

Review Paper

Overview of drug evaluation system in China

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Developing a drug requires great amount of research work in chemistry, manufacturing, controls (CMC), preclinical science and clinical trials. Drug reviewers in regulatory agencies around the world bear the responsibility of evaluating whether the research data support the safety, effectiveness and quality control of a new drug product to serve the public health. This article provides an overview of the drug evaluation procedure implemented in China's drug regulatory agency, State Food and Drug Administration (SFDA). Several unique features are discussed in details. This article provides insight into the drug evaluation system and requirements in China. As a developing country, China developed its own unique drug evaluation system along its drug development history while learning from those systems established in developed countries. China uses this system to reach a goal: ensuring safe and effective drug products for patients around the world.

Key words: China, State Food and Drug Administration (SFDA), Center for Drug Evaluation (CDE), drug evaluation system.

INTRODUCTION

Health is one of the basic rights for human being. Drug products are developed to maintain the public health. Therefore, every country around the world puts significant efforts into drug research and development. Developing a compound to a new drug product, however, requires great amount of research work by many scientists in various areas. Before a drug product is marketed, drug reviewers in regulatory agencies need to apply review science to thoroughly evaluate whether the research results support the safety, effectiveness and quality control of the new drug product. Several tragic accidents happened in the history of drug development due to neglect in drug evaluation or incomplete safety requirements, such as the death of ten children due to diethylene glycol contained in the elixir sulfanilamide in 1938 in US and the birth of thousands of phocomely babies due to thalidomide across Europe in 1960. A recent example is Merck Co.'s blockbuster Rofecoxib (Vioxx), which was withdrawn by the company due to cardiovascular adverse events (Couzin, 2004). All these events led to a tremendous loss

for the public health and the pharmaceutical companies involved, highlighting the importance of rigorous drug evaluation for public health and the development of pharmaceutical industry.

Economic reformation in China has being ongoing for almost three decades, creating opportunities for rapid growth in many areas including pharmaceutical industry. Drug research and development in China went through a revolutionary change during this period as indicated by the large number of scientific institutes for drug research, the impressive depth of drug research in many therapeutic areas and the rapidly increasing number of new drugs. A new era of drug research and development is on the horizon with the introduction of new scientific breakthroughs, such as biomarkers and pharmacogenomics. A unique drug evaluation system is needed in China not only to keep up with the scientific development in drug research and development but also fit into the current overall economic environment in China.

This article outlines the overall structure of China's drug evaluation system with the goal of enhancing the exchange of information and collaboration with other regulatory agencies around the world to further improve the drug evaluation system in China.

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Table 1. Organizational structure of SFDA.

Name	Abbreviation
National institute of the control of pharmaceutical and biological products	NICPBP
Chinese pharmacopoeia commission	CPC
Center for drug evaluation	CDE
Center for certification of drugs (GMP Inspection)	CCD
Center for drug reevaluation (Postmarketing)	CDR
National committee on the assessment of the protected traditional Chinese medicinal products	NCAPTCMP
Center for medical device evaluation	CMDE
Other centers and associations	

OVERVIEW OF GUIDANCE AND ORGANIZATIONAL STRUCTURE FOR DRUG EVALUATION

The ministry of health was in charge of drug registration and evaluation from 1949 to 1998. Then State Food and Drug Administration (SFDA) took over this function in 1998 (Li, 2004). There are three laws in China regulating the drug evaluation and registration process, namely drug administration Law of the People's Republic of China, regulations for implementation of drug administration law of the People's Republic of China, and Provisions for Drug Registration. The latest version of Provisions for Drug Registration was issued on October 1, 2007 to further improve the legal system for the drug evaluation and registration process (Cao, 2004). In addition to these laws, SFDA has published 47 technical guidance documents since 2005 and more guidance documents are under development. These guidance documents represent SFDA's current thinking and advice on CMC, safety and effectiveness of drug products. Implementation is not mandatory. These guidance documents are updated when new techniques emerge in a certain area.

There are seven major centers in SFDA (Table 1) and the Center for Drug Evaluation (CDE) is responsible for the evaluation of chemistry drugs, traditional Chinese medicines and biologic products.

DEVELOPMENT OF DRUG EVALUATION IN CHINA

The Drug evaluation system in China has been defined by three major stages: initiation stage, development stage and establishment stage.

The initiation stage started in 1949 when the People's Republic of China was founded and ended in the 1970s. The landmark event was the joint publication of Draft Regulations for New Drug Products by Ministry of Health and Ministry of Chemistry and Industry. That was the first time when the evaluation of new drug products was regulated by certain laws. In 1979, the Ministry of Health and State Drug Administration jointly issued a New Drug Administration Law, which includes detailed explanations about the definition of new drug, the classification of a new drug, and the requirements of the data and clinical

trials for new drug evaluation. The Ministry of Health was in charge of new drug evaluation and approval according to this law. However, the review science, regulatory procedures and related documents were not well established. As a result, the overall review process was not standardized.

The development stage started in the 1970s and ended in the 1990s. The landmark event was the implementation of the Drug Administration Law of the People's Republic of China in 1984. This new law requires that rigorous monitoring and regulation be implemented for a new drug application. According to the law, no clinical trial can be started until all required documents and samples are submitted to and approved by the health regulatory agent at the province level or above. Before a new drug is marketed, the results of relevant clinical trials must be reviewed by an advisory committee and an approval letter with a registration number from the Ministry of Health must be obtained. To make the drug evaluation and approval process more efficient, the Ministry of Health has established a new office, Office for Drug Evaluation, in 1986 to be specifically responsible for drug evaluation. In 1995, this new office developed into an independent center, Center for Drug Evaluation (CDE). Despite the formation of the CDE, the main body of drug reviewers was the advisory committee at that time. When a new drug application was submitted, CDE was only responsible for randomly selecting the members of the advisory committee with the appropriate background from a database of experts for drug review. Those selected members would form a temporary advisory committee for this specific new drug and have meetings twice a year to discuss the review.

Starting from the 1990s, the drug evaluation system in China went into the establishment stage. Since the establishment of the State Drug Administration (SDA), Drug Administration Law of the People's Republic of China has been amended by SDA to further standardize the drug evaluation process. During this stage, the main body of drug evaluation shifted from the external advisory committee to the internal reviewers in CDE. CDE reviewers will evaluate all the applications first. If there are challenging issues based on preliminary review, CDE will organize an advisory committee meeting monthly to have

a consulting discussion with experts in the relevant areas before making the final approval decisions. For those applications that do not contain controversial issues, CDE directly makes the final decisions. This standard evaluation process has improved the review efficiency dramatically. In March 2003, SDA was renamed as the State Food and Drug Administration (SFDA) after food regulation was added to the function of SDA.

STANDARD PROCEDURE FOR DRUG EVALUATION IN CHINA

Currently, there are five types of drug registration application in China: New drug application, generic drug application, imported drug application, supplemental application and renewal application. For the first three types of application, there are two major stages that are under regulation in China: application to initiate clinical trials (including bioequivalent trials) and application to market or import a drug. According to the Drug Administration Law, approval by SFDA is required before clinical trials can be conducted in China or new drugs can be marketed in or imported into China. The detailed application procedure and review process for these two stages are outlined in the 2007 version of Drug Registration Regulations. For supplemental application, the review process will depend on the magnitude of change in the product and the specific application documents. Clinical trials are required if necessary. For renewal application, each approved drug should be re-evaluated after 5 years and the renewal approval will depend on whether the post-marketing data suggest serious drug safety issues or not during the last 5 years.

Overall, the review processes for these applications in CDE are similar to those implemented by US FDA (Li, 2003). There are review teams that are made of reviewers with expertise in different disciplines. The review team is responsible for evaluating whether the submitted data and documents support the safety and efficacy of the new drug as indicated. During the review process, reviewers may interact with external experts and the drug developers to reduce the uncertainty about the drug's safety and effectiveness based on the submitted information. The final decision for approval will be based on the risk/benefit balance for a specific indication after all the submitted information for the new drug is integrated during the drug evaluation process. For new molecular entities that are developed for serious or life-threatening diseases or diseases for which there is no available treatment, there exists fast track evaluation to accelerate the evaluation process (Yin, 2006). But based on the short history of twenty-five years (from 1984 to 2009) and the large number of applications (Figure 1, obtained from the CDE's internal annual report, not published), the drug evaluation system in China is different from any other countries'. It has its own characteristics with the quality control of the review, open-minded review, promoting

research within CDE and integrating the post-marketing review.

FEATURES OF DRUG EVALUATION SYSTEM IN CHINA

Quality control of review

It is CDE's longstanding policy that the quality of the reviews should be monitored and evaluated through systematic analysis. To ensure the quality of the reviews, CDE has established clear responsibilities for each position and published standards and templates for the reviews. Different from the Good Review Practice (GRP) implemented in CDER (The Center for Drug Evaluation and Research) at US FDA, the review practice in CDE only requires key points, instead of all submitted information, be reviewed in details. This practice is suitable for dealing with the huge number of re-submissions of the same product given the limited review resource. Currently, CDE is planning to adopt CDER's GRP systematically by adjusting the responsibilities at each review level and improving the standards and templates for the review after integrating advice from various sources. The ultimate goal is to have a system to ensure the quality of the review with clear responsibility from reviewers at each level (Chen et al., 2004).

To minimize the impact of reviewer turnover on the quality of review, CDE has established a series of training classes for the new reviewers to improve their technical and regulatory skills. CDE also provides many opportunities for the reviewers to share their experience within CDE via internal meetings and keep up with the development of the latest science in drug development by attending national and international meetings. In addition, CDE offers reviewers training opportunities with the analytical laboratories, hospitals and pharmaceutical companies so that the reviewers can get the firsthand experience in various areas of drug development, which significantly helps the reviewers with their review work.

Open-minded review

Drug evaluation requires the collaboration of scientist in many different disciplines. So, it is very important for the reviewers to be open-minded during the review. Especially when CDE confronts scarcity of reviewing resources, it seems more important to keep that. Two examples of open-mindedness are the advisory committee meeting and the interaction with the industry during the review.

The main participants for advisory committee meetings in China are CDE reviewers and external experts. Some meetings may include the applicant(s). Due to the lack of a training mechanism for patient, consumer and industry representatives prior to the meeting, there are currently no representatives for these groups of interest in most of

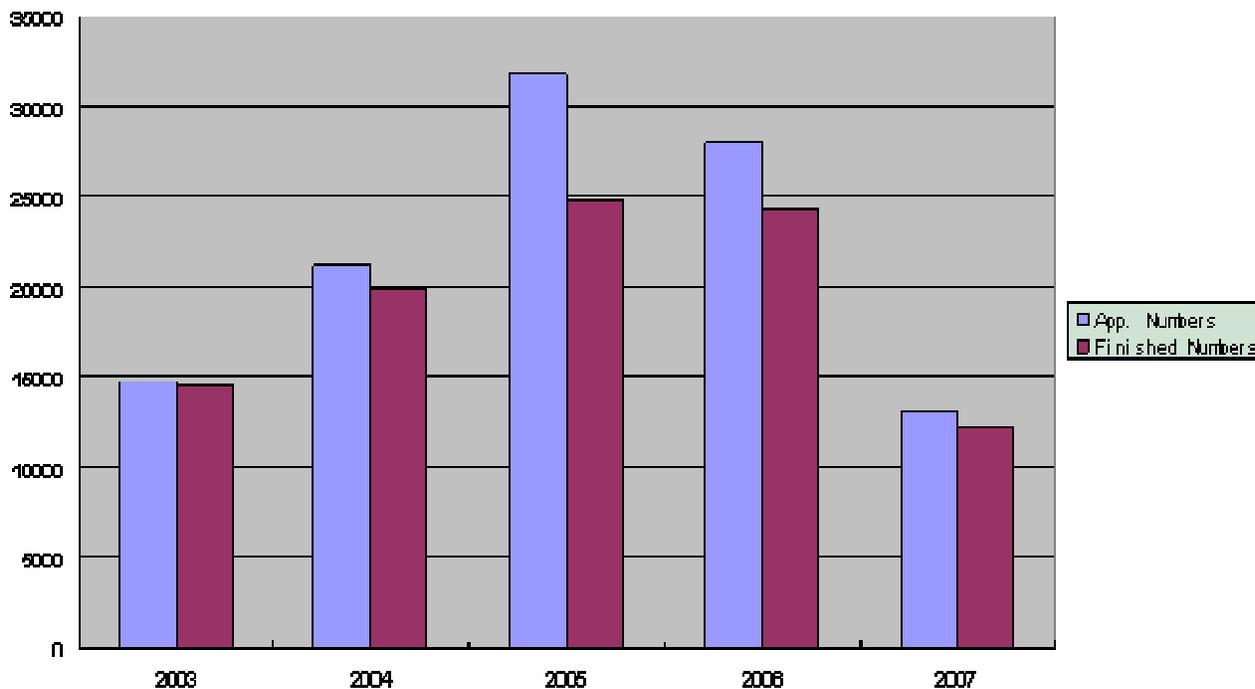


Figure 1. The application numbers and finished numbers in CDE from 2003 to 2007: The applications include new drug application, generic drug application, imported drug application and supplement application.

current advisory committee meetings in China, which is different from the advisory committee meetings organized by US FDA. Most times, CDE accepts the final advice from the advisory committee (Zhang et al., 2003), but maintains the independence in making the final decision.

The external experts are selected randomly from a database based on the specific technical fields involved in the issues for discussion. Compared to US FDA's mechanism of selecting experts, we believe that our system, together with a flexible mechanism of temporary experts, has the advantages of maintaining the experienced experts in the advisory committee and ensuring the productive discussion during the meeting. Another unique feature related to advisory committee is about the conflict of interest. While US FDA requests the experts to claim the conflict of interest, we recommend experts with conflict of interest be excluded from the advisory committee in China, a system called Experts Exclusion Mechanism. All selected experts are required to keep the review materials confidential.

The overall procedure to schedule an advisory committee meeting by CDE is similar to that by FDA. The meeting preparation, however, may not be sufficient due to the larger number of cases in China. Different from the public feature of FDA's advisory committee meetings, CDE only publishes meeting minutes with definite conclusions that are agreed on by all participating parties and will provide guidance for future drug development.

Two other aspects are worth mentioning. First, industry representatives can be invited to part of the meeting for discussion, although they can not attend the entire meeting. As the review continues, the communication with the industry will become more transparent. Second, a preliminary mechanism has been implemented for Provincial FDA members to audit the meetings so that they can understand the meeting process and oversee the quality of the meeting.

CDE communicates with the industry in multiple ways, including formal and informal meetings such as consulting meeting, discussion meeting for a specific question, face-to-face meeting, telephone conference, online Q&A, and etc. These meetings help the sponsors resolve many technical questions in the drug development. However there is still room for improvement. Since we have not established a mechanism to screen and categorize the consulting questions, the sponsors have not used these communication methods effectively. We need to clarify the contents of consultation and the responsible contacts for specific questions so that sponsors can avoid asking questions that are not related to consulting such as the decision of the final review, requesting information that is already published online, or consulting on issues that are too general to be resolved. CDE will use a special approval process as a pilot program to widen the communication with the applicants and improve the efficiency of the communication. The article 45 in current

version of Provisions for Drug Registration said that "SFDA may use special approval process for the following new drug, where detail regulation will be promulgated separately: 1) New drug material and its preparation, active ingredients and its preparation extracted from plant, animal and minerals, which have not been marketed in China and; 2) chemical drug raw material and its preparations and/or biological product that have not been marketed domestically or outside China; 3) new drugs for AIDS, cancer and orphan disease that are superior to the marketed drugs. 4) New drugs which treat diseases for which there is no effective therapy". Detailed provision of special approval process shows that the applicants of drugs mentioned above can use telephone communication, face-to-face conversation, submitting additional documents or consulting meeting to communicate with reviewers.

In addition, we established the "Open House Day" system under which we periodically invite applicants to CDE and explain the review process and related quality control system to them. This system not only provides an opportunity for the applicants to better understand the review process, but also allows us to collect their questions and advice. Through this system, we believe that some problems can be prevented effectively, it is easier to build up mutual understanding, and eventually the efficiency of drug development can be improved indirectly.

EVALUATION AND RESEARCH

The obvious difference between CDER at US FDA and CDE in China is "R" or Research. CDE does not have an internal research department and can not undertake any research that involves experiments. However we have started to collaborate with other research entities in certain areas such as establishing guidance, developing research topics together, etc. Our goal is to establish a department such as Product Quality Research Institute (PQRI), whether independently or jointly with other research institutes, so that we can provide research support to solve the technical and management questions in drug evaluation.

POST-MARKET EVALUATION

Due to the limited research conducted before the drug is commercialized, rare or long-term adverse events may not be discovered before drug approval. These adverse events may be discovered in a larger population during the post-marketing period. To ensure the identification of potential adverse events during the post-marketing period, CDE has invested significant efforts and resources in recent years to establish a monitoring and management system for the post-marketing drugs, which includes drug withdrawal, phase 4 clinical trials and adverse events monitoring. The adverse events monitoring system has

been fully established. Since Center for Drug Re-evaluation (CDR) is responsible for the post-marketing evaluation while CDE is in charge of pre-marketing evaluation, collaboration between these two centers is needed for better integration of the overall information about a drug product. Despite the initial efforts in post-marketing evaluation, we recognize more systematic regulations and technical requirements need to be developed so that post-marketing evaluation in China can be further strengthened in various areas such as efficacy, safety, product quality and economics.

CONCLUSION

"Safe and effective drugs with quality control" is the principle of drug evaluation in China. Given the short history of drug evaluation in China, the drug evaluation system is still evolving to become more organized and efficient with the accumulation of experience in various areas. While we keep learning from the developed system from other countries around the world, we modify and adjust the regulations and guidance based on the reality in China to create an adaptive drug evaluation system and improve our technical and regulatory evaluation skills. Ultimately, our goal is to serve the overall drug development and ensure the safe use of medicines by the people.

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