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Drug Safety Surveillance in China and Other Countries: A Review and Comparison

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ABSTRACT

Objectives: Drug safety and postmarketing surveillance have become important public health issues in China. This study reviews the relatively new drug safety surveillance system in China and compares it with the systems in the United States and Europe.

Methods: An extensive literature review was conducted in the following four areas: 1) the organizational structure of the State Food and Drug Administration (SFDA) in China; 2) the development of an adverse drug reaction (ADR) monitoring system in China; 3) regulatory issues related to drug safety in China; and 4) similarities and differences between drug safety surveillance in China and surveillance in the United States and Europe.

Results: The SFDA oversees an extensive network of drug safety “watchdogs,” including the China National Center for ADR Monitoring and 32 regional centers throughout China. China’s system has faced a number of recent challenges. It has had to respond quickly to the withdrawal of various high-profile drugs like Vioxx (rofecoxib) and Baycol (cerivastatin) from other markets. Together with China’s Ministry of Health, the SFDA has faced several unique drug safety

events. Three of those events, involving the injectable form of the heartleaf houttuynia herb (Yu Xing Cao), Armillarisi A injections, and clindamycin glucose infusions (Xinfu), are discussed. The rapid development of drug safety surveillance in China is manifested in extensive organizational structure, development of large databases, and laws and regulations supporting drug safety. The two major laws are the China Drug Administration Law issued in February 2001 and the Regulation for the Administration of ADR Reporting and Monitoring issued in March 2004. The study also discusses and compares recent developments in drug safety surveillance in the United States and the European Union. These developments will most likely have implications for the Chinese system in the near future.

Conclusions: While postmarketing surveillance guidelines are not yet available in China, we fully expect their eventual issuance after adaptation to the particular culture and clinical practices in China.

Keywords: adverse drug reaction, China, drug safety, surveillance.

Introduction

Just as China’s economy grows and develops at a very fast pace, its system for watching over drug safety is evolving very quickly as well. Whereas two decades ago, it would have been next to impossible to identify a noncentralized safety problem, nowadays, the national drug safety system, headed by the State Food and Drug Administration (SFDA) is quite likely to identify it, investigate it, and solve it. Although patterned loosely after more developed systems, like the system involving the Food and Drug Administration (FDA) in the United States, the Chinese system has some unique features, stemming partly from its very large 1.3 billion population, its extreme regional demographic disparities, and different clinical practices. The system has already been

tested heavily. Shortly after several high-profile pharmaceuticals like Vioxx (rofecoxib), Baycol (cerivastatin), and Propusid (cisapride) were withdrawn from the US market, the SFDA was able to react quickly by either issuing a drug-use warning or withdrawing the drug from the Chinese market as well. Moreover, it has faced several challenges within its own borders. In this review article, we first describe the Chinese system for drug safety surveillance, which relies strongly on the adverse drug reaction (ADR) reporting and monitoring system and some major Chinese drug-safety regulations. We also describe the system’s response to three drug safety events, one involving a traditional Chinese medicine (TCM), the heartleaf houttuynia herb, one involving the Armillarisi A injection, and the third involving clindamycin glucose infusions. We conclude by comparing the Chinese system with drug safety frameworks in the United States and the European Union.

Because the Chinese system is so new, there is no scholarly literature as yet on the economics of

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improved drug safety in China. However, in the United States, where a longer surveillance history exists, drug-related morbidity and mortality are major patient safety issues that have an estimated US\$177.4 billion annual cost because of treatment failures and new medical problems they generate [1]. The overall incidence of serious and fatal ADRs in US hospitals is estimated to be 6.7% and 0.32% of hospitalized patients, respectively [2]. This estimation implies 76,000–137,000 fatal ADRs each year in the mid-1990s, making ADR mortality the sixth leading cause of death in the United States. By the time that Vioxx® was withdrawn from the market in September 2004, the number of people who suffered heart attacks, strokes, and blood clots (often with significant health care costs and resource utilization) because of the drug was estimated to be over 100,000 [3]. Hence, improvements in either the ADR reporting system or in the techniques used to screen ADRs are expected to lead to significant improvements in clinical as well as economic outcomes in any country.

The National Center for Adverse Drug Reaction Monitoring

At the foundation of China's drug safety surveillance program is its National Center for ADR Monitoring. As early as 1988, the national ADR monitoring project was initiated with the support of the China Ministry of Health (MOH), and involved 10 regional medical organizations within several cities and provinces, including Beijing, Shanghai, Hubei, Heilongjiang, and other provinces [4,5]. In late 1989, the National Center for ADR Monitoring was formally established and primarily focused on 85 hospitals nationwide that were responsible for monitoring ADR events [4,5]. In 1998, the National Center joined the World Health Organization's Collaborating Center for International Drug Monitoring (called the Uppsala Monitoring Center) [4,5]. In 1999, the National Center for ADR Monitoring which also houses the Center for Drug Reevaluation (CDR) joined the SFDA and reports to both the SFDA and the MOH. The National Center consists of five divisions and has a network of 32 provincial centers for ADR monitoring that are affiliated with local SFDA offices in different provinces, autonomous regions, and municipal governments [6].

Individuals may file an ADR or Adverse Drug Event (ADE) report either directly with the National Center or through one of the regional centers. Hospitals, drug distributors, pharmacies, and pharmaceutical companies, on the other hand, submit ADR/ADE reports to regional centers (see Fig. 1). It is the responsibility of the regional center to report all new ADRs/ADEs and all serious ADRs/ADEs within three days to the National Center. Other ADR/ADE reports are sent from the regional centers to the National Center on a

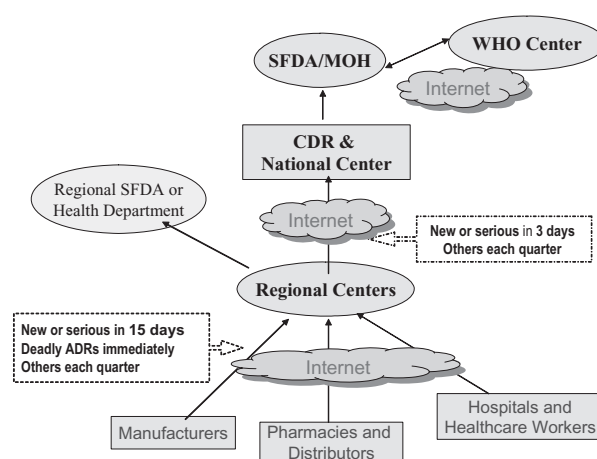


Figure 1 Structure and procedures for the ADR monitoring and reporting network in China [1–3].

quarterly basis. The Internet is used for the filing of all reports, and advanced information technology supports the system. Whereas the National Center received a total of 4700 reports in the 11 years from 1988 through 1999, it received 17,000 in the year 2002 alone, and an incredible 173,000 in 2005 (see Fig. 2) [4,7]. The system is clearly now receiving heavy use. This spontaneous reporting system can be used by any alert physician or other health care professional who thinks that a disease, symptom, or disorder might be related to the use of a particular drug.

As ADR/ADE reports are collected by the system, their nature and frequency can help uncover problems with marketed drugs, especially new drugs. While the system is used—as we discuss below—to detect and confirm rather rare cases of ADRs not detected during pre-marketing testing, it also provides a significant amount of data for researchers to test general hypotheses concerning pharmaceutical safety. Of course, the easy-to-use, inexpensive spontaneous reporting system has its limitations. The number of ADR/ADE reports alone does not provide an ADR/ADE incidence rate, because we do not generally know the number of people exposed to a specific drug. Moreover, the information on the ADR/ADE reports may have inaccuracies and omissions. Finally, even with the large number of reports being submitted, it is still probably the case that significant under-reporting is still occurring in some parts of China.

The ADR/ADE reporting system covers both ADRs and ADEs. According to the International Conference on Harmonization (ICH), an ADR is defined as “a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function [8].” On the other hand, an ADE is defined as “any untoward medical occurrence that may present during treatment

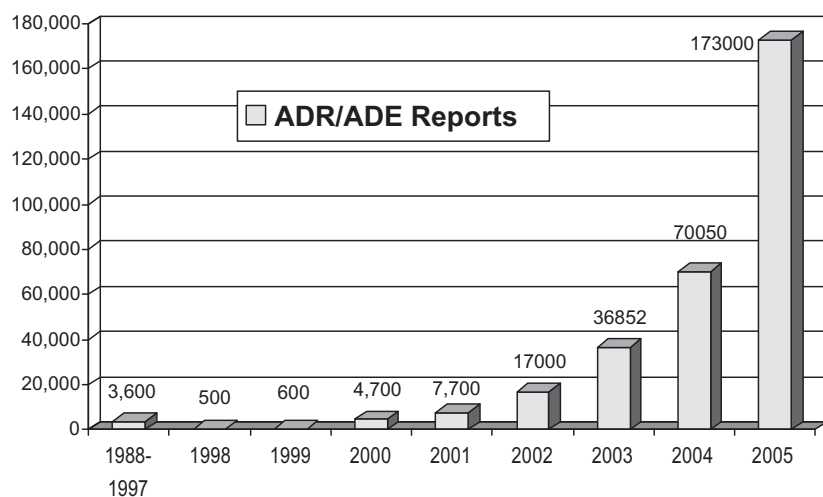


Figure 2 Adverse drug reaction and adverse drug event reports collected by the national center for ADR monitoring from 1988 to 2005 [1,3,4,17]. Source: Center for Drug Re-evaluation, SFDA. Available at: <http://www.cdr.gov.cn/>

with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment [8].” According to the definitions, the concept of an ADR is an ADE with a causal link to a drug.

Both western medicines and TCMs are covered by the ADR/ADE reporting system and are regulated by the SFDA. However, although information from the FDA or the European Medicines Agency (EMeA) is available for western medicines to help guide SFDA policy, the SFDA must be more creative in its regulation of TCMs. According to the Chinese Medical Institute & Register, growing demand for TCMs in western countries has put the spotlight on education, proper practice, and safety to facilitate the integration of TCMs and western medical practice [9].

Drug Safety Regulations and Requirements

The fundamental legal document governing the administration of the pharmaceutical industry in China is the “Drug Administration Law of the People’s Republic of China” (“The Law”) issued in February 2001 [10]. Chapter 5 of The Law contains the mandate for drug safety surveillance [10].

Based on The Law, there are several specific regulations focused on drug safety surveillance in China. The most important one is the “Regulation for the Administration of Adverse Drug Reaction Reporting and Monitoring,” which was issued jointly by the SFDA and the MOH in 1999, and revised and disseminated in March 2004 [4,11]. This regulation includes administrative responsibilities, reporting procedures, and measures for evaluation and control [11]. It also lists the penalties for not following these regulations and provides the basis for establishing the provincial-level regional ADR centers. The Regulation requires pharmaceutical companies, distributors, pharmacies, and medical organizations to monitor and report all

ADRs/ADEs. For any new or serious ADE, the designated staff has 15 days to report it to the regional center. All other events must be submitted on a quarterly basis. Deadly ADRs/ADEs must be reported immediately to the provincial monitoring center, which is then required to investigate and verify the event, as well as report it to the National Center within three days. Those reports should be accompanied by suggestions for follow-up action.

The “Regulation for the Administration of Adverse Drug Reaction Reporting and Monitoring” requires the National Center to compile statistical data on all ADRs/ADEs for the SFDA and the MOH every six months. The National Center also periodically organizes scientific research or initiates pharmacoepidemiologic studies on particular drug therapies. Additionally, the National Center is required to investigate, analyze, and evaluate quickly, for the SFDA and the MOH, any new, serious, or uncommon ADR/ADE.

Besides the Regulation, there are several other regulations that support drug safety surveillance in China, such as “Provisions for Chinese Traditional Medicines Administration of the People’s Republic of China,” “Provisions for Quality Control for Pharmaceutical Manufacturing,” and “Provisions for Quality Control for Clinical Trials,” among others [12]. Other types of regulations are being discussed as well. For example, regulations for post-marketing evaluation have been discussed recently in the CDR [13]. The post-marketing drug evaluations might focus on drug safety and effectiveness for recently approved new chemical entities.

Publications and Media

Good communication between the government and the public regarding drug safety is critical. For the system to be successful, doctors, pharmacists, and

patients need to feel confident that the government is reacting quickly and appropriately to any ADR/ADE emergency. On its side, the government must balance its concern over the health of its citizens with the importance of a thorough investigation so as not to place any blame too quickly and frighten individuals needlessly. In order to facilitate communication with the public about drug safety, the National Center for ADR Monitoring launched its Web pages <http://www.cdr.gov.cn> and <http://www.adr.gov.cn> [6,14]. These Web sites are the most active media for drug label changes and warnings, and are used as well for conducting nationwide questionnaire surveys on drug safety surveillance. Moreover, the National Center has two publications including the *ADR Information Bulletin* and the *Chinese Journal of Pharmacovigilance*. The *Bulletin*, which has been available to the public since 2001, announces the ADR/ADE reports involving serious injury or fatalities. Some warnings and safety signals generated by analysis of the national ADR database have been published in the *Bulletin*. The *Bulletin* covers western pharmaceutical products and TCMs, as well as different formulations (oral and injectable) of drugs. The *Chinese Journal of Pharmacovigilance* is an academic journal covering a wide range of drug safety issues including official regulations about drug safety; vaccine safety; medical device safety; new developments in drug safety research, and pharmacovigilance; current developments and issues in international pharmacovigilance; and post-marketing surveillance in the pharmaceutical industry and the medical-device industry.

Recent Drug Safety Events in China

China's system for ensuring drug safety has faced several big, unique tests in recent years. The first challenge described in this section came from a TCM: heartleaf houttuynia herb (*Yu Xing Cao*) which has been orally administered in China for more than 2000 years [15,16]. In the 1980s, however, injectable formulations of the heartleaf houttuynia herb were approved by the SFDA, and because of their cheap prices and rapid effect, became widely used in clinical practice for infections. From 1988 to 2003, the National Center for ADR Monitoring received 272 ADR/ADE reports, 52 of which were for severe ADRs/ADEs, related to its injection [17–19]. In August 2003, the National Center issued a warning letter to health professionals [18]. Then, on June 1, 2006, the SFDA temporarily withdrew all seven injectable forms of the heartleaf houttuynia herb from the market [20]. After a three-month evaluation, the SFDA decided to let the injection return to the market step by step with risk-management (e.g., collecting ADR/ADE reports and alerting clinicians about appropriate use) [21]. In

addition, production of the heartleaf houttuynia herb must follow strict requirements.

Another unique drug safety event threatened the Chinese people in the summer of 2006. After receiving injections of clindamycin phosphate glucose, many people were becoming violently ill with multiple symptoms including chest distress, abdominal pain, pain in the kidney, diarrhea, nausea, vomiting, and anaphylactic shock [22]. More than 100 severe ADRs/ADEs, including nine fatalities, across 15 provinces, were reported to the National Center for ADR Monitoring [22,23]. On July 27, just three days after the first suspected fatal case, the SFDA posted an ADR warning for the clindamycin injection on its Web site. After a preliminary investigation, the SFDA asked for a nationwide recall of the injections on August 4 [24]. Soon it was found that a single brand of clindamycin, *Xinfu*, produced by the Anhui Huayuan Company, was responsible for the ADEs. The ADEs were caused by bacterial infections during production. Throughout the investigation process, the MOH worked closely with the SFDA to develop guidance for physicians and hospitals regarding treatment of patients reacting to the *Xinfu* injection. On August 3, the MOH activated its emergency daily reporting system—last used during the severe acute respiratory syndrome (SARS) outbreak in China—in 2003 [24].

Overall, the handling of the *Xinfu* disaster was an impressive performance for the fledgling Chinese ADR reporting system. Nevertheless, the *Xinfu* clindamycin event also provided a wake up call for the government to try to reduce prescription antibiotic drug abuse in China, as well as the overuse of riskier intravenous formulations of antibiotics. Moreover, it is very clear that the Chinese government still has significant work to do regarding safe manufacturing practices. The Anhui Huayuan Pharmacy Company is not the first company to violate Good Manufacturing Practice standards. In fact, in Spring 2006, shortly before the *Xinfu* events, at least 11 people fell ill and five people died after taking an injection of Armillarisi A (a drug used to treat gall bladder, liver, and gastric disorders) made by Qiqihar No. 2 Pharmaceutical Co. in China's Heilongjiang Province [25]. The drug company used diglycol instead of propylene glycol for the production of the Armillarisi A in September 2005. Diglycol caused acute kidney failure for patients taking Armillarisi A. The disaster caused a national outcry and prompted the government to shut down the Qiqihar Company.

Drug Safety Surveillance in the United States and the European Union

Because the SFDA in China looks to the United States and Europe and other developed countries for features of their drug-safety systems that are worth adopting, it

is important to review drug safety in these countries in order to predict future development of the system in China. However, doing so is not an easy task, because systems in the United States and Europe are continually evolving themselves in response to new problems that challenge the systems' abilities. In the past decade, for example, more than a dozen high-profile drugs, including rofecoxib (Vioxx), cisapride (Propulsid), troglizatin (Rezulin), terfenadine (Seldane), and cerivastatin (Baycol), were withdrawn from the market. In response to so many withdrawals, pressure has been building to reform drug safety regulations, and there have been significant developments in both the United States and the European Union (E.U.).

Recent Developments in the United States

Under the Prescription Drug User Fee Act, first enacted by the Congress in 1992 and revised in 1997 and 2002, the FDA has been charged with developing risk-management guidance for the pharmaceutical industry. In March 2005, three separate guidances were issued by the FDA including 1) Premarketing Risk Assessment; 2) Development and Use of Risk Minimization Action Plans (RiskMAP); and 3) Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment [26]. According to the Guidance for Industry, drug safety risk-management is defined as "an iterative process designed to optimize the benefit-risk balance for regulated products [27]" and RiskMAP as "a strategic safety program designed to meet specific goals and objectives in minimizing known risks of a product while preserving its benefits [28]." A variety of RiskMAP tools are currently used in risk minimization plans, such as targeted education and outreach, and reminder systems that prompt, remind, double-check or otherwise guide health care practitioners and/or patients in prescribing, dispensing, receiving, or using a product in ways that minimize risk. The FDA Guidance requires companies to identify and describe drug safety signals, to investigate signals beyond case review, and to interpret signals in terms of risk. The Guidance also specifies the pharmacoepidemiologic research methods that are commonly used for risk assessment. In addition, the Guidance discusses how important it is to develop disease and drug registries as well as conduct patient or health provider surveys for drug safety surveillance [29].

Recent Developments in the European Union

In November 2005, eight months after the US FDA issued its Industry Guidance, the EMeA issued its risk-management guideline [30]. The Guideline is based on E.U. regulations for marketing authorization applications and marketing authorization holders. The EMeA defines drug safety risk-management as "a set of phar-

macovigilance activities and interventions designed to proactively identify, characterize, prevent or minimize risks relating to medicinal products, including risk communication and the assessment of the effectiveness of risk minimization interventions." The Guideline includes at least three major components: drug safety specifications, a risk minimization plan (RMP), and risk minimization tools.

The E.U. Guideline follows the ICH and requires safety specifications to include both non-clinical and clinical elements [30]. Nonclinical specification elements are toxicity, general pharmacology (e.g., QT interval prolongation), and drug interactions. Elements for clinical specification involve limitations of clinical trial safety data, postmarketing exposure, populations not studied, identified and potential ADRs/ADEs, disease epidemiology, potential medication error, and class effects. The RMP requires that pharmaceutical companies collect drug safety data once a drug is marketed in order to identify safety risks and benefits. The EU-RMP activity includes signal detection, adverse reaction reporting, periodic utilization reports, and pharmacoepidemiological studies. The EU-RMP is needed primarily for newly marketed products. It is useful as well when there are significant changes to marketing authorization with a new dosage form, a new route of administration, or new indications/patient populations. To protect public health and reduce the burden of ADRs/ADEs, the Guideline discusses risk minimization tools that might effectively reduce risk for patients and/or populations, including label changes, warnings, educational programs for health care professionals and the public, such as letters, a physician's guide to prescribing, a pharmacist's guide to dispensing, patient information brochures, patient registries, informed consent, and so on.

A Three-Way Comparison

Whereas the United States and the E.U. have recently issued risk-management guidelines, China is not quite there yet. Moreover, in many other respects, the Chinese system has yet to issue guidelines for the pharmaceutical industry in areas such as the initiation of safety surveillance, in government-industry communication, in the assessment of ADRs/ADEs, and in filing a new drug application. These results are summarized in Table 1. China's SFDA may work shortly to develop guidelines similar to those in the western countries. Any guidelines should utilize both prescriptive and predictive approaches. The prescriptive approach to drug safety surveillance assesses the benefits and risks throughout the drug's life cycle, from discovery through postmarketing surveillance. The predictive approach develops strategies and regulations that could prevent or minimize risks.

Table I Features of drug safety surveillance systems in China, the United States, and the European Union

Feature	China	United States	European Union
Major regulation bases for drug safety surveillance	China Drug Administration Law & Regulation for the Administration of Adverse Drug Reaction Reporting and Monitoring	Food and Drug Cosmetic Act, FDA Modernization Act, Prescription Drug User Fee Act	Marketing Authorization Applicant (MAA), Marketing Authorization Holder (MAH) & International Conference on Harmonization (ICH)
Drug safety guidance for industry Initiation of safety surveillance	No clear guidance No clear guidance	Guidance issued in March 2005 Required for new chemical entities, but not clear as to when it should be initiated. It is done on a case by case basis.	Guideline issued in November 2005 Clear guidance given as to when to initiate EU-RMP in terms of product categories or situations.
Communication between industry and agency Assessment of ADRs/ADEs	No clear guidance No clear guidance	Guidance given as to communication Guidance given for using pharmacoepidemiologic study methods	Guidance given as to communication Guidance given for using pharmacoepidemiologic study methods
New drug application submission	No clear guidance	It is done on a case by case basis. Guidance allows sponsor to select the evaluation plan and RiskMAP tools.	RMP specification and plan should be provided in application dossier.

Implications and Conclusion

There is no gold standard for a drug safety surveillance system. Variations in culture and clinical practice across countries make it impossible for China to simply adopt another country's practices without modification. However, what the China's SFDA has been doing and will continue to do is, first, learn from its own unique challenges, as it was forced to do with *Yu Xing Cao* and *Xinfu*. These drug safety events were unique to China, and it was up to China's relatively new system to handle the crises. Second, China does have some well-developed systems in other countries that it can try to mimic, to the extent that it makes sense. It can watch the new developments across the globe to find best practices for application. In particular, both the United States and the E.U. have recently issued risk-management guidelines which attempt to balance the benefits of pharmaceuticals with their safety risks of adverse reactions. Third, the evolution of thinking about drug safety surveillance is that there should be a multidisciplinary approach to drug safety, making use of expertise in all relevant disciplines. It also should apply to the entire life of a drug from investigation, through new drug application, marketing, and withdrawal (if necessary) from the market.

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