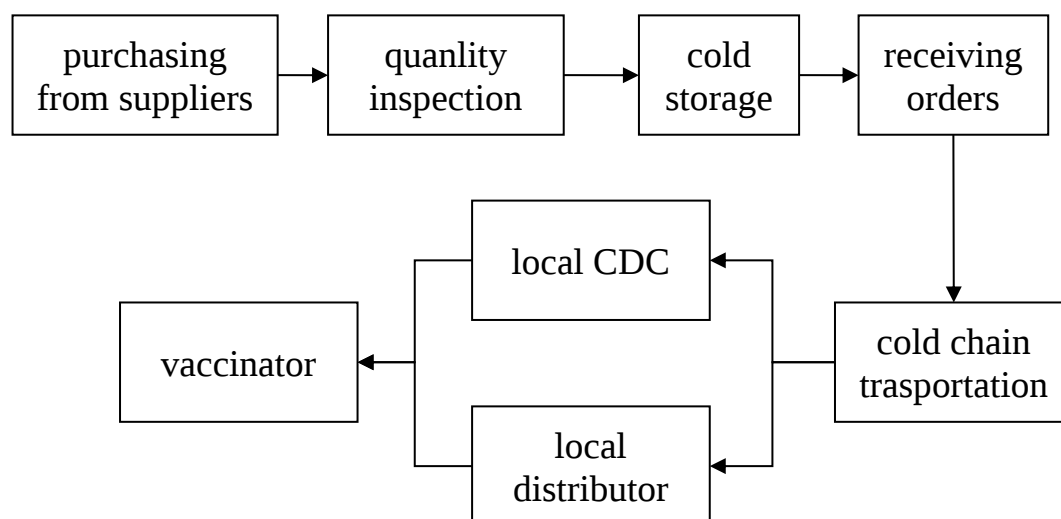


Fig. 2 Circulation process diagram of Class II vaccines

Irregularities in circulation facilitate the low-cost purchase of vaccines by inoculation units, which affects the middle and downstream distribution process of the entire second-class vaccine supply chain. The profits space gets huge after the price increase, even if it flows in the disease control system. It becomes the profit basis of the vaccine dealers. For example, manufacturers sell vaccines to disease control departments through agents, who distribute them to different levels and vaccination sites. During the transmission, the price of each group is different and increases layer by layer. In this case, the perpetrators took advantage of the irregularity to obtain huge profits by purchasing vaccines from illegal agents at low prices and selling them at high.

Given the lack of clear rules and regulations management, the continuous escalation of interests eventually led to a vicious expansion within the disease control department, individual vaccine dealers who acquire revenues, and cross-border smuggling of vaccines also appeared. In 2021, a Guangxi court decided on a case of smuggling nine-valent cervical cancer vaccines from Hong Kong. The smuggled vaccines of the perpetrators failed to pass through normal Customs channels and non-standard circulation measures for national vaccines and pharmaceuticals. This has destroyed social

stability and national security and caused substantial hidden dangers to the quality of vaccines and vaccination safety.

4.3.2 No strict requirements for storage and cold chain transportation

In this case, the vaccine's lack of strict cold-chain transportation is also a severe problem in the relevant supply chain. The temperature sensitivity of the vaccine itself makes it possible to denature and inactivate due to high temperature from production to where used. It is a time and labor-consuming but low-economic yield work to ensure the regular operation of vaccine cold chain transportation and related supporting facilities.

For most vaccines, the cold chain storage temperature is between 2°C and 8°C; some need to be below -20°C. During the cold chain transportation of vaccines, the transporter must regularly detect and record the temperature to ensure the vaccines are at the specified ambient temperature. The recipient must witness and check the temperature monitoring records from the vaccine transporter. The vaccines should be stored neatly, with clear labels, and a certain distance should be maintained between vaccines to keep the air conditioner free. Appropriate cold chain equipment also needs management by authorized personnel, mainly for temperature recording, maintenance, cleaning, repairing, etc.

These requirements are only part of the vaccine cold chain management, but people who focus on interests will not consider the various vaccine logistics issues. In this case, by the statement of the police handling the case, the perpetrator sent vaccines to different destinations just in a foam plastic box with ice cubes after receiving the goods. The warehouse temperature reached 14 °C, exceeding the standard storage temperature for conventional vaccines, and there was no refrigeration equipment. Most vaccines were piled up in a disorderly manner. Such storage conditions were far from the standard requirements. It would inevitably cause a severe vaccine safety disaster once these vaccines were on the market.

4.3.3 Lack of information sharing

The coordinated operation of the supply chain is based on the high-quality information transmission and sharing of each node enterprise. The biopharmaceutical supply chain's safe, standardized, and smooth process affects users' health. Therefore, it is even more necessary for the information on each link in the supply chain to be highly transparent and highly shared. In this case, if the traceability investigation of illegal vaccines is carried out, it is not difficult to find the information in many links opaque. The non-transparency and non-sharing of information allow vaccine dealers to take advantage. For example, in terms of price, because the current vaccine supply chain in China is long and complex-structured, and has not formed strict regulations to monitor the information transparency in the supply chain, information asymmetry is prevalent. From raw material suppliers, medicine manufacturers, and medicine wholesalers to medical service institutions and retailers, the non-sharing of price information at all levels of the supply chain leads to huge room for price increases. Illegal operators can buy at low prices and sell at high prices to make huge profits.

Another example is the transportation of cold chain vaccines. The previous article has introduced the strictness of vaccine storage and transportation requirements. Still, surprisingly, Mrs. Pang and her daughter in the case dared to store the vaccines in an environment of 14 degrees Celsius for their interests and even piled them up in a disorderly manner. A large part of the reason can be attributed to the lack of information sharing. To effectively prevent the recurrence of similar cases, the detection indicators of vaccines in cold chain transportation must be transparent and shared with the entire supply chain.

5. Current measures to deal with pharmaceutical supply chain problems

The causes of biomedical supply chain problems and medicine safety accidents can be roughly divided into three categories: backward technology and unfavorable coordination in supply chain and logistics, and the lack of rules and regulations in supply chain administration. Moreover, the extent

of information sharing and transparency is low. These problems can be solved from the following aspects.

5.1 Strengthen supply chain information management

For example, cold chain logistics is the representative of logistics engineering in the pharmaceutical supply chain, directly determining the supply chain's efficiency by its degree of informatization. The core technology and essential equipment of cold chain logistics should be updated and improved promptly, such as the automatic upgrade of the temperature control alarm system so that managers can take measures more timely and effectively.

The traditional paper management method has many problems in the record management of cold chain transportation, such as low efficiency, high cost, short validity period, and low authenticity. Currently, many hospitals in China have completed the docking and sharing of medical information with medicine companies by establishing supply chain information platforms. The function of electronic cold chain transportation records is gradually being developed and improved. In the future, electronic information technology will completely replace paper management methods, and efficiency and accuracy will significantly improve.

5.2 Improve the pharmaceutical supply chain development management system

The timely formulation of specific medicine circulation rules and standardization of circulation channels and procedures will prevent illegal circulation in the current pharmaceutical supply chain. For example, in the case of illegal vaccines in this article, the market circulation of Class II vaccines lacks rules and regulations, and the sources are chaotic, which is far less manageable than a single channel for Class I vaccines. China should promptly incorporate risky medicines such as vaccines into the standardized management system and, at the same time, strengthen policy support for pharmaceutical manufacturing and distribution enterprises so that enterprises can meet costs and increase income to ensure the medicine quality.

Censorship and penalties should also be strengthened. All regulatory departments should cooperate in reviewing the legality and safety of the medicine strictly. For example, the medicine regulatory department is responsible for the supervision of medicine quality and circulation, and the health department is responsible for the supervision and management of medicine use. Electronic information systems can track the specific circulation process of medicines, find out where the problems lie, and hold responsible persons or enterprises accountable. Punishment methods such as revocation of medicine business licenses can be used for enterprises to enhance the law's binding force and degree of warning.

5.3 Use supply chain control tower and blockchain to achieve information sharing

The supply chain control tower is not a new concept, and there is a considerable amount of public information and discussion in the field of supply chain management. For example, Gartner defines the supply chain control tower as "a physical or virtual dashboard" that strengthens the supply chain, which emphasizes the visualization characteristics of the chain control tower; Accenture's definition is "a shared service center," and its definition highlights the comprehensive business guidance capabilities of the supply chain control tower.

A blockchain is a chain consisting of one block after another. Each block stores a certain amount of information, and they are connected into a chain according to the time sequence of their generation. Compared with traditional networks, blockchain has two core characteristics: one is that data is difficult to tamper with, and the other is decentralization. Based on these two characteristics, the information the blockchain records is more authentic and reliable, which can help solve the problem of mutual distrust between people.

Due to the particularity of bio-medicine, its supply chain undoubtedly has higher requirements for information sharing. The control tower dramatically improves the visibility of the supply chain, which can not only make better planning and decision-making, but also quickly identify problems, identify

root causes, and alert business leaders to solve problems quickly and effectively. Blockchain technology can completely record and store information on the whole process of vaccine development, production, transportation, and vaccination. It can ensure the authenticity and reliability of vaccine information. Since it is difficult to forge and tamper, it can achieve absolute traceability and supervision. If the supply chain control tower and blockchain technology can be well used in the biomedical supply chain, information sharing and transparency will be significantly improved, and medication safety will be further guaranteed.

6. Conclusion

After an overview of the pharmaceutical supply chain and related case analysis, this paper summarizes the problems that may lead to medicine safety accidents in the pharmaceutical supply chain. In general, China's bio-pharmaceutical supply chain is still at an immature stage. Whether the coordination degree of the supply chain, the level of logistics technology, the level of administrative management, or the technology of bio-medicine itself, a gap exists between China and developed countries. Correspondingly, medicine safety problems occur frequently in my country, which is now one of the world's hardest-hit areas for medicine safety. Although not all medical issues are related to the pharmaceutical supply chain, developing a sound pharmaceutical supply chain system is undoubtedly significant to ensure medicine safety.

This paper mainly puts forward suggestions on the development of the pharmaceutical supply chain from three aspects: to strengthen information management, to improve the management system, and to elevate the extent of information sharing. China's pharmaceutical supply chain industry still has a long way to go to develop to a mature level. The above three aspects and other aspects, such as supply chain digital upgrading, logistics automation, core technology innovation, and strengthening personnel training, are all essential directions of chain development. As a vital link in people's livelihood issues, it is necessary to increase investment in the pharmaceutical industry, correctly solve various irregularities in the pharmaceutical supply chain, and build a sound pharmaceutical supply chain system. Improving the supply chain's efficiency while also ensuring the safety of medicines is the ultimate goal of the development of the pharmaceutical supply chain.

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