Drug administration column

The impact of drug administration in USA, Europe and Japan on the reform plan in China

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Abstract: It is critical to ensure the safety and efficacy of human drugs through drug administration. Drug administration has a long history in developed countries, such as USA, European Union and Japan, and has achieved great success. In this study, we summarized the important changes in the practice of drug administration in USA, European Union and Japan since 1990s. We also discussed how these changes and experience could be applied in the reform plan in drug administration in China Food and Drug Administration (CFDA). Our suggestions on future development of CFDA include improving post-market surveillance, advancing regulatory science, strengthening service-oriented regulation, and international cooperation.

Keywords: Drug administration; International drug administration; China drug administration

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1. Introduction

As treatment with drugs plays a key role in maintaining a healthy life, it is necessary to ensure the safety and efficacy of human drugs through drug administration. Drug administration has a long history in developed countries, such as USA, European Union and Japan, and has achieved great success in terms of their highly developed pharmaceutical industry and health security. Based on these reports, several modifications have been made in drug administration in China recently to improve quality and efficiency, and particularly the reform of drug administration system in 2008 and 2013[1]. In this study, we summarized important changes of drug administration in USA, European and Japan, and discussed how these changes could be applied in reform plan in China.

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2. Drug administration development in USA, Europe, and Japan

2.1. Drug administration in USA

In USA, Food and Drug Administration (FDA) is responsible for ensuring the safety, efficacy and security of biological therapeutic agents. In recent years, FDA has make important changes to strengthen risk management through legislation, independent drug safety offices establishment, compliance system reform, and regulatory science research promotion, which could be widely used internationally.

2.1.1. Administration system for imported foods and drugs

With the economic and technological changes, USA has imported large amount of foods and drugs and their ingredients and components in 2011, accounting for 20%–25% of all US consumer expenditure. Approximately 80% of active pharmaceutical ingredients, 80% of seafood, 40% of finished dosage drugs, 50% of fresh fruits and 20% of fresh vegetables were imported from foreigner countries. In order to ensure that these foreign

products meet the standards in USA, FDA has carried out some actions, such as international offices and posts establishment, globalization initiation, and international communication promotion.

International offices and posts In 2007 and 2008, several serious incidents were reported, such as the urgent recall of heparin sodium injection (Baxter), indicating disadvantages in risk management of imported materials. With supports from the Congress, FDA has established several international offices and posts in China, India, Latin America, Europe, Sub-Saharan Africa, the Middle East and North Africa[2] to report economic and other related information to USA, which helps FDA to ensure the safety of products imported from these countries.

Global operations and policies In 2011, FDA established Office of Global Operations and Policies (OGOP) comprised of Office of Regulatory Affairs (ORA) and Office of International Programs (OIP). OGOP aimed to ensure the quality and safety of domestic and imported products through global collaboration and data-sharing, development of standards, field operations, compliance, and enforcement of activities[3].

Better communication As a leader in drug administration worldwide, FDA in USA has performed several events to promote communication, such as international regulatory authority's forum for discussion on drugs, medical devices and biology products. In addition, FDA's National Center for Toxicity Research (NCTR) established the International Scientist Exchange Program (ISEP) in 2009, which aimed to build global regulatory science capacity by training students, regulators, and academicians in developing countries[4].

2.1.2. Administration system for risk management

Vioxx (Rofecoxib), a COX-2 selective drug used to relieve signs and symptoms of arthritis, acute pain in adults, and painful menstrual cycles, was withdrawn from market by Merck because of concerns about increased risk of heart attack and stroke associated with long-term, high-dosage use. Considering such serious safety concerns, Food and Drug Administration Amendments Act (FDAAA) provided better authority and allocated more resources to FDA in post-market safety oversight, which helps to develop a better risk management system in USA.

Legislation Congress passed the FDAAA in 2007, authorizing legal guarantee for FDA's drug regulation. It includes several modifications to enhance post-market surveillance, such as requirement on clinical trials for pharmaceutical products without enough data.

Surveillance and epidemiology In 2005, FDA created Drug Safety Board (DSB) to provide advice to the director of the Center of Drug Evaluation and Research (CDER) on handling and communicating of important and drug safety issues. The DSB meets monthly and provides a forum for discussion and input about how to address potential drug safety issues. In 2007, Office of Surveillance and Epidemiology (OSE) was developed by FDA, to separate the function of drug approval and post-market oversight. Information on adverse drug events was used in OSE to identify drug safety, as well as to provide recommendation to improve drug safety. The activities included better labeling system with detailed information, implement of risk management program, and reevaluation on approval or marketing decisions made by CDER.

2.1.3. Reformed compliance system

After the recall of heparin from Baxter, FDA has made adjustment in Office of Compliance (OC) to develop a better compliance system[5]. First, FDA established Office of Drug Security, Integrity and Recall (ODSIR)[6] to address supply chain integrity and security issues, such as counterfeit, diverted, or intentionally adulterated drugs, drug imports and exports, and drug recalls. Second, FDA explored new regulatory tools, such as the Predictive Risk-Based Evaluation for Dynamic Import Compliance Targeting (PREDICT) to assist entry reviewers in targeting higher-risk shipments for examination[7]. Third, FDA extended *Good Manufacturing Practices* (GMP) inspection to the upstream of supply chain and manufactures of active pharmaceutical ingredients.

2.1.4. Advanced regulatory science

In recent years, regulatory science has received much attention. On Feb. 24, 2010, FDA launched Advancing Regulatory Science Initiative (ARSI) to improve the way medical products are developed, evaluated, and manufactured. On Oct. 6, 2010, FDA Commissioner, Margaret A. Hamburg, gave a speech titled "*Advancing Regulatory Science for Public Health*", which outlined a broad vision for advancing regulatory science and unleashing its potential to improve public health. In Aug. 2011, FDA lunched Strategic Plan for Regulatory

Science, aiming to develop new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products. To implement science-based regulation, FDA has been collaborating with universities to advance regulatory science. In October 2011, FDA awarded $2 million to launch Centers of Excellence in Regulatory Science and Innovation (CERSI) at University of Maryland and Georgetown University, a part of FDA's effect to foster a robust, collaborative, and regulatory science culture that enables FDA to address the scientific challenges presented by revolutions in medical product development and to improve food safety and quality[8]. FDA created Office of Information Management (OIM) in each center in 2008 to provide professional information, communication and knowledge infrastructure, and services to protect and promote the public health[9].

2.2. Drug administration in Europe

European Medicines Agency (EMA) is responsible for the scientific evaluation of medicines developed by pharmaceutical companies in the European Union[10]. Advanced therapy medicines, medical products based on genes, cells and tissues are groundbreaking treatments for multiple diseases and injures. It includes four main groups: gene-therapy medicines; somatic-cell therapy medicines; tissue-engineered medicines; and combined advanced-therapy medicines. Over the last decade, EMA enhanced its risk management system and created Committee of Advanced Therapies to guarantee the review on advanced drugs. In addition, EMA worked closely with pharmaceutical industries to promote industrial development.

2.2.1. Administration system for risk management

New Pharmacovigilance Legislation In 2010, the European Parliament and the European Council issued the New Pharmacovigilance Legislation: Regulation (EU) 1235/2010 and Directive 2010/84/EU. In 2012, the European Commission issued the corresponding implementing regulation. According to the new legislation, market authorization holders (MAH) should submit adverse drug reaction (ADR) reports electronically to the official website of Pharmacovigilance in Europe, together with the adverse events caused by medical errors. EMA also established a risk evaluation system of new drugs based on the analysis of these reports[11].

Pharmacovigilance Risk Assessing Committee In 2012, EMA created the Pharmacovigilance Risk Assessing Committee, which is responsible for assessing and monitoring safety issues for medicines, including detection, assessment, minimization and communication related to the risk of adverse reactions. In addition, this committee is also responsible for the design and evaluation of post-authorization safety studies and pharmacovigilance audit[12].

2.2.2. Review of advanced therapies medicinal product (ATMP)

Legislation on ATMP In 2008, the first legislation on advanced therapies came into force in Europe, which provides the definition authorization, supervision and monitoring of ATMPs to ensure safety and efficacy, thus serving as legal basis for the review of ATMPs. The new legislation also provides incentives to encourage research and development in advanced therapies, by providing fee reductions for scientific advice and application for marketing authorization[13].

Committee for advanced therapies (CAT) The CAT was established in accordance with Regulation (EC) 1394/2007 on ATMPs[14]. CAT is a multidisciplinary expert Committee, gathering the top scientists in Europe to assess the safety, quality and efficacy of ATMPs, as well as to keep pace with the scientific progress in pharmaceutical field.

2.2.3. Recent changes for new drug research and development

In 2005, in order to promote innovation and development of new medicinal products by micro, small and medium-sized enterprises (SMEs), the European Commission issued Commission Regulation (EC) 2049/2005 including several policies for the encouragement of SMEs. Meanwhile, EMA created the SME office to provide service to SMEs specifically, such as assistant to communicate among SMEs and personnel within the agency, monitor applications, organize workshops and train sessions for SMEs[15]. After years of hard work, SME office has achieved great success. The number of registered SMEs as increased rapidly, and the Marketing Authorization Applications (MAPs) submitted by these enterprises increase every year with a success rate of 63%[16].

2.3. Drug administration development in Japan

According to the pharmaceutical affairs law in Japan, Pharmaceuticals and Medical Devices Agency (PMDA) was established in 2004 for drug and medical device testing, as well as post-marketing drug safety and victim compensation. PMDA has experienced great changes in recent years, such as setting up the office of international programs, paying attention to regulatory science, and enhancing post-market safety oversight.

2.3.1. Office of International Programs

In 2009, PMDA established the Office of International Programs (OIP) and trained international liaison officers. OIP is composed of two divisions, Division of Planning and Coordination (DPC) and Division of Regulatory Cooperation (DRC). The major responsibility of DPC is to promote personnel exchanges, and organize international meetings sponsored by PMDA.

2.3.2. Advanced regulatory science

In 2009, PMDA established the Office of Regulatory Science Operations to distribute safe and effective drugs and medical devices, thus further promote of medical innovations. Three years later, PMDA established the Science Board as a high-level consultative organization for scientific discussion on pharmaceuticals and medical devices. The purposes of Science Board include advancing regulatory science and evaluating products with advanced science and technology through more cooperation and communication with academia and medical institutions. So far, there are four subcommittees made up of top scientists, including Pharmaceuticals Subcommittee, Medical Devices Subcommittee, Bio-products Subcommittee, and Cellular and Tissue-based Products Subcommittee[17].

2.3.3. Post-market surveillance

PMDA puts great importance on post-market surveillance. According to the amended Pharmaceutical Affairs Law in 2002, PMDA is responsible to collect ADR report in Japan and other countries. The previous Good Post-Marketing Surveillance Practice was divided into two parts, including Good Vigilance Practice that guides ADR report and risk communications, and Good Post-Marketing Study Practice that guides researches on post-market safety issues[18].

3. Trends of reformation in drug administration

3.1. Internationalization of administration practice

Tremendous changes have been made in different drug regulatory agencies worldwide. The newly established or enlarged international program offices, posts and offices indicate the necessarity in internationalization of drug administration. Furthermore, in order to protect public health in areas with limited resources, cooperation with drug administration offices in those areas becomes an important alternative resource.

3.2. Administration in multiple stages

Because some side effects occur after clinical trials, post-marketing surveillance plays an important role to identify adverse events that did not appear during the drug approval process. In some developed countries, compliance activity was even extended to the upstream of supply chain for drug quality improvement, which is inspired by recent medication incidents caused by the poor drug compounding quality. Currently, regulation affairs have been optimized to function from product manufacture, through registration and post-market viability.

3.3. Collaboration in regulatory science

With the development of new technologies in medicinal field, FDA has been committed to addressing the special consideration for regulatory science. So far, collaboration with universities and institutions is the major method for research regulatory research promotion.

3.4. Service-oriented drug administration

In addition to providing intervention and regulation for drugs, government is also responsible to provide service and convenience for drug development in industry. The high cost and risk of new drug research and development discouraged SMEs from innovation, although the research in early stage is an import source for potential candidate compounds discovery. Among these new drugs, advanced-therapies medicinal products are the ones that needed high-technology process and professional reviewers. Because the profit of company was largely affected by review procedure, FDA aimed

to reduce the time by optimizing the process, provide professional advice, thus to facilitate innovation process and increase the success rate.

4. Drug administration in China

4.1. Enhance post-market surveillance

Drug administration has been engaged in research, production, distribution and use of drugs in China[19]. Although CFDA has achieved some success in drug registration, production and distribution, the regulations need to be improved, especially for post-market surveillance. ADR reports are needed to monitor ADR data in large Chinese populations. However, only small portion of patients report ADR with limited data. Therefore, the current ADR reporting system in China needs to be improved by the following strategies. First, Drug Administration Law should be amended to enhance post-market surveillance, such as requirement on clinical trials for products without enough data. Second, uniform standards and advanced tools should be developed to facilitate risk analysis scientifically. Third, FDA inspection should be extended to manufactures of active pharmaceutical ingredients and excipients.

4.2. Perform scientific supervision

Currently, scientific supervision and science-based decision-making become important in China. In 2006, State Food and Drug Administration (SFDA) put forward the idea of scientific supervision. In the 12th Five-Year Plan for drug safety, scientific decision-making has been regarded as an important principle in drug administration[20]. Therefore, the regulatory science in China, especially in drug standard, registration and risk management, needs to be improved to meet the requirement. Based on the experience in developed countries, CFDA could collaborate with universities to promote regulatory science.

4.3. Perform service-oriented regulation

In recent years, service-oriented government has been established by CFDA to improve public service and to keep pace with the scientific progress in pharmaceutical field. However, several problems in drug regulation have negatively affected the development of pharmaceutical industry. For example, the complicated approval procedures reduce the review efficiency. Although Provisions for Drug Registration has requirement on the review time, it is hard for CFDA to meet the requirement due to lack of auditing and punishment. CFDA has issued multiple regulations, however, most documents have no sufficient guidance for the industry or drug manufactures. In turn, during drug registration procedure, the submitted materials by applicants were of low quality. It has been reported that the applicants even could not find proper office for submission[21]. Therefore, we believe that punishment on such situations should be added by CFDA to optimize the review process, increase review resources, and offer better counseling to the industry in time.

Currently, instead of new chemical entities (NCEs), ATMPs, such as biologic products, are new and break through products in Chinese pharmaceutical industry. To guarantee the procedure and quality of ATMPs review, CFDA needs to build a review panel or office for ATMPs.

4.4. Strengthen international cooperation

With the rapid development of pharmaceutical industry in China, international trade in medicinal area is becoming more frequent. However, drug export from developed countries, including China, has been hindered by the low quality caused by unsatisfied technology in pharmaceutical preparation. Therefore, CFDA aims to increase cooperation and communication with foreign offices and posts (i.e. FDA, EMA or PMDA) in order to follow advanced experiences and keep up with the update standards, thus to promote drug safety in China ultimately.

5. Future directions

Reports in this new field remain very limited, and the majority literatures are online reports or documents from drug administration agencies. More related literatures and reports (i.e. from source other than website) are needed for CFDA to develop a feasible implementation plan to improve drug safety in China.

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美欧日药品监管趋势对中国药品监管变革的启示

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摘要: 通过检索并分析国内外一手文献, 梳理了上个世纪九十年代以来, 美国、欧盟和日本这三个全球最大的医药经济体在药品监管实践中的最新进展和重大变革趋势, 结合国内药品监管实践, 探讨了中国药品监管变革的路径。作者认为, 在全球化时代, 国家食品药品监督管理总局应该实施全程化监管, 尤其是加强上市后监测, 通过提高监管科学以改善决策, 提供更好的服务以促进产业发展, 并加强国际交流合作, 使监管标准与发达国家保持一致, 从而促进药品安全。

关键词: 药品监督管理; 国际药品监管; 中国药品监管