On August 31, 2012, a 60 cm high bronze statue called "the sick child" was unveiled in Stolberg, West Germany. On the left of the bronze statue is a girl born without arms and with defected legs leaning in a chair and the right side is an empty chair. In the middle of the foundation, the following words are carved: "In memory of the dead and survived thalidomide victims". This year marks the 50th anniversary of thalidomide incident.

It is this tragedy that once shocked the world. In the 1950s, a German drug manufacturer introduced the sedative of thalidomide, which became popular in many countries for its effectiveness in alleviating the symptoms of morning sickness during early stages of women’s pregnancy. Meanwhile, a medical officer, named Frances Oldham Kelsey at the US Food and Drug Administration (FDA) was reviewing information submitted by this German company. Because of her concern over the data, thalidomide’s approval was withheld in the United States. Later, when congenital missing limbs of newborn infants, i.e. thalidomide babies emerged from Europe, Australia, Canada and Japan where the drug was used, it became clear that, with the support of scientific evidence, the culprit of missing limbs in newborn infants is thalidomide. By then, there were almost 10,000 thalidomide babies born around the world.

It is also this tragedy that has driven the reform effort in improving scientific review and approval system in various countries of Europe and the US since the 1960s.
China’s escape from the tragedy is mainly due to relatively underdeveloped innovated drug sector and lack of the connectivity of pharmaceutical industry to the rest of the world. However, China had its own challenges, mainly a serious shortage of drugs as most of drug research and development in China focused on generic drugs and the supply of drug products was limited.

The world has undergone great transformation over the past half a century and globalization of research and development activities and supply of drug products is now the reality. After the tragedy, Europe and the US introduced state legislation, government regulation and established a complete science-based drug review system. After 1949, China established its drug standards and drug testing system. By the middle of 1980s, a drug review and approval system was also established which has been in the process of continuous improvement with the progress of China’s health industry and pharmaceutical economics.

Currently, the Center for Drug Evaluation (CDE) under China Food and Drug Administration (CFDA) is the institution responsible for drug review and evaluation. Basically, it has two functions: first, to review drug clinical trial application to ensure patients/subjects safety and ethical standards conformity of the clinical trial. Secondly, to review drug marketing application to ensure the product’s efficacy, safety and quality. Drug review requires comprehensive analysis and assessment on product’s clinical value, scope of unmet medical needs for the underlying disease, product’s accessibility and affordability issues, efficacy and risk profiles, risk management and control measures, and quality controls etc. This is an evidence-based analysis and review process that require highly qualified drug reviewers who has the critical discretion and technical expertise supported by the external experts from various disciplines who are free of conflict of interest, and a process that allows effective communication among reviewers and sponsors to freely exchange the information and knowledge. Assessment must strike a balance between risk and benefit. So making a review conclusion, whether it is “approval” or “disapproval”, is a challenge that tests the capabilities of this drug evaluation institution.

Mission of CDE: To protect and promote public health.
Vision of CDE: To become one of the most reliable and trusted public health agencies in the world.

Guiding principles of CDE: Quality, efficiency, transparency, clarity, consistency and predictability. These are consistent with the core value of Good Review Practice (GRP) recognized by many regulatory agencies in the world.

We are keenly aware that the current capacity and capabilities of CDE is not compatible with what is needed to fulfill its public health mission. However our strategic objectives for organizational development are clear – An institute where there is an adequate mechanism for ensuring its professional conduct, measuring its performance and supporting a sustained organizational development. To achieve those goals, we openly endorse following core values within CDE: Openness, innovation, fairness, data-driven, teamwork and responsibility. These are elements of our pursuit and organizational culture that have been developed over the course of CDE’s development. Drawn upon the experiences in the development of international regulatory science, we plan to enhance our capability for conducting a science-based review, to strengthen the development of review process and system in order to support our mission of protecting and promoting public health.

The 2012 China Drug Review Annual Report hereby represents just one of our many efforts of becoming a regulatory body that is open to the oversight by its stakeholders.

I. Major Activities in 2012

In 2012, the CDE has taken measures in various aspects in the attempt to better address public health needs.

(1) Adjusting review strategies in line with the patterns of drug research and development
Encouraging innovation, research and development (R&D) to address unmet clinical needs and promoting the R&D of generic drugs in clinical shortage are common concerns for global drug evaluation institutions. Given the different attributes in R&D of innovative drugs and generic drugs, evaluation institutions should adopt different review strategies according to their respective patterns of R&D to ensure the science-based nature and efficiency of review.

**Innovative drug review**

The top priority in drug innovation in today’s world is to address unmet clinical needs. The process of drug innovation must undergo the two steps of "clinical admittance" and "market admittance". Evaluation institutions are charged with the task to encourage innovation and contain risks in both steps.

In 2012, CDE has adopted the following measures to better fulfill its above-mentioned roles:

- Encouraging clinical-value-oriented drug innovation and playing guiding role of review. The invention of drugs with positive therapeutic effect to major diseases in China and the R&D of pediatric drugs and drugs for rare diseases are encouraged. The review of innovative drugs in the above-mentioned scope is defined as priority tasks and subject to full-process supervision and management. Meanwhile, communication has been made with the Management Office of National Science and Technology Major Projects in a timely manner to expedite the review of drug products listed in national science and technology major projects to make review activities better reflect national strategies on drug innovation.

- Initiated the drafting of *Outline Summary on Clinical Trial Application*. "Targeted review" has been carried out based on clinical trial protocols to transform the habitual philosophies of drug R&D and review inherited from generic drugs. For the initial clinical application of innovative drug, professional clinical reviewers will normally conduct an abbreviated evaluation on the scope of application and existing means of treatment for indications under application within one month after CDE accepts a task and...
prior to the comprehensive review based on clinical trial protocol, focusing on the clinical value of application and the basic facts about clinical trial protocol in order to help determine the level of priority for the review task and more importantly, help safety and CMC (chemistry, manufacturing and control) review to determine reasonable technical requirements such as requirements on long-term toxicity research and stability research, etc.

- The dynamic follow-up CMC review model has been established based on different stages of innovative drug development, and the philosophies of CMC review and R&D for innovative drugs have been totally transformed. According to the attributes of different research stages, pre-clinical CMC review template and annual report system during research period for innovative drugs have been established. CMC technical requirements have been made basically consistent with international practices; so that rolling submission is enabled for CMC data update or amendment. After official implementation of the above measures in May 2012, CMC discipline review for innovative drugs is no longer a bottleneck in the review process.

- To make the risk measurable, assessable and predictable, explorations and researches have been made regarding the establishment of a risk management model for the clinical admittance and market admittance of innovative drugs. With the objective of implementing effective risk management and in accordance with the benefit-risk assessment for the R&D stage of innovative drugs and the conditions of post-marketing clinical use, risk management requirements have been made for applicants, investigators and contract research organizations (CROs), etc. through clinical trial approval letter, evaluation suggestion letter, manufacturing and marketing approval letter (import approval letter), risk control plan and labeling, etc. For the clinical trials of innovative drugs, in particular, various parties involved in human research are obligated to take part in risk management to ensure the rights and interests of clinical trial subjects.

- Promulgating Guidelines for Clinical Trial Data Management and launching drug clinical trial registration and information disclosure platform to ensure consistency of clinical research with internationally recognized data management principles. Data management and data standardization work
platform has been set up, which have laid the foundation for further enhancing the full-process and dynamic supervision and management of clinical trials and ensuring the truthfulness, standardization and traceability of clinical trial data.

- Transforming the pattern of communication and developing and implementing *Quality Management Practice for the Communication between the Drug Registration Applicants and CDE* to ensure that all decisions of the CDE are made on the basis of integrated information collection to improve the quality and efficiency of decision-making. Both the applicants and the CDE may request communication on key technical issues of R&D, exchange information and opinions and develop meeting minutes to be signed and recognized by both parties. In 2012, the CDE has held 37 communication meetings and developed 37 meeting minutes. By increasing the communication windows with applicants and opening the avenue of rolling submission of application documents, the unnecessary queuing time caused by supplementary data requested as the only way to amendment is reducing. In 2011, 41.1% of clinical trial applications of innovative drugs were requested for supplementary data while this figure has dropped to 33.9% in 2012.

- Encouraging innovation that embodies the clinical attributes of TCM (Traditional Chinese Medicines). Following the patterns and characteristics of TCM R&D, further attempts have been made regarding the establishment of a modern TCM review system for the efficacy and safety. Research and evaluation workshops on new TCM drugs were organized and reputed experts were invited from China and abroad to discuss the future directions and share ideas on the innovative research of TCM. Firstly, in the review of new TCM drugs, sufficiently consideration is given to their value of clinical application and efficacy attributes, enhancing the review for clinical efficacy assumptions and research logic of new TCM drugs and promoting the transition of TCM clinical trials from validating research to exploratory research. Secondly, given the complex ingredients of TCM drugs that require full-process quality control, it is stressed that the stability and evenness of drug quality must be guaranteed and that manufacturing process research should fully reflect the feasibility of mass manufacturing. Thirdly, manufacturing process research should be integrated with clinical efficacy
and quality control system to ensure post-marketing quality consistency between different batches of product.

- Adopting categorized review for TCM drugs. Attributes of different types of TCM drugs should be properly understood. For effective fraction new drugs and effective ingredient new drugs, the focus should be on the scientific rationale and safety research. For combination TCM new drugs applied for dominant diseases and non-dominant diseases treated by TCM, exploratory assessment on the efficacy difference are made based on human use experiences. For TCM injections, safety risks are brought under strict control to embody clinical advantage.

**Generic drug review**

- Both developed economy and emerging economy countries have attached great importance to the R&D of generic drugs in order to address the burdens of drug accessibility and affordability on national pharmaceutical payment system and individual citizens. Evaluation institutions play an important review role in the marketing admittance of generic drugs and are responsible to assess the consistency and substitutability with brand name drugs.

Due to various reasons, the problems in China, such as the great number of generic drug applications, repetitive applications and limited capabilities for industrialization are not yet resolved. Meanwhile, there has also been a shortage of generic drugs with great clinical treatment value and in urgent clinical demand. The CDE has adopted a series of reform initiatives in the area of generic drugs with a view to better meet clinical needs and promote the healthy development of China’s generic drug industry:

journey of generic drugs in China, this report examines the key problems existing in the market admittance system for generic drugs and proposes recommendations for the improvement of China’s admittance system for generic drugs to meet public health needs and national strategic needs.

• Exploring the priority review mechanism for generic drugs and promoting the solution to the problems regarding accessibility of generic drugs with clinical value and in urgent clinical needs. Based on piloting experience, the basic conditions for priority review of generic drugs have been proposed, i.e. the product is with relatively high clinical value and clinical needs for it has not yet been effectively resolved; Secondly, the product can be manufactured on industrial scale and effectively supplied; Thirdly, comprehensive and systematic drug quality control system in line with international technical standards is established. Under the leadership of the CFDA and after communication with multiple ministerial agencies, the mechanism for generating the catalogue of generic drugs for priority review has been developed and the registration process for the priority review of generic drugs has been created.

• Exploring the working mechanism on combining manufacturing on-site inspection and scientific review to address the low capacity of industrial manufacturing of generic drug. Tigecycline, Decitabine and Capecitabine have been put on the pilot product list. The production on-site inspection has been involved in the technical review process, the front-line reviewers have been dispatched to on-site inspection and the combination on data-review and on-site inspection has realized. In this way, the product and production knowledge of reviewers have been enhanced and the quality and industrial production of the approved drugs are ensured.

• Continue to promote application in CTD format to bring the research and review of generic drugs in line with international technical standards. As a modular data submission requirement for application documentation, CTD format embodies the research philosophies, logic and full-process management level of researchers and avoids the loss of data collection by some reviewers. The CDE encourages applicants to conduct research according to the research philosophies and technical requirements embodied in CTD format and grant
separate queuing and priority review for generic drug applications in CTD format. Common issues identified in the CTD format application review are summarized and published on the CDE’s website (www.cde.org.cn/dzkw.do?method=largePage&id=312898).

In 2012, the CDE continued to grant priority review for generic drugs including HIV/AIDS drugs, anti-resistance tuberculosis drugs and CFC replacements according to relevant national requirements and allocated limited review resources to generic drugs with great clinical value and in urgent clinical needs.

(2) Information disclosure, public services and public oversight

The drug evaluation’s ultimate service customers are patients and the public, professional service customers are clinical physicians and medical institutions, and direct service customers are industry and drug research institutions. Various parties have the right to know the processes and results of drug review. The public have the right to know why the drugs they take are effective, what are the potential adverse reactions and what are the precautions for use; Clinical physicians have the right to learn about the attributes, clinical pharmacology, indications and adverse reactions of drug products in an accurate, comprehensive and in-depth manner; and researchers and investors have the right to know the decision-making justifications and expected outcomes of evaluation.

Evaluation institutions should convert the scientific data and model of evaluation decision-making to plain language understandable to the public and publish them to society for accepting the supervision of professionals, the industry and the public. In 2012, the CDE further enhanced information disclosure to better serve the public and receive their supervision.

The follow measures have been taken regarding public information disclosure:

- Promulgating Approval Summary of drug products newly marketed in China through the CDE’s website. The Approval Summary clearly informs the public what data and empirical evidence the CDE’s decisions made on drug approval
are based on. The Approval Summary includes the following information: description of the diseases and the pains a patient may suffer; the causes of the disease and the major differences in these causes across the world; whether there is any effective therapy for the disease and if yes, the shortcoming of current therapy; the studies made regarding this drug, the affected disease period and the definite benefits to patients proved by the research outcome; the safety signals exposed in the drug research and their control measures taken based on the safety signals and the benefit-risk analysis; what the potential safety issues are and whether we have corresponding precaution and control measures and the post-marketing requirements, etc. In 2012, 38 Approval Summaries were released.

- Enhancing the disclosure of drug clinical trial information. A system of Clinical Trial Registration and Disclosure is established on the CDE’s website (http://www.cde.org.cn/news.do?method=changePage&pageName=serviceLcsy&frameStr=125). The system discloses the drug products which have already entered clinical research and information about clinical trial project, investigator and location; so that the research activity will be conducted under the conditions recognized by social ethics and improve the subject protection.

- Proactively open to public media organizations and receiving media oversight. In 2012, the professional media organizations including Science and Technology Daily, China Pharmaceutical News and Medicine Economic News and academic institutions participated in the open day, forum, expert consulting meeting and workshops held by the CDE to understand drug review activities from a third-party perspective.

The following measures have been adopted regarding information disclosure to applicants:

- Promulgating the queuing sequence of drug applications. Based on the CDE’s website, the task list and sequences of all chemical drug registration applications accepted by the CDE have been publicized. In this way, all applicants are able to know the position of their applications and expected
timeline for the completion of review, which makes it convenient for applicants to schedule their work plan.

- Promulgating the drug applications under “accelerated review” and the justifications for such acceleration. For drug products under accelerated review, justifications will be indicated on the CDE’s website for the public to know the reasons for priority allocation of review resources.

- Monthly review plan and completion status of chemical drug applications are all publicized on the website. The completion status and review conclusions are publicized on a regular basis to enable applicants to oversee the review process.

- The review reports are publicized to the applicants for unapproved drug applications through “Applicants’ Window”. For drug application for which technical review conclusion is “disapproval”, technical review report is publicized in full to its applicants for them to learn about the reasons for the disapproval and make an appeal within 15 days. In 2012, we received appeals for 214 disapproved drug applications and fully considered the opinions of applicants before finalizing review conclusions.

- Publicizing the information about review consulting meetings. Information of all expert consulting meetings is published after the meeting. In 2012, the CDE held 11 expert consulting meetings involving 189 drug applications and 1,590 experts were invited.

- Promulgating drug application re-evaluation plan and re-evaluation conclusions. In 2012, the CDE received 170 re-evaluation applications and completed 196 re-evaluation cases. Among them, original conclusions were maintained for 161 re-evaluation cases, accounting for 82.1% and original review conclusions were corrected for 35 re-evaluation cases, accounting for 17.9%.

- Publicizing the information about existing product approval numbers and drug applications currently under reviewing. Regarding repetitive research and applications of generic drugs, in order to lead the orientation of drug R&D, the CDE has already conducted a comprehensive and systematic summary
and analysis on drug products already approved for marketing and currently under review and published such information on its official website (http://www.cde.org.cn/drugInfo.do?method=init).

- Developing and revising drug research technical guidance and promulgating technical standards. In order to guide R&D activities and clearly elaborate the technical standards and requirements for drug R&D, in 2012, the CDE continued to improve the system of technical guidance for drug R&D and initiated the drafting of 36 guidance and the revision of seven guidance. Currently, three of the guidance have already been promulgated by the SFDA for implementation and 8 others are released for soliciting public comments. In addition, regarding some specific technical issues arising from R&D activities, the CDE has established a special column of “Answers to Common Questions” on its official website, which addresses 103 questions; Regarding the research of new problems and questions arising from research, development and review activities, the CDE has published 40 articles on its special column of electronic publications to share its forward-looking views on these questions.

- Organizing the 3rd China Drug Innovation Forum. Based on the survey data on almost 800 manufacturers from China and abroad, the forum reviewed R&D pattern, capabilities and risk control competencies of Chinese drug manufacturers and discussed the countermeasures for drug review in China.

- Continuing to conduct communication through multiple approaches. The CDE held eight open day activities in 2012 to introduce the basic facts about the CDE and these activities had 236 participants. CDE held 16 workshops on drug technical review to share the technical requirements and standards with the industry regarding drug research, development and evaluation, which had a total of 6,829 participants. In addition, 533 questions were addressed through the information feedback platform of CDE’s website and CDE director’s mailbox.

(3) Introducing assessment mechanism and improving capacity building

- Regarding Research on the Orientation and Roles of Drug Review System in China, the CDE entrusted the School of Public Policy and Management, Tsinghua
University and China Project Office of Harvard Medical School to establish a joint research group to examine the orientation, regulation system, mechanism and capacity building of drug review in China.

- Regarding the development of decision-making quality and review quality control system for review institutions, the CDE invited representatives from Center for Innovation in Regulatory Science (CIRS) to examine its quality control system. In May 2012, the CIRS communicated with the CDE on the implementation of Good Review Practice (GRP) and conducted a baseline survey. In September, CIRS conducted a questionnaire survey on the CDE’s management team. In November, it reported comments of preliminary assessment to the CDE.

- Regarding the development of quality control system for vaccine application review and WHO assessment requirements for vaccine supervisory system, the CDE has carried out ISO-9001 evaluation and certification activities. In August 2012, the CDE conducted an internal assessor training and by September, completed the drafting and revision of Quality Manual and Procedure Document and requested offices to formulate relevant office-level documents. Currently, the CDE has already brought vaccine quality control system into operation and entered the phase-II assessment for ISO-9001 certification.

- Regarding review capabilities and efficiency, the CDE has developed Measures for the Reviewer Promotion Management and Measures for Performance to assess the efficiency of the CDE’s work by suing quantitative indicator and data.

(4) Enhancing regulation system building and institutional development

The role of drug review institution is to safeguard and promote public health. We should continuously increase institutional capacity to meet the health needs of 1.3 billion people; as coordinator and promoter of innovation, we should strive to advance innovation while effectively putting the risks of innovation under control and avoiding becoming barriers in the way of innovation. These requirements pose great challenges to us.
Sound development requires institutional base. Based on reality, the CDE has developed and streamlined administrative systems and review procedures to build a framework of professional drug review system. Under the overarching principle of Drug Review Principles and Procedures, the CDE has promulgated a total of ten procedure documents including Procedures for Review Decision-making Pathways, Procedures for Review Task Management, Procedures for Review package Management and Quality Management Procedure for Communication with the Applicants for Drug Registration Application. These procedure documents focus on not only review procedures but more importantly, evidence-based review. Quality, efficiency, transparency, clarity, consistency and predictability are established as the principles for review work and assessment indicators for review decision-making quality.

Sound development requires a squadron of highly qualified professionals with international background and expertise. All decisions are made by people and high-quality decisions can only be made with highly qualified people. With limited human resources yet responsible for drug review for a country of 1.3 billion people, the CDE urgently needs highly qualified people and has taken the following measures in this respect:

- Exploring a new talent recruitment mechanism and stepping up in-house staff training, development and assessment. In 2012, the CDE hired three senior reviewers openly from public candidates and conducted training on special disciplines, management and English language for 60 trainees.

- Enhancing skills training. Strengthened training on communication skills for internal and external communication. Internal training focused on tackling communication barriers among teams, within individual disciplines, across disciplines and organizations, with a view to ensuring high quality and efficient decision-making. Training on external communication aims to develop skills of listening, analysis and communication. Trainees are taught to listen to the opinions of the public, the industry, physicians and the media, analyze their requests and communicate the philosophies of the review institution.
Increasing international communication and cooperation and drawing upon advanced international experience. At the 4th DIA China Annual Conference, a special session was set for CDE and the CDE made an comprehensive introduction to the technical standards, current hot technical topics in drug review and development R&D, as well as future direction. CDE and FDA Alumni Association held the 4th Academic Workshop on Regulatory Science-Based Decision-making and conducted scientific demonstration and discussions through simulative multi-discipline joint meeting, reaffirmed the importance of establishing an internal consulting mechanism and improving improved the review team’s capabilities on identifying and resolving problems.

Sound development requires involving social expertise and maintains openness

Continuing to implement and improve expert consultation system. At consulting meetings, the focus should be put on the fairness of experts and the quality of meetings and issues concerning conflict of interest and confidentiality should be resolved properly. Regarding difficult issues, expert opinions were sufficiently collected. For major drug products, voting system for collective decision-making were adopted.

Established working mechanism with relevant specialty committees of Chinese Medical Association to enhance the acquisition of information on drug products urgently needed for clinical treatment. Preliminary contacts with the Respiratory Disease Committee, the Urology Committee and the Blood Diseases Committee, etc. have been established. The committees were requested to confirm which diseases is lack of effective and affordable drugs. The CDE will accelerate the review for these drugs to meet the needs of the public.

Increasing the openness of drug review and extensively incorporating national and international experts into the deliberation and decision-making under the strict qualification screening, the avoidance of conflict of interest and the confidentiality management. For instance, the CDE carried out pilot programs of contract procurement services regarding non-clinical
safety review and invited pharmaceutical experts from manufacturing companies to take part in the generic drug review as visiting review experts.

II. Drugs Approved in 2012 for Major Therapeutic Disciplines

In 2012, through CDE review, drug products are recommended for approval in the following major therapeutic areas to provide possibility for patients to access the latest treatment methods and guarantee drug accessibility and affordability:

(1) HIV/AIDS drugs

The following latest therapies have been provided synchronizing with global drug marketing regarding HIV/AIDS drug resistance and treatment compliance:

1. Rilpivirine tablet (approval number: H20120561) is a diarylpyrimidine derivative and belongs to a new type of non-nucleoside reverse transcriptase inhibitors (NNRTI). It shows high activity against wild-type HIV-1 and drug resistant mutants and has therapeutic effect on drug-resistant HIV patients. It was approved by the FDA in May 2011. In 2012, China has approved the marketing of this drug for Chinese patients timely acquiring this latest means of treatment.

2. Emtricitabine and tenofovir disoproxil fumarate tablet (approval number: H20120568): a combination of emtricitabine and tenofovir disoproxil fumarate, which is a new therapeutic strategy recommended by global HIV-1 infection treatment guidance. Introduction of the combination preparation has improved the compliance for the treatment of HIV patients, which has great significance for the enhancement of treatment efficacy and provides an important new means of HIV control for China.

(2) Drugs for rare diseases

1. Decitabine injection (approval number: H20123294, H20120066, H20120067) is a drug for the treatment of myelodysplastic syndromes (MDS), which is a rare disease and can only be treated with imported drugs in China. In 2012,
the mechanism of “document review plus site visits” was established to enhance inspection of industrial manufacturing and quality control capabilities of applicants. With high quality standards testified through third-party validation, the products of two local manufacturers were approved for marketing.

2. Sunitinib malate capsules (approval number: H20100776-783): the drug that produces an anti-tumor effect and anti-angiogenesis effect through inhibition of multiple targets. In 2012, the new indication of this drug product were approved for the treatment of pancreatic neuroendocrine tumor, which has a very low incidence (about 0.3/100,000) yet causes extreme pain to patients and cannot be resectable through surgical operation. Pancreatic neuroendocrine tumor has a high transfer rate and there is currently no effective means of treatment for this disease. This drug is approved for marketing with the review strategy of exempting clinical trial on the basis of comprehensive examination of global clinical research data.

(3) Pediatric drugs

1. Caffeine citrate injection (approval number: H20130109) is the only drug approved internationally for the treatment of premature apnea. Premature apnea is a disease that may cause injury and life-threatening. Effective drugs for treatment are unmet according to previous medical practice in China. Based on comprehensive examination of global clinical research data, the review strategy of exempting clinical trial for registration is adopted to provide a new means of treatment for saving the lives of infants suffering from this disease.

2. Jiuwei Xifeng Keli (approval number: Z20120034) is the first TCM combination preparation for children tic-coprolalia syndrome treatment. This indication is a common disease of children and has an increasing incidence over recent years. Currently, major drugs for the treatment of this disease are all chemical drugs such as haloperidol, which have many adverse reactions and some of these reactions are unbearable for child patients. For child patients suffering from slight to moderate levels of this disease, this TCM preparation demonstrates a certain efficacy with limited adverse
reactions and is thus easy to be accepted by child patients and their parents. This product is the first TCM drug for the treatment of this disease.

(4) Oncology Products

1. Dicycloplatin injection (new drug certificate: H20120020) is a new type of platinum compound discovered by Chinese scientists. It has the attributes of strong water solubility, high stability in water solution and relatively low toxicity and has been verified to have certain therapeutic effect in the treatment of non-small cell lung cancer. Meanwhile, its potential value for the treatment of prostatic neoplasm has been observed. After new drug certificate is authorized, further explorations in this area are being made.

2. Crizotinib capsules (approval number: H20130067, H20130068 and H20130076-79) is a drug with milestone significance for tumor targeted therapy after Gefitinib and Erlotinib. It specifically has a targeted therapeutic effect on ALK-positive non-small cell lung cancer and was approved for marketing by the US FDA in August 2011. After accepting the application in February 2012, the CDE completed review in December 2012 and the marketing was then approved by the CFDA.

3. Lenalidomide capsule (approval number: H20130069-72) is for the treatment of relapsing and multiple myeloma of adult patients and is urgently needed in clinical treatment. Considering that this product is a thalidomide analogue, it has definite reproductive toxicity. Marketing decision for this drug is made on the basis of risk control strategies including strict evaluation of the “risk control capabilities” and “risk control measures” of applicants.

(5) Psychotropic drugs

Paliperidone palmitate injection (approval number: H20120429-0433) is a new drug for the treatment of schizophrenia during acute period and maintaining period. The drug is a selective monoaminergic receptor antagonist and has antagonistic effect on dopamine D2 receptor and 5-hydroxytryptamine 5-HT2A receptor. It is one of the internationally recognized drugs for front-line treatment. Although Pailperidone extended-release tablets (once-daily oral
intake) are already marketed in China, the currently approved drug is a once-monthly injection. The application of this preparation technology in this area of treatment has greatly increased the compliance of treatment and strengthened efficacy.

(6) Anti-virus and anti-infection drugs

Tigecycline injection (approval number: H20123339, H20123394) is for the treatment of “super bacteria” infection. This drug is recognized internationally to be an effective drug for the treatment of New Delhi Metallo \( \beta \)-lactamase 1 (NDM-1), referred to as “NDM-1 super virus” for short. The brand name drug was approved in November 9, 2010 to be imported to China. Domestic manufacturing of this drug product in China can help build up major drugs stockpile for the treatment of the above-mentioned drug resistant virus infection in China.

In order to effectively protect this antibiotic resource, the scope of usage of the product is clearly defined in the insert sheet review to prevent clinical misuse.

(7) Drugs for cardiovascular diseases

1. Ticagrelor tablets (approval number: H20120486) is for the treatment of platelet aggregation. Platelet aggregation is a major cause of cardiovascular events. This is the first drug with reversible inhibition effect. In 2011, there were almost a million new patients suffering from acute coronary syndrome (ACS) with increasing incidence and mortality of the disease. In addition to interventional therapy, the combination therapy of Aspirin plus Clopidogrel is the only means of drug therapy. The drug was approved for marketing in the United States in July 2011 and the import of this drug product provides the latest means of therapy for Chinese patients suffering from acute coronary syndrome.

2. Allisartan isoproxil (new drug certificate: H20120026) is an antihypertensive oral medication. It is an angiotensin II receptor (AT1 receptor) antagonist. This product is an innovative drug supported by Major
Drug Invention Program of China’s 12th Five-year Plan. Marketing of this product provides a new option for Chinese hypertensive patients.

(8) Rheumatism and immunity drugs

Febuxostat tablets (approval number: H20130009) is for the treatment of hyperuricaemia in patients with gout. Over the years, Allopurinol is the only drug for the clinical treatment in this area yet due to its significant adverse reactions, the extensive application of Allopurinol is restricted. Marketing of this drug product provides a more effective, safer and new mean of management of hyperuricaemia in patients with gout.

(9) Respiratory system drugs

1. Indacaterol maleate powder for inhalation (approval number: H20120232) is the latest long-acting inhaled β2 adrenergic receptor agonist, which is for the treatment of asthma or chronic obstructive pulmonary disease (COPD). With the attributes of fast action and long endurance, this product is a once-daily administration drug for patients suffering from asthma or chronic obstructive pulmonary disease (COPD) and can increase the drug compliance of patients.

2. Ciclesonide aerosol (approval number: H20120114, H20120110, H20120112 and H20120108) is a non-halogenated inhaled glucocorticosteroid for the maintenance treatment of asthma in adults and adolescents above the age of 12 and not yet marketed in China. Over the past few years, we have always been encouraging and supporting the replacements of CFC propellants and approved this type of products from two manufacturers in 2012, which is a specific move of China in the fulfillment of Montreal Protocol on Substances Depleting the Ozone Layer. Compared with twice-daily beclomethasone, budesonide and fluticasone propionate that have already been marketed, this product can be used once daily, which is more convenient for the long-term use by patients.

(10) Other therapeutic areas
1. Hemoporfin injection (new drug certificate: H20120076) is for the treatment of epidermal port-wine stains. As a congenital disease, epidermal port-wine stains usually spread on face with trigeminal never and the area of port-wine stains will expand and the color will deepen as child patients grow up. This disease seriously affects the physical and mental development and social acceptance of patients. Supported by optical dynamic equipment, Hemoporfin highly selectively removes expanded blood capillary in superficial dermis and while removing diseased region, protects the upper and lower dermis and deep tissues to achieve the purpose of effectively removing port-wine stains without leaving any scars. This drug is an innovative product of China and supported by the New Drug Invention Program under the national 12th Five-year Plan.

2. Prucalopride succinate tablets (approval number: H20120562-65) is a highly selective 5-HT4 receptor antagonist for the treatment of chronic constipation. Currently, conventional drugs for chronic constipation include such categories as aperient, prokinetic agents, dietary fiber and fiber preparation but all have somewhat of safety or efficacy issues. More effective and safer drugs are needed for clinical treatment. Prucalopride succinate tablets are more suitable to patients whose symptoms cannot be fully alleviated by using aperients.

(11) Biological products

Recombinant human coagulation factor IX for injection (approval number: S20120053-56) is for the treatment of haemophilia. Since products extracted from blood are insufficient for the treatment of haemophilia, this product is developed with recombinant technology and reviewed through priority review procedure. Registration for the import of the first recombinant human coagulation factor IX provides a specific drug therapy for the patients suffering from haemophilia B.

In addition, in major therapeutic areas such as HIV, Alzheimer’s disease and severe infection of influenza virus A or B, the CDE has completed the review of China’s first tenofovir disoproxil fumarate tablets, memantine oral solution and peramivir injection. Currently, these products have proceeded to the stage of manufacturing site inspection.
III. Acceptance and Review in 2012

In 2012, the CDE has accepted a total of 6,919 new registration applications (by acceptance numbers). Figure 1 shows the comparison of accepted drug applications with previous years.

Figure 1: Accepted drug applications from 2009 to 2012

Figure 1 shows that the total number of yearly accepted drug applications is in the range of 6,500 to 7,000 with a slight increase over the past two years. In 2012, there is a slight increase in the accepted numbers of chemical drug applications, a slight decrease in the accepted numbers of TCM applications and roughly the same level for biological products. Over the past few years, the accepted applications of chemical drugs generally accounted for 80% to 85% of the total number of accepted cases across various years.

In 2012, the CDE completed 4,941 drug review tasks and submitted them for review and approval by the CFDA. Of which, 3,323 are suggested for approval and 1,618 are suggested for disapproval. In 2012, there is a gap of 2,000 between accepted and completed tasks of the CDE and most of them are related to chemical drugs.

The table below shows the approvals by the SFDA by the end of 2012 (excluding supplementary applications):
Table 1: Approval of drugs in 2012

<table>
<thead>
<tr>
<th>Registration category</th>
<th>New drug</th>
<th>Changed dosage form</th>
<th>Generic drug</th>
<th>Imported drug</th>
<th>Sub-total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical drug</td>
<td>103</td>
<td>13</td>
<td>336</td>
<td>80</td>
<td>532</td>
</tr>
<tr>
<td>TCM</td>
<td>21</td>
<td>14</td>
<td>2</td>
<td>/</td>
<td>37</td>
</tr>
<tr>
<td>Biological product</td>
<td>29</td>
<td>2</td>
<td>17</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>615</td>
</tr>
</tbody>
</table>

Note: by acceptance number (the same below)

Table 2: Approval of drug clinical research in 2012:

<table>
<thead>
<tr>
<th>Registration category</th>
<th>Clinical trial</th>
<th>Bioequivalence study</th>
<th>Sub-total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical drug</td>
<td>425</td>
<td>178</td>
<td>603</td>
</tr>
<tr>
<td>TCM</td>
<td>37</td>
<td>2</td>
<td>39</td>
</tr>
<tr>
<td>Biologics</td>
<td>62</td>
<td>/</td>
<td>62</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>704</td>
</tr>
</tbody>
</table>

Below are the annual acceptance and review data of 2012 for chemical drugs, TCM drugs and biologic products.

(1) Acceptance and review of chemical drug applications in 2012

1. Acceptance of new chemical drug applications

Table 3: Number of various registration applications

<table>
<thead>
<tr>
<th></th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1.1 new drugs</td>
<td>42</td>
<td>69</td>
<td>79</td>
<td>78</td>
</tr>
<tr>
<td>Other new drugs above Category 3</td>
<td>656</td>
<td>718</td>
<td>793</td>
<td>942</td>
</tr>
<tr>
<td>Category 4 to 6</td>
<td>1,314</td>
<td>1,358</td>
<td>1,806</td>
<td>1,852</td>
</tr>
<tr>
<td>Global multi-centered clinical trial</td>
<td>157</td>
<td>150</td>
<td>179</td>
<td>138</td>
</tr>
<tr>
<td>Imported drug</td>
<td>365</td>
<td>410</td>
<td>459</td>
<td>442</td>
</tr>
</tbody>
</table>

Table 3 indicates that the number of Category 1.1 applications stayed around 70 over recent years and Category 3 new drugs increased by almost a hundred
per year. National innovation encouragement policies began to demonstrate preliminary effects on the structure of drug registration applications.

In 2011, the CDE has implemented *CDE Procedures for Review Task Management* in line with international practices to enforce six-channel management of drug review tasks and the data below are all accounted by drug review channels.

![Figure 2 Acceptance of chemical drug applications in 2012](image)

In 2012, there are 5,944 new chemical drug applications by acceptance numbers. Of which, investigational new drug (IND) applications include registration Category 1, registration Category 2 and global multi-centered clinical trial applications; Bridging clinical trial applications include registration Category 3 and 4 clinical trial applications; New drug applications (NDA) are manufacturing/marketing applications after the completion of clinical trials; Abbreviated new drug applications (ANDA) are bioequivalence test applications and manufacturing/marketing applications of Category 5 and 6; Supplementary applications are change applications of marketed products (of which, phase II and III clinical trial applications of innovative drugs submitted in the form of supplementary applications are already included in the IND statistics).
2. Therapeutic areas covered by IND applications

No matter for global multi-center clinical trial applications or domestic IND applications, the biggest share all comes from oncology drugs. Among domestic IND oncology drug applications accepted in 2012, tinib category drugs (tyrosine kinase inhibitors) accounted for 64.7% of total applications, which is roughly the same level with 2011.

3. Repetitive applications of generic drugs
Figure 4 indicates a total of 2,095 ANDA applications newly submitted in 2012 (by acceptance numbers, excluding excipients). There are still 1,272 applications of drugs that each already has more than 20 approval numbers, accounting for 60.7% of ANDA applications in 2012; ANDA applications that each has fewer than ten approval numbers only account for 20.6% of total applications. These figures suggest that repetitive research, development and applications of generic drugs remain to be a serious concern.

In addition, according to the performance of pilot programs of "Speak up" mechanism (for details, please refer to page 11 of Study Report on the Development of Generic Drugs in China), there exists obvious limitations in the industrialization capabilities of generic drug research and development. Among drug products covered by the pilot programs, only one third of manufacturers proposed manufacturing site inspections within six months after the issuance of documents by the SFDA.

4. Completion of drug review
In 2012, the CDE completed the review of 5,461 chemical drug applications (by acceptance numbers, excluding 284 applications withdrawn by applicants) with specific information listed below.

Table 4: Completion of chemical drug review in 2012

<table>
<thead>
<tr>
<th></th>
<th>Approval suggestion</th>
<th>disapproval suggestion</th>
<th>Request for amendment data</th>
<th>Site inspection</th>
</tr>
</thead>
<tbody>
<tr>
<td>IND</td>
<td>202</td>
<td>14</td>
<td>55</td>
<td>--------</td>
</tr>
<tr>
<td>Bridging clinical trial</td>
<td>354</td>
<td>99</td>
<td>304</td>
<td>--------</td>
</tr>
<tr>
<td>NDA</td>
<td>165</td>
<td>27</td>
<td>182</td>
<td>81</td>
</tr>
<tr>
<td>ANDA</td>
<td>479</td>
<td>225</td>
<td>340</td>
<td>20</td>
</tr>
<tr>
<td>Supplementary application</td>
<td>1,473</td>
<td>923</td>
<td>347</td>
<td>101</td>
</tr>
<tr>
<td>Import re-registration</td>
<td>50</td>
<td>5</td>
<td>15</td>
<td>--------</td>
</tr>
<tr>
<td>Total</td>
<td>2,723</td>
<td>1,293</td>
<td>1,243</td>
<td>202</td>
</tr>
</tbody>
</table>

Among 4,016 chemical drug products that review have been completed to, 32% are not approved and the overall disapproval rate has stayed around 30% for three consecutive years.
Figure 5 Comparison of review completions in channels in 2011 and 2012

Note: Drug products that have completed review include those submitted to the SFDA and those notified for manufacturing site inspection.

Figure 5 indicates that the completion of reviews in four channels of IND, bridging clinical trial, NDA and supplementary applications has certain extent increase in 2012 than 2011, and the review completion of ANDA in 2012 basically maintained the same level compared with 2011.

5. Review timeline

<table>
<thead>
<tr>
<th>Sequence</th>
<th>January 2012</th>
<th>December 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reception date</td>
<td>Waiting time (month)</td>
</tr>
<tr>
<td>IND</td>
<td>May 2011</td>
<td>6</td>
</tr>
<tr>
<td>Bridging clinical trial</td>
<td>December 2010</td>
<td>12</td>
</tr>
<tr>
<td>NDA</td>
<td>January 2011</td>
<td>11</td>
</tr>
</tbody>
</table>
Table 5 shows that in 2012, the CDE strives to expedite the review of applications for clinical trials of innovative drugs and shortened the review waiting time for review to roughly the level of four months or so; Review waiting time for post-marketing supplementary applications has been reduced from five months by the beginning of 2012 to three months by the end of 2012; However, the review waiting time for ANDA has been prolonged from 14 months in early 2012 to 24 months by the end of the year. Meanwhile, the review waiting time for NDA and bridging clinical trial applications has also been prolonged to a certain extent.

5.1 Review timeline for chemical drug clinical trials applications

For chemical drug IND applications submitted by domestic applicants in 2012, review for most applications took fewer than eight months (72%) (including waiting time), most of them took six to seven months (45%), 11% took fewer than five months and most of those that took more than nine months (15%) are combination product applications. In terms of therapeutic areas, oncology drug application review took the shortest time. Regarding the timeline of discipline review, CMC review significantly shortened the review time. Among the IND applications that have been completed review in 2012, prior to the release of CMC review template and annual report system in May 2012, the average CMC review time was seven months and gradually shortened thereafter, reaching four to five months by the end of the year. In order to encourage global synchronized research and development by domestic applicants and expedite the review of such applications, domestic approval of clinical trial has been synchronized with overseas for such products as metatinib tromethamine tablets and hezetimibe tablets. The CDE has achieved preliminary effects regarding its strategies to encourage innovation and allocate review resources in a reasonable manner.
Table 6: Review timelines of clinical trial applications in major therapeutic areas

<table>
<thead>
<tr>
<th>Indication*</th>
<th>Proportion (%)*</th>
<th>Average review time (month)</th>
<th>Shortest review time (month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncology</td>
<td>32%</td>
<td>6.1</td>
<td>4.2</td>
</tr>
<tr>
<td>Endocrine</td>
<td>17%</td>
<td>6.7</td>
<td>5.8</td>
</tr>
<tr>
<td>Psychology and neurology</td>
<td>15%</td>
<td>7.3</td>
<td>5.8</td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>13%</td>
<td>7.6</td>
<td>5.6</td>
</tr>
</tbody>
</table>

Note: * Therapeutic areas with limited proportions are not listed here; Data in the table originate from the domestic IND applications for 47 chemical entities in 2012.

5.2 Comparison of domestic and international approval timelines for the import of chemical drugs

Some imported brand-name drugs play an important role in resolving unmet clinical needs in China and providing the latest therapies. The CDE attaches great importance to the review of imported drugs urgently needed by clinical treatment in China in order for Chinese patients to access the latest drugs from across the world as early as possible. By properly allocating review resources, the CDE has strived to reduce the gaps between domestic and international marketing timelines for imported drugs with major clinical value. For instance, there is only a one-year gap with the US FDA’s marketing approval for sunitinib malate capsules (new indications), crizotinib capsules, rilpivirine tablets and ticagrelor tablets, etc. approved for marketing in 2012.

(2) Acceptance and review of TCM drug applications in 2012

1. Acceptance of new applications
There are 519 new TCM applications (by acceptance numbers).

2. Completion of drug review

In 2012, the CDE completed 726 TCM application review (by acceptance numbers, excluding 72 applications withdrawn by applicants) with specific information listed below.
Table 7: Completion of TCM review in 2012

<table>
<thead>
<tr>
<th></th>
<th>Approval suggested</th>
<th>disapproval suggested</th>
<th>Request for amendment data</th>
<th>Site inspection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical trial application</td>
<td>32</td>
<td>39</td>
<td>28</td>
<td>--------</td>
</tr>
<tr>
<td>New drug marketing application</td>
<td>19</td>
<td>17</td>
<td>45</td>
<td>10</td>
</tr>
<tr>
<td>generic drug or dosage form changing application</td>
<td>12</td>
<td>41</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Supplementary application</td>
<td>230</td>
<td>174</td>
<td>70</td>
<td>--------</td>
</tr>
<tr>
<td>Total</td>
<td>293</td>
<td>271</td>
<td>149</td>
<td>13</td>
</tr>
</tbody>
</table>

3. Review timeline

Currently, the queuing and waiting time for TCM drug review is not a major issue.

(3) Acceptance and review of biological product applications in 2012

1. Acceptance of new applications

![Figure 7 Acceptance of biological products in 2012](image)
There are a total of 456 new applications of biological products (by acceptance numbers).

2. Completion of drug review

In 2012, the CDE completed the review of 533 applications of biological products (by acceptance numbers, excluding 45 applications withdrawn by applicants) with specific information listed below.

<table>
<thead>
<tr>
<th></th>
<th>Approval suggested</th>
<th>Disapproval suggested</th>
<th>Request for amendment data</th>
<th>Site inspection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Domestic clinical trial application</td>
<td>45</td>
<td>16</td>
<td>60</td>
<td>--------</td>
</tr>
<tr>
<td>Global multi-center clinical trial application</td>
<td>26</td>
<td>1</td>
<td>19</td>
<td>--------</td>
</tr>
<tr>
<td>Marketing application</td>
<td>47</td>
<td>10</td>
<td>22</td>
<td>6</td>
</tr>
<tr>
<td>Supplementary application</td>
<td>189</td>
<td>27</td>
<td>48</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>307</td>
<td>54</td>
<td>149</td>
<td>23</td>
</tr>
</tbody>
</table>

3. Review timeline

The review timeline for biological products remains to be great pressures.

**IV. Concluding remarks**

Guided by the spirit of the 18th Communist Party of China Congress and in accordance with the requirements of the 12th Five-year Plan on National Drug Safety and Plan for the Development of Biological Industry, the CDE will continue to fulfill its duties and conduct technical review based on science and empirical evidence for the protection and promotion of public health.
Here is CDE’s special acknowledgement to Dr. Zili Li, Dr. Li Xu and RDPAC (R & D-Based Pharmaceutical Association Committee, China Association of Enterprises with Foreign Investment) for their help in translation of the annual report.