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Analysis of Compliance Management Practice of American Drug Registration Applicants and Its Enlightenment to China

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Abstract

In order to achieve the goal of drug safety, effectiveness and quality control, corporate compliance management construction is significant. Therefore, this paper systematically analyzes the seven elements of compliance management for U.S. pharmaceutical manufacturers as described in the *Compliance Program Guidance for Pharmaceutical Manufacturers* issued by the HHS-Office of Inspector General, as well as further analyzes the implementation of the guidance by representative multinational companies in different drug registration stages. Finally, some suggestions and implications are proposed to strengthen the construction of compliance management for Chinese drug registration applicants based on the former practical experience.

Keywords

Drug Registration, Compliance Management, Compliance Program, Pharmaceutical Manufacturers

1. Introduction

"The Belt and Road" Initiative and "Going Out" Strategy have provided opportunities for Chinese pharmaceutical enterprises to develop internationally. However, standards and compliance issues have been a constraint in the internationalization process of Chinese pharmaceuticals [1]. The international market possesses its complexity and the market access system of different countries varies. Enterprises on the road to internationalization are first faced with the risk of compliance in the process of drug registration and marketing in foreign countries. Compliance not only determines whether the drug can meet the foreign market access requirements, but also decides the speed of drug marketing, which

is crucial to the economic efficiency and corporate reputation of China pharmaceutical enterprises and even the national reputation. Therefore, it is urgent for pharmaceutical enterprises to strengthen the construction of corporate compliance management in the process of "Going Out". Moreover, they should focus on the drug registration process to carry out specific compliance management. In March 2021, *Pharmaceutical Industry Compliance Management Practices* in China was officially released, providing standards and references for pharmaceutical enterprises to implement compliance management. However, its content mainly focuses on anti-commercial bribery, anti-monopoly, finance and taxation, product promotion, centralized purchasing, environment, health and safety, adverse reaction reporting, data compliance and cyber security, etc., while the compliance management of drug research and development (R&D) and registration process has not formed a structured system yet. As the starting point of drug regulatory activities and pharmaceutical enterprise marketing activities, the importance of drug registration cannot be doubted. Therefore, it is urgent for pharmaceutical enterprises to conduct the compliance management in the process of R&D and registration. As a leading global pharmaceutical regulator, America has always attached great importance to the role of pharmaceutical enterprise compliance management in risk prevention and control. The FDA has issued *Compliance Program Guidance for Pharmaceutical Manufacturers* to instruct enterprises to strengthen the construction of the compliance management system. Based on *Compliance Program Guidance for Pharmaceutical Manufacturers*, this paper systematically studies the seven elements of internal compliance management for U.S. pharmaceutical manufacturers. This paper also analyzes the implementation of the guidelines by representative multinational enterprises in different aspects of drug registration, in order to provide inspirations for Chinese pharmaceutical enterprises to build internal compliance management in the field of drug registration.

2. Analysis of Key Elements of American Pharmaceutical Manufacturers Compliance Program

Corporate compliance management began in the field of anti-monopoly and anti-bribery in the United States. With the promulgation of the *Organizational Sentencing Guidelines* in 1991, a criminal compliance incentive system was gradually formed in the United States. Companies began to implement compliance management generally. In the field of medicine, the United States also started the construction of compliance management earlier. In April 2003, the *Office of Inspector General in the U.S. Department of Health and Human Services* issued the *Compliance Program Guidance for Pharmaceutical Manufacturers* (OIG Guidelines). The guide is designed to assist companies that research and develop, manufacture, market drugs or biological products in developing and implementing internal control procedures, which plays an important role in strengthening the construction of pharmaceutical enterprise compliance management

in the United States. This part will systematically introduce the seven elements of a comprehensive compliance scheme as specified in *the OIG Guidelines*.

2.1. Establish and Disseminate Written Standards of Practice

The OIG Guidelines suggests that companies should establish and disseminate written standards of practice to guide employees in their daily work. Among the numerous written standards, the code of practice summarizes the ethical and legal principles to be observed in corporate operations. The code of practice is a manifestation of the "rules" in corporate compliance. While in the field of drug registration, the code of practice is reflected in the laws and regulations, industry guidelines, internal rules and regulations of the reporting applicant, ethics and morals related to drug registration that employees should abide by in all aspects of R&D and registration process. Many applicants have established global codes of conduct internally. At the same time, applicants have also established regulatory documents such as global risk control policies, crisis management policies, and supplier codes of conduct. For example, to better guide internal compliance management, Pfizer has established *the Blue Book* and Eli Lilly has established *the Red Book* as its internal code of conduct. Pfizer has also developed *the White Guide* to provide employees with guidance on laws and regulations to ensure that there are internal regulations to follow in drug development, clinical trials, and data disclosure. In contrast, Merck Sharp & Dohme (MSD) has established a *Code of Practice for Business Partners* to manage compliance among suppliers and other business partners.

Written standards of conduct should be established under the supervision and guidance of the compliance officer, compliance committee and operational manager. The guidance encourages the enterprise board of directors, chief executive officer, CEO, executives and others to actively participate in the establishment of written standards, especially codes of practice, thereby demonstrating a strong and clear commitment to compliance.

2.2. Designated Compliance Officer and Compliance Committee

Companies should designate a compliance officer to coordinate compliance activities and provide appropriate authority and adequate resources to enable the compliance officer to perform his or her duties. For example, the compliance officer should have direct access to the board of directors, the CEO and other executives, adequate funding and personnel, as well as the ability to implement corporate reforms when necessary. In addition, the company should set up a compliance committee that provides advice to the compliance officer to assist them in compliance management. Some small companies or companies with limited budget may not be able to establish a compliance committee. *The OIG Guidelines* recommends the establishment of a "task force" to address potential compliance issues as they arise.

Based on the establishment of compliance officers and compliance commit-

tees, large U.S. pharmaceutical enterprises have gradually formed an organizational structure for compliance management, which can generally be divided into three levels: decision-making, management, and implementation. On the decision-making level, the board of directors, compliance committee (or "ethics and compliance committee", "executive compliance committee") and audit committee of the applicants act as decision-making institutions to establish compliance management objectives, review and approve compliance management systems, listen to the compliance management work report and supervise and evaluate compliance management work directly. On the management level, the applicant generally sets up a compliance department and establishes a chief compliance officer (or "chief ethics compliance officer"), who is responsible for the overall coordination of internal compliance management, including compliance training, compliance monitoring, and investigation of non-compliance. The Compliance Department is under the direct supervision of the Compliance Committee and the Chief Compliance Officer. The Chief Compliance Officer is responsible for supervising the compliance scheme, reporting directly to the Chief Executive Officer, elaborating compliance status to the Corporate Audit Committee and the Compliance Committee on a regular basis. On the execution level, the applicant shall set up compliance officers in each functional department to cooperate with the compliance department to carry out compliance work in order to achieve all-round internal compliance management. In addition, the applicant should also establish compliance departments and staff compliance officers in all branches. For example, Pfizer Compliance Committee, comprised of senior corporate officers, provides supervision and support for the proper conducting of business worldwide, while the corporate Chief Compliance, Quality and Risk Officer is responsible for overseeing global compliance program. As head of the compliance department, compliance department is also responsible for the overall management of the compliance program.

2.3. Training and Education on Compliance

Appropriate education and training for corporate employees and suppliers, agents, etc. is a key element for effective compliance management. According to the requirements of *the OIG Guidelines*, enterprises should adopt appropriate training methods and conduct regular compliance training for employees, so as to convey the external and internal latest updates of laws and regulations to employees, which promotes compliance in their daily work.

In-house compliance training can be mainly divided into basic compliance training and professional compliance training. Training on compliance-related policies and procedures is provided to each new employee at the time of induction. The training can be conducted in a variety of ways, from online courses and tests to offline lectures and case sharing. Among them, online training is mostly "online learning + test". Only after passing the test can we enter the next part of the compliance learning, which to a certain extent ensures the effective-

ness of new employees compliance training. Later, in order to ensure the behavior of relevant technical staff and professionals meets the requirements in the drug registration process, the compliance department will formulate different professionalized and specific compliance training content for different functions of the applicant. For example, Eli Lilly provides specialized training for research and development staff on the care and use of research animals. The training covers modules such as supervision and care of each species. Eli Lilly also provides individual training on a variety of procedures such as anesthesia and surgery, which provides a degree of assurance that R&D staff will have more professional and systematic positive feedback on compliance in this step.

2.4. Establish Effective Compliance Communication Channels

In order to fulfill the role of compliance management, companies need effective communication channels for employees to raise questions and report compliance issues. There are generally open channels for communication of compliance-related issues within the U.S. drug registration applicant. Such communication can be divided into three aspects: Firstly, any employee can communicate with their superior leaders, other managers or compliance department through face-to-face interviews, emails, phone calls, faxes, compliance service hotlines, etc., in order to solve the compliance doubts and problems in drug registration work, or provide compliance-related suggestions; Secondly, if employees find any potential non-compliance in the registration process of the applicant, they can report it in real name or anonymously through various channels mentioned above. The compliance department should promptly investigate the reported situation, and the whistle-blower should be protected by the anti-retaliation and confidentiality policy of the enterprise. *The OIG Guide* also recommends that companies set up an "employee departure interview program" to collect potential non-compliance information from departing employees; The last is the communication between the chief compliance officer or the compliance department and the board of directors, the compliance committee, the audit committee. The former should report to the latter on the management of drug registration compliance, which generally includes compliance risk assessment, compliance training, violations and disposition, etc. For example, to enhance compliance communication, Pfizer maintains an *Open Door Policy* that encourages employees to discuss any questions, concerns or suggestions with their directors or other managers without fear of retaliation.

2.5. Compliance Audit and Supervision

In order to supervise the implementation of compliance policies and identify compliance risks in the registration process in a timely manner, it is also necessary to implement regular compliance audits of the applicant and improve the non-compliance behavior of registration-related personnel based on the results of the audits. The OIG Guidelines recommends that the audit should be con-

ducted by an internal or external assessor with relevant expertise. The review can be a prospective systematic review of corporate processes and protocols, or a retrospective review of practices in a specific area. The audit reports are disclosed so that applicants are aware of the importance of enhancing internal compliance management. For example, Lilly continuously monitors and evaluates the implementation of its compliance program and reports its findings to senior management and the Corporate Governance Committee. The auditor communicates closely with the compliance committee, compliance departments and quality management to promote understanding of the methods and experiences of the entire internal organization in addressing compliance risks. The auditor will also go to each branch or company to assess the effectiveness of internal controls and assist in improving internal controls related to compliance research and training, etc.

2.6. Appropriate Disciplinary Action against the Violating Employee or Supplier

Companies should formulate clear and specific disciplinary guidelines and carry out appropriate disciplinary actions to establish an internal deterrent mechanism. In response to non-compliance by employees or suppliers, the applicant should impose penalties on the concerned parties when necessary. Generally, the compliance department first records and analyzes the impact of the employee's non-compliance behavior. Depending on the severity, different penalties are recommended, and a report is formed to make the final decision on penalties. Penalties include fines, verbal warnings, mandatory training and even dismissal (termination of cooperation). As the "post-compliance" in the internal compliance management, it forms a certain constraint on the behavior of the relevant personnel in the drug registration. For example, MSD requires the supplier to fulfill the contract, and non-compliance may lead to the termination of the partnership. MSD will no longer cooperate with the supplier in the future, thus imposing certain compliance constraints on the supplier. If the non-compliance arises from the negligence of the individual concerned rather than intentionally, the company should analyze each case on its own merits and impose disciplinary action as appropriate.

2.7. Respond to Non-Compliance Issues and Take Corrective Action

When a potential non-compliance problem is identified in the enterprise, the compliance officer and other relevant personnel should immediately conduct an investigation to determine the root cause of the problem. If the investigation reveals that the non-compliance violates criminal, civil or administrative law, the enterprise should report to the relevant authorities within 60 days. Proactive reporting can be used as a mitigating factor for enterprises to mitigate administrative penalties. For example, Eli Lilly investigates all potential violations through standard procedures. If a violation occurs, a root cause analysis is conducted and

its procedures, processes and business practices are reviewed to determine whether improvements are needed to prevent further violations.

In addition to the seven elements mentioned above, *the OIG Guidelines* also believes that the compliance program should foster compliance culture that starts from management and gradually permeates the entire enterprise. The formation of the compliance culture relies on both its attention to compliance management and the intentional cultivation by FDA. At the level of the applicant, the establishment of a compliance department and the implementation of various compliance management systems provide institutional and political safeguards for compliance management. Under normal circumstances, the acquisition of both organizational and individual employee benefits depends on compliance management, which makes the concept of compliance deeply rooted in people's minds. Some companies, such as Johnson & Johnson, also specify compliance as the responsibility of each employee in their code of conduct. Managers and other executives are also required to set an example by upholding ethical behavior in the performance of their duties and implementing a culture of compliance in a top-down manner. Since 1963, FDA has been committed to cultivating the compliance awareness of drug registration reporting entities by means of education and training. The Communication Office of the *Center for Drug Evaluation and Research* (*CDER*) is responsible for providing training on laws and regulations as well as professional knowledge of drug registration for the industry from time to time. On the one hand, the review department actively develops policy-interpretation documents and operational guidelines for the industry. On the other hand, the review department takes the initiative to explain compliance requirements and precautions that they do not understand for applicants at the pre-submission meeting stage. From their own functions, each department takes various measures to help the applicants comply with the relevant legal and regulatory requirements in the drug registration process. Besides, each department should continuously cultivate their compliance awareness, externalize this awareness to the form, and consciously comply with laws and regulations in the R&D or application process.

3 American Drug Registration Applicant Compliance Management Practices

In the compliance management of drug registration, the U.S. applicants models its code of conduct, conducts compliance training and education for all aspects of drug registration, and implements its compliance scheme in pre-clinical research, clinical research, pilot manufacturing, quality management, and communication for drug registration.

3.1. Written Practice Standards Guide Compliance Management of Pre-Clinical and Clinical Research

Pre-clinical research and clinical research are two highly significant phases in drug registration. Pre-clinical researches include pharmacological research, an-

imal trials, toxicological studies, etc. In this stage, the sponsor needs to carry out R&D trials in accordance with relevant laws and regulations and the *Good Laboratory Practice* (*GLP*), as well as the technical guidelines issued by FDA and *The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use* (*ICH*). For animal trials, *the* 3*R Principle* (Reduction, Replacement, Refinement) should be followed to seek alternatives to animal trials whenever possible. Pre-clinical researches should support the development and use of non-animal validated trial methods to evaluate the safety and efficacy of potential new drugs [2]. If animal trials are unavoidable, researchers are also expected to follow corporate animal welfare guidelines and policies for the ethical and humane treatment of animals used in scientific research. Lilly, for example, has a global policy on the care and use of animals to ensure that research animals are treated appropriately and humanely, setting forth the standards and principles that employees must abide by *in vivo* research. All Lilly employees who care for or use animals in research must receive appropriate training and be qualified in the care, use and welfare of animals. New trainees must be instructed and assessed for competency. In addition, Lilly has established supervisory committees at all animal care sites to approve and oversee animal researches and care programs, review animal use protocols and conduct program or facility evaluations [3].

Clinical research has a long life-cycle and high investment. Its results generally have a direct impact on the outcome of drug registration. Therefore, it is much more essential to strictly follow the compliance requirements and treat clinical researches with caution. In the process of carrying out clinical researches, the sponsor should follow the *Good Clinical Practice* (*GCP*) as well as other relevant laws and regulations. Clinical trials involve sponsors, investigators, ethics committees and other parties. The sponsor is the initiator of the clinical trial and is responsible for the management and funding of the clinical trial. The investigator is the operator of the clinical trial and is responsible for the implementation and quality of the clinical trial as well as the rights and safety of the clinical trial volunteers. The ethics committee, on the other hand, is an independent party in the supervision of clinical trials, reviewing informed consent, trial protocols and other relevant documents and information to ensure that the rights and safety of clinical trial volunteers are protected. To prevent investigators from being influenced by stakeholders in clinical studies that could compromise the authenticity of the research, Pfizer requires that decisions to appoint *Healthcare Professionals* (*HCPs*) as investigators must be made by its non-business departments. Lilly instead relies on its medical department for the design, approval, implementation and scientific disclosure of medical research [4]. Clinical trials should ensure informed consent of clinical trial volunteers. The sponsor can assist in the formulation of informed consent documents. Besides, the sponsor should protect the safety and privacy of the clinical trial volunteers from disclosure. Clinical trials should ensure informed consent of clinical trial volunteers. The sponsor can assist in the formulation of informed consent documents. Besides, the spon-

sor should protect the safety and privacy of the clinical trial volunteers from disclosure. Many enterprises such as Pfizer, Johnson & Johnson, MSD, and Eli Lilly have privacy policies to protect the information collected and stored about volunteers in the process of clinical trials in accordance with security policies. For example, Lilly clearly lists in its privacy statement about the personal information that is likely to be collected, the uses of personal information, how to protect personal information, etc.

Pre-clinical and clinical researches involve a high volume of experimental data. Ensuring the integrity and authenticity of the data is also one of the main compliance points of the sponsor. For example, to maintain data integrity, Pfizer has adopted the *ALCOA Principles* (traceability, clarity, synchronization, originality, and accuracy). For example, to maintain data integrity, Pfizer has adopted the *ALCOA Principles* as traceability, clarity, synchronization, originality, and accuracy. Recording data in an ALCOA-compliant manner indicates that the original or authentic recording was made by a known recorder at the time of the event, ensuring that the data can be reliably read, accessed or used.

3.2. Compliance Training and Education to Strengthen Pilot Manufacture and Quality Compliance Management

The *New Drug Application* (*NDA*) in the U.S. requires not only various experimental data and study reports, but also manufacturing information. The FDA also conducts on-site inspections of manufacturing sites during the drug registration review process. Therefore, it is particularly crucial for the sponsor to manage the compliance of the drug trial manufacturing so as to meet the drug registration requirements. The sponsor shall comply with the *Good Manufacturing Practice* (*GMP*) and strict internal quality standards to ensure that the technical parameters and manufacturing equipment meet the manufacturing requirements, achieving controllable drug manufacturing quality. In manufacturing, relevant responsible personnel are required to receive regular compliance training and keep detailed manufacturing records as demanded, such as deviation records, training records, inspection batch records, manufacturing batch records, etc.

FDA divides drug quality management into three phases in the order of drug life-cycle: pre-event phases, event phases and post-event phases. The drug registration review phase as the "pre-event" phase has very strict requirements for the management of drug quality [5]. In order to achieve controllable drug quality and meet quality compliance requirements, pharmaceutical manufacturers have established a drug quality management system. The system can be broadly divided into four aspects: firstly, the system controls personnel, facilities, environment, materials and other elements in the process of achieving product quality through the development of management procedures for relevant quality activities, such as ensuring personnel qualification through personnel qualification selection, personnel training or other procedures and guaranteeing that materials are qualified through procedures such as supplier management, sampling

and inspection; secondly, self-inspection, deviation management, and change control provide assurance that quality requirements are met; thirdly, document management is implemented through a quality management documentation system; fourthly, quality risk management is carried out. U.S. enterprises control all factors that affect quality throughout the drug life cycle, thereby providing comprehensive and effective assurance of product quality and implementing whole life-cycle quality management. Pfizer stipulates in its *White Guidelines* that if any suspected quality event is identified in a clinical trial, Pfizer employees and all parties contracted with Pfizer who support clinical trials must report it to the Pfizer Quality Assurance team within 1 working day. The Pfizer Quality Assurance team is required to initiate action to investigate quality issues, remedy them as soon as possible, and prevent re-occurrences in the future.

3.3. Compliance Auditing and Compliance Management of Surveillance and Regulating Personnel

In the drug registration, the applicant interacts with external personnel, mainly including HCPs, government officers and partners. If compliance is not adequately implemented, interest conflicts or corrupt bribery are more likely to occur. Under the constraints of many U.S. laws and regulations, applicants have to prudently consider how they interact with relevant persons and the information or financial disclosures during the interaction. In addition, enterprises conduct anti-corruption training on relevant policies and procedures, and test them through regular audits and surveillance.

When interacting with HCPs, applicants should comply with *Code of Conduct for Interactions with Healthcare Professionals* issued by the *Pharmaceutical Research and Manufacturers of America* (*PhRMA*). During the clinical trial phase, the sponsor should have no interest with the investigator to ensure that the results of the research are objective and authentic. After *The Physician Payment Sunshine Act* (*PPSA*) came into effect in 2013, pharmaceutical enterprises are required to disclose to the U.S. *Department of Health and Human Services* (*HHS*) and the public about the information related to compensation paid to physicians on time [6]. Therefore, the sponsor is in favor of disclosing financial and other interests in research, education or clinical practice and the relationship with HCPs.

When interacting with government officials, the sponsor should strictly comply with anti-corruption and anti-bribery laws. Political events initiated by enterprises and meetings with government officials must be coordinated by the Government Affairs and Policy Division [7]. Prior to formal submission of a application, the applicant is able to request a pre-submission meeting to obtain FDA compliance guidance on drug registration. To improve efficiency, the applicant should adequately prepare for the pre-submission meeting by thoroughly and explicitly listing any problems that exist in the drug registration. During the review, the regulatory program manager of the review department is the main contact point for communication between the applicant and FDA [8].

There are many partners of the applicant, such as raw material suppliers, clinical research collaborators, etc. Before establishing a partnership, the applicant will conduct due diligence on the potential partner to assess the risk. Once a partnership is established, the applicant will systematically manage the compliance of its partners. MSD has a specific *Business Partner Code of Conduct* that its partners are required to follow. Compliance training is provided to MSD employees who are responsible for selecting and managing suppliers. Suppliers are audited through interviews, facility inspections, and review of relevant documents. MSD also establishes procedures to monitor and track corrective actions adopted by business partners for non-compliance. As a penalty for non-compliance by suppliers, MSD may terminate their relationship.

4. Suggestions and Implications for Chinese Pharmaceutical Enterprises to conduct Compliance Management

Compliance management of pharmaceutical enterprises is the mandatory way to enhance the competitiveness of our enterprises and achieve the public goal of drug safe, effective and quality-controlled. For this purpose, based on the compliance management of U.S. pharmaceutical enterprises and their compliance practices in the field of drug registration, this paper puts forward the following reflections on the construction in internal compliance management of China drug registration applicants.

4.1. Transform the Compliance Concept of the Applicant and Promote the Compliance Culture Construction Led by the Executives

In recent years, there have been several cases of domestic enterprises being sanctioned by foreign countries for non-compliance in China. The "Zhongxing Telecom Equipment (ZTE) Sanctions by the U.S." incident in 2018 was a sensation. In spite of the huge fines, ZTE was required to establish and implement a compliance program within the enterprise. These cases have gradually drawn the attention of China to the issue of corporate compliance [9]. However, the corporate compliance guidelines in the drug registration issued by the regulatory authorities are too general and abstract, which makes enterprises lack effective guidance and supervision in improving the compliance system. In the short term, it is much exhausted for enterprises to conduct internal compliance management. The enterprise compliance motivation is not enough, and the compliance concept mostly stays at the level of "require me to comply". The deepening of the concept of compliance management is significant to drug registration. On the one hand, under the guidance of this concept, the applicant takes the initiative to self-examine the application materials to minimize the key data errors. Anticipating the registration progress and possible problems in the application can avoid economic losses caused by non-compliance, creating managerial and economic value for enterprises. On the other hand, it can also avoid the loss of social resources caused by non-compliance to the state and society, thus providing

a positive external effect and social value to the whole society. The frequency of drug supplementary application should be reduced in the drug registration application so as to alleviate the duplicate review by administrative personnel. Accordingly, it is especially vital to promote the construction of corporate compliance culture and encourage the change of compliance concept from "I have to comply" to "I want to comply".

The shift in compliance concept is driven more from the top to the bottom in the enterprise. If the upper executives attach sufficient importance to compliance, set an example in their work and establish a compliance benchmark. The employees will also follow suit, thus forming a compliance culture in the whole enterprise. Hence, executives should emphasize the construction of compliance culture. They should practically undertake the responsibility of promoting the value of compliance culture in the whole enterprise, acting as a good example and setting a good role model for employees, so that the compliance concept can be deeply rooted in employees [10].

4.2. Improve the Code of Conduct for Drug Registration, So That Drug Registration Has Rules to Follow

The code of conduct is the basis for pharmaceutical employees to perform their duties and guide their behavior in line with the norms. Currently, some applicants in China have established compliance policies, procedures, compliance practice guidelines and other basic institutions within their companies in the areas of anti-bribery, anti-monopoly, finance and taxation, product promotion, centralized purchasing, adverse reaction reporting, data compliance, etc., which clarify and refine work priorities, objectives and tasks at different stages. Conduct manuals and operating procedures are formulated in risk-prone areas for use and reference by personnel in various positions to promote compliance management with rules and regulations. However, in the drug registration, the code of conduct is relatively general and fragmented, lacking a systematic code of conduct. Drug registration involves many procedures. The fragmentation or even the absence of the code of conduct will add difficulties for employees who act in accordance with the codes, resulting the inevitable non-compliance due to negligence in their work. Consequently, the conduct of relevant personnel can be regulated in different aspects of drug registration. Then it is systematized to form a code of conduct for drug registration, which distinguishes from other pharmaceutical marketing activities, so that employees can undertake targeted learning.

4.3. Strengthen Compliance Management in Priority Fields and Promote Compliance in Weak Sections of Drug Registration

Each drug registration section involves a large amount of data information. The integrity and authenticity of data are an essential component of compliance regulation, which directly affects whether the drug can pass the review. On May 4, 2016, the former *China Food and Drug Administration* issued the *Notice on the Requirements for the New Chemical Drug Application* (*Trial Implementation*).

The self-assessment report section of the notice requires that "the applicant shall establish a scientific committee to conduct a comprehensive review of the R&D process and results of the drug to ensure the scientific, integrity and authenticity of the data. The applicant shall submit a self-assessment report on the research data together". Under this requirement, the problems of data reliability such as untrue application materials and untraceable data are no longer obvious. For example, irresponsible personnel records the experimental data arbitrarily regarding the test results during the minor trial in the R&D period [11]. In some enterprises, the non-clinical research data of drug combination in new drug application are insufficient. As a result, pharmaceutical enterprises should devote particular efforts to strengthening data management during drug registration compliance management. Pharmaceutical enterprises should emphasize the importance of data compliance management in their codes of conduct and clarify data recording requirements. Compliance training is provided for data recording personnel in different steps to ensure that their records are complete, authentic, standardized. In addition, enterprises should arrange compliance personnel to check the data records of each section irregularly and promptly remedy the data non-compliance problems that arise from the inspection.

4.4. Administrative Officials and Industry Associations Actively Guide and Facilitate the Construction of Compliance Management Systems for Enterprises

Building a compliance management system not only relies on the efforts of enterprises but also requires administrative officials and industry associations to create a favorable external environment. For administrative officials, on the one hand, the government should focus on the improvement of corporate compliance management capabilities while strengthening its own regulatory capacity. The concept of social co-governance should be formed in the field of drug registration compliance, transforming the one-way regulatory mechanism of administrative agencies into the interaction between administrative agencies and applicants on the basis of integrity. Specifically, the practice of *the OIG Guidelines* can be referenced to promulgate some guidance documents to assist enterprises in establishing an effective compliance management system, which can provide guidance for enterprises that have the willingness to conform compliance but are inadequate in compliance management capabilities. As an increasing number of applicants conduct drug registration compliance management, the effect of drug registration compliance management in the industry will eventually be formed. On the other hand, applicants in China have insufficient motivation for compliance management at present, in which the government should adopt appropriate measures to stimulate enterprises motivation. The U.S. has established a criminal compliance incentive system through the *Organizational Sentencing Guidelines*, which allows enterprises to avoid prosecution and receive a reduction in penalties for internal non-compliance issues by establishing an effective compliance system in accordance with legal requirements. This incentive system

is well suited to the characteristics of tendency to avoid hazards in enterprises, thus stimulating the motivation of enterprises to strengthen compliance management construction. Hence, China can also draw on this practice and establish appropriate compliance incentive mechanisms to positively guide enterprises to strengthen their compliance management. For instance, enterprises are found to be in violation of laws and regulations during routine supervision and inspection in the domain of administrative supervision. If the enterprise can prove that it has established and implemented an effective compliance management system, it can be given a chance to rectify the incidental violations within a deadline. The enterprises that cannot rectify are exempted from more severe administrative penalties by increasing the amount of fines [12].

For industry associations, pharmaceutical industry associations should function as a bridge between administrative officials and applicants. Combining the government compliance regulation requirements and the practical needs of enterprise compliance management, authoritative experts and representative enterprises should communicate and explore the formation of a corporate code of conduct for the R&D registration process, which can be accepted and emulated by most applicants and form self-discipline within the industry. Moreover, industry associations can use their resources to cooperate with multinational enterprises and learn the audit process, methods and contents of their internal personnel specialized in registration to ensure the practicability of the code of conduct.

5. Conclusion and Discussion

The analysis of compliance management elements and practices of U.S. pharmaceutical companies reveals that U.S. drug applicants establish compliance programs under the *Compliance Program Guidance for Pharmaceutical Manufacturers*. Through written policies, personnel support as well as training, communication and auditing, the compliance program is guaranteed to operate effectively in all aspects of drug registration. The compliance management practice of U.S. drug registration applicants provides a beneficial reference for Chinese pharmaceutical enterprises to explore the road of compliance management. Chinese pharmaceutical enterprises are required to transform their compliance concepts, improve the code of conduct for drug registration and strengthen compliance management in key sectors, while also relying on positive guidance from administrative officials and industry associations. In view of the large number of drug registration applicants in the U.S., this paper selects representative large multinational pharmaceutical enterprises for analysis without covering sufficient medium-sized and small enterprises. Moreover, compliance management for Chinese pharmaceutical enterprises is not a quick and easy process, nor is it a one-size-fits-all process. The U.S. experience can definitely offer references. However, due to the differences in the national conditions and pharmaceutical management systems of China and the U.S., Chinese pharmaceutical enterprises have to specifically analyze the compliance risks faced by their organizations in the

context of the formulation and revision of Chinese medical and health policies, the scope and scale of pharmaceutical enterprise distribution and other factors, so as to establish a compliance management system with different emphasis for their own purposes. Further research can broaden the sample selection of enterprises, covering pharmaceutical enterprises of different scales, systematically analyzing the current situation and dilemma of compliance management of Chinese pharmaceutical enterprises to provide more valuable references for Chinese pharmaceutical enterprises in carrying out compliance management.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] China Business News Network (2021) Promote the Standard of Chinese Medicine to Go Out with High Quality. https://baijiahao.baidu.com/s?id=1694263191159708832,2021-03-15

[2] Pfizer (2021) Blue Book: Pfizer's Code of Conduct. https://www.pfizer.com/purpose/transparency/code-of-conduct,2021-10-19

[3] Lilly, E. (2021) Animal Care and Use. https://www.lilly.com.cn/science/discovery/MedicalResearch/AnimalCareandUse/,2021-10-23

[4] Lilly, E. (2021) Medical Research Guidelines. https://www.lilly.com.cn/science/discovery/PrinciplesofMedicalResearch/,2021-10-23

[5] Hu, J., Xue, L.J. and Rong, S. (2019) Research and Inspiration on the Characteristics of Drug Quality Management in Developed Countries. *China Journal of Pharmaceutical Industry*, **50**, 1072-1078.

[6] Xu, Y.H. (2015) A Review of the U.S. Physician Revenue Sunshine Act. *China Health Legal System*, **23**, 16-20.

[7] Johnson & Johnson (2021) Code of Business Conduct. https://www.jnj.com/code-of-business-conduct,2021-10-19

[8] FDA (2021) Best Practices for Communication between FDA and IND Sponsors during Drug Development. https://www.accessdata.fda.gov/cder/ind_sponsors/ind_scripts/index.htm,2021-10-20

[9] Zhu, X.Q. (2021) Some Difficult Issues on Corporate Compliance. *Rule of Law Research*, **5**, 3-17.

[10] Xie, L. (2019) Corporate Compliance Management Research. Anhui University of Technology, Anhui.

[11] Yu, H. (2020) Analysis of the Problems and Countermeasures of Pharmaceutical Companies in the Quality Management of Drug Research and Development. *Chemical Management*, **8**, 58-59.

[12] Zhao, Y.J., Wu, L. and Chen, Y.F. (2021) Analysis of Foreign Enterprises Compliance Management Promotion Mechanism and Its Inspiration to China Pharmaceutical Industry. *China Journal of Pharmaceutical Industry*, **52**, 964-970.