Overview of PRC Regulations

Regulations on Company Establishment and Foreign Investment

The establishment, operation and management of companies in China is governed by the PRC Company Law (中華人民共和國公司法), as amended in 2005 and 2013. Under the PRC Company Law, companies established in the PRC are either limited liability companies or joint stock limited liability companies. The PRC Company Law applies to both PRC domestic companies and foreign-invested companies. Investments in the PRC by foreign investors are regulated by the Foreign-Owned Enterprise Law of the PRC (中華人民共和國外資企業法) promulgated on April 12, 1986 and amended on October 31, 2000 and September 3, 2016, the Implementing Rules for the Foreign-Owned Enterprise Law of the PRC (中華人民共和國外資企業法實施細則) promulgated on December 12, 1990 and amended on April 12, 2001 and February 19, 2014, and the Interim Administrative Measures for the Record-filing of the Incorporation and Change of Foreign-invested Enterprises (外商投資企業設立及變更備案管理暫行辦法) promulgated on October 8, 2016 and amended on and effective from July 30, 2017. Under these laws and regulations, the establishment of a wholly foreign-owned enterprise is subject to the approval of, or the filing with, MOFCOM or its local counterpart and such wholly foreign-owned enterprises must register and file with the appropriate administrative bureau of industry and commerce. We hold approvals from MOFCOM or its local counterpart for our interests in our wholly-owned PRC subsidiaries.

Foreign investment in China is subject to the Catalogue for the Guidance of Foreign Investment Industries (2017 Revision) (外商投資產業指導目錄(2017年修訂)) effective from July 28, 2017, or the 2017 Catalogue, which comprises the favored foreign-invested industries catalogue and the special access administrative measures for foreign investment, the latter of which sets out restrictions such as shareholding requirements and qualifications of senior management. Foreign investments in business sectors that are not subject to special access administrative measures are only required to complete a filing as opposed to obtaining an approval. Pursuant to the Provisional Administrative Measures on Establishment and Modifications (Filing) for Foreign Investment Enterprises, the establishment of and changes to foreign-invested enterprises not subject to approval under the special entry management measures shall be filed with the relevant commerce authorities. Additionally, the registration for a PRC Company's establishment, modification, and termination must comply with the provision of Regulation of the People's Republic of China on the Administration of Company Registration (中華人民共和國公司登記管理條例), which was issued by the State Council on February 6, 2016. The industry in which our PRC subsidiaries are primarily engaged does not fall into the category of industries subject to special access administrative measures.

On August 8, 2006, six PRC regulatory agencies, MOFCOM, the State-owned Assets Supervision and Administration Commission of the PRC, the State Administration of Taxation, the State Administration for Industry and Commerce, the China Securities Regulatory Commission, and the State Administration of Foreign Exchange, or the SAFE, jointly adopted the Regulations on Mergers and Acquisitions of Domestic Enterprises by Foreign Investors (關於外國投資者併購境內企業的規定), or the M&A Rules, which became effective on September 8, 2006 and were amended by MOFCOM on June 22, 2009. The M&A Rules require, among other things, that a foreign investor (i)

acquiring an equity interest in a non-foreign-invested PRC enterprise or (ii) purchasing and operating the assets of such an enterprise through the establishment of a foreign-invested enterprise must comply with relevant foreign investment industry policies and be subject to approval/filing by MOFCOM or its local counterpart.

Drug Regulatory Regime

We operate our business in China through Hua Shanghai under a legal regime consisting of the Standing Committee of the National People's Congress, the SCNPC, the State Council and several ministries and agencies under its authority including, among others, the CFDA and the National Health and Family Planning Commission of the PRC, or the NHFPC. According to the Institutional Reform Program of the State Council (國務院機構改革方案) promulgated by the PRC National People's Congress on March 17, 2018, or 2018 Institutional Reform, the NHFPC will be incorporated into the newly organized National Health Commission and the CFDA's functions with respect to drug supervision will be transferred to China Drug Administration, or the CDA, a newly established regulatory authority responsible for registration and supervision of pharmaceutical products, cosmetics and medical equipment under the supervision of State Administration for Market Regulation, or the SAMR, a newly established national institution for supervising and administrating the market in China. Neither the CFDA nor the NHFPC will be retained following the structure reform of administrative organs led by the State Council. There will be no drug supervision institutions at municipal and county level, instead, the local SAMRs are entitled to perform the drug supervision functions such as drug sales and operation. Pursuant to the Program for Deepening the Reform of the Party and the State Institutions (深化黨和國家機構改革方案) promulgated by the Central Committee of the PRC Communist Party on March 21, 2018, the reform of the central and state institutions is expected to be completed before the end of the fiscal year of 2018.

Pharmaceutical Product Development

In the PRC, the China Food and Drug Administration, or the CFDA, monitors and supervises the administration of pharmaceutical products, as well as medical devices and equipment. Local provincial drug administrative authorities are responsible for supervision and administration of drugs within their respective administrative regions. Pursuant to the above institutional reform of the State Council in March 2018, CDA has been newly established to carry on CFDA's functions with respect to drug supervision. The PRC Drug Administration Law (中華人民共和國藥品管理法) promulgated by the SCNPC in 1984, as amended in 2001, 2013 and 2015, and the Implementing Measures of the PRC Drug Administration Law (中華人民共和國藥品管理法實施辦法) as promulgated by the Ministry of Health, or the MOH, in 1989, which was replaced by the Implementing Measures of the PRC Drug Administration Law (中華人民共和國藥品管理法實施條例) promulgated by the State Council effective in September 2002 and amended on February 6, 2016, have laid down the legal framework for the administration of pharmaceutical products, including the research, development and manufacturing of new drugs. The PRC Drug Administration Law applies to entities and individuals engaged in the development, production, trade, application, supervision and administration of pharmaceutical products. It regulates and prescribes a framework for the administration of pharmaceutical manufacturers, pharmaceutical trading companies, and medicinal preparations of

medical institutions and the development, research, manufacturing, distribution, packaging, pricing and advertisements of pharmaceutical products. The Implementing Measures of the PRC Drug Administration Law serve to provide detailed implementation regulations for the revised PRC Drug Administration Law.

We are required to follow these regulations for non-clinical research, clinical trials and production of new drugs.

Non-Clinical Research and Animal Testing

To improve the quality of non-clinical research, the CFDA promulgated the Administrative Measures for Good Laboratories Practice of Non-clinical Laboratory (藥物非臨床研究質量管理規範) in 2003, which was revised on July 27, 2017, and has conducted Good Laboratories Practice, or GLP Certifications since 2003. In April 2007, the CFDA issued the Circular on Measures for Certification of Good Laboratory Practice for Non-clinical Laboratory (藥物非臨床研究質量管理規範認證管理辦法), or CFDA Circular 214, which provides that the CFDA is responsible for the certification of non-clinical research institutions. Under CFDA Circular 214, the CFDA decides whether an institution is qualified for undertaking pharmaceutical non-clinical research upon the evaluation of the institution's organizational administration, its research personnel, its equipment and facilities and its operation and management of non-clinical pharmaceutical projects. If all requirements are met, a GLP Certification will be issued by the CFDA and the result will be published on the CFDA's website.

According to the Regulations for the Administration of Affairs Concerning Experimental Animals (實驗動物管理條例) promulgated by the State Science and Technology Commission in November 1988, as amended in January 2011, July 2013 and March 2017 by the State Council, the Administration Measures on Good Practice of Experimental Animals (實驗動物質量管理辦法) jointly promulgated by the State Science and Technology Commission and the State Bureau of Quality and Technical Supervision in December 1997, and the Administrative Measures on the Certificate for Experimental Animals (Trial) (實驗動物許可證管理辦法(試行)) promulgated by the State Science and Technology Commission and other regulatory authorities in December 2001, performing experimentation on animals requires a Certificate for Use of Laboratory Animals.

To date, we have used WuXi AppTec (Suzhou) Co., Ltd. for our non-clinical studies in China. WuXi AppTec (Suzhou) Co., Ltd. holds Certificates for GLP and Use of Laboratory Animals and conducted our studies following GLP based on CFDA requirements.

Clinical Trials and Registration of New Drugs

In July 2007, the CFDA promulgated the Administrative Measures for Drug Registration (藥品註冊管理辦法) which took effect on October 1, 2007, providing the standards and requirements for clinical trials and drug registration applications. According to the Administrative Measures for Drug Registration, drug registration applications are divided into three different types, Domestic New Drug Applications, Domestic Generic Drug Applications, and Imported Drug Applications. Drugs fall into one of three general types divided by working mechanism, including chemical medicine, biological product or traditional Chinese or natural medicine. Pursuant to the Administrative Measures for Drug Registration, the PRC Drug Administration Law and Implementing Measures of the PRC Drug

Administration Law, upon completion of non-clinical research, clinical trials must be conducted for the application of a new drug registration, and research institutions must apply for approval of a Clinical Trial Application, or CTA, from the CFDA, or the Center for Drug Evaluation, or the CDE, as of May 1, 2017, before conducting clinical trials.

Reform of Evaluation and Approval System for Drugs

On August 9, 2015, the State Council promulgated the Opinions on the Reform of Evaluation and Approval System for Drugs and Medical Devices and Equipment (關於改革藥品醫療器械審評審批制度的意見), or the Reform Opinions, which established a framework for reforming the evaluation and approval system for drugs and medical devices and equipment. The Reform Opinions indicated enhancing the standard of approval for drug registration and accelerating the evaluation and approval process for innovative drugs.

In November 2015, the CFDA promulgated the Circular Concerning Several Policies on Drug Registration Review and Approval (關於藥品註冊審評審批若干政策的公告), or the Several Policies Circular, which further clarified the measures and policies regarding simplifying and accelerating the approval process on the basis of the Reform Opinions.

In March 2016, the CFDA issued the Reform Plan for Registration Category of Chemical Medicine (化學藥品註冊分類改革工作方案), or the Reform Plan, which outlined the reclassifications of drug applications under the Administrative Measures for Drug Registration. Under the Reform Plan, Category 1 drugs are adjusted from "new drugs that have not been marketed within the territory of the PRC" to "new drugs that have not been marketed anywhere in the world". Category 1 drugs can be registered through the Domestic New Drug Application procedures under the Administrative Measures for Drug Registration.

According to the Decision of the CFDA on Adjusting the Approval Procedures under the Administrative Approval Items for Certain Drugs (國家食品藥品監督管理總局關於調整部分藥品行政審批事項審批程序的決定) promulgated on March 17, 2017, and that came into effect as of May 1, 2017, the approval for a CTA can be directly issued by the CDE on behalf of the CFDA.

On October 8, 2017, the General Office of the State Council promulgated the Opinions on Deepening the Reform of the Evaluation and Approval System and Inspiring Innovation of Drugs and Medical Devices and Equipment (關於深化審評審批制度改革鼓勵藥品醫療器械創新的意見), or the Deepening Reform Opinions, to further promote the structural adjustment to and technical innovations of drugs and medical devices and equipment.

On December 21, 2017, the CFDA promulgated the Opinions on Encouraging the Prioritized Evaluation and Approval for Drug Innovations (關於鼓勵藥品創新實行優先審評審批的意見), or the Encouraging Opinions, replacing the Opinions on Priority Review and Approval for Resolving Drug Registration Applications Backlog (關於解決藥品註冊申請積壓實行優先審評審批的意見) promulgated in February 2016, which further clarified that a fast track clinical trial approval or drug registration pathway will be available for innovative drugs.

In addition, on May 17, 2018, the CDA and National Health Commission jointly promulgated the Circular on Issues Concerning Optimizing Drug Registration Review and Approval (關於優化藥品註冊審評審批有關事宜的公告), which further simplified and accelerated the clinical trial approval process.

Special Examination and Fast Track Approval for Category 1 Drugs under Current Reform Frame

According to the Provisions on the Administration of Special Examination and Approval of Registration of New Drugs (新藥註冊特殊審批管理規定) promulgated by the CFDA in January 2009, the CFDA conducts special examination and approval for new drug registration applications when, among others, (1) the effective constituent of a drug extracted from plants, animals, minerals, etc., as well as the preparations thereof, have never been marketed in China, and the material medicines and the preparations thereof are newly discovered, or (2) the chemical raw materials for medicines as well as the preparations thereof and the biological product have not been approved for marketing, either in China or abroad. The Provisions on the Administration of Special Examination and Approval of Registration of New Drugs provide that the applicant may file for special examination and approval at the CTA stage if the drug candidate falls within items (1) or (2).

On November 11, 2015, the Several Policies Circular further clarified this policy, potentially simplifying and accelerating the approval process of clinical trials under the following reform framework: (1) a one-time umbrella approval procedure allowing the comprehensive approval of all phases of a new drug's clinical trials, replacing the current phase-by-phase application and approval procedure, will be adopted for new drugs' CTAs, and (2) a fast track drug registration or clinical trial approval pathway for certain types of drug applications.

In addition, on December 21, 2017, the Encouraging Opinions further clarified that a fast track clinical trial approval or drug registration pathway will be available to both innovative drugs with distinctive clinical benefits which have not been sold within or outside China as well as drugs using advanced technology, innovative treatment methods or having distinctive treatment advantages.

The Reform Opinions promulgated in 2015 provide that the composition of the examiner team of the CDE shall be strengthened by, among others, (1) recruiting professional evaluation talent from the public as contractors, (2) engaging relevant experts to participate in professional examination and evaluation, and (3) establishing a system of chief professional positions. The Encouraging Opinions further emphasized the improvement of the examination and evaluation system which requires the establishment of a new drug examination and evaluation team comprising professionals specialized in clinical medicine, pharmaceutical sciences, pharmacology, toxicology and statistics. As a result, since 2015, the CFDA and the CDE have started a large-scale expansion of examiners which could greatly accelerate new drug approval in the PRC.

Under the Administrative Measures for Drug Registration, a Category 1 drug refers to a new drug that has never been marketed in any country. We believe that our current drug candidates fall within Category 1 and that we may file an application for special examination and approval at the CTA stage, which may enable us to pursue an expedited path to approval in China and bring therapies to patients more quickly.

Four Phases of Clinical Trials

According to the Administrative Measures for Drug Registration, a clinical development program consists of Phases I, II, III and IV. Phase I refers to the initial clinical pharmacology and safety evaluation studies in humans. Phase II refers to the preliminary evaluation of a drug candidate's therapeutic effectiveness and safety for particular indications in patients, to provide evidence and support for the design of Phase III clinical trials and to settle the administrative dose regimen. Phase III refers to clinical trials undertaken to confirm the therapeutic effectiveness of a drug. Phase III is used to further verify the drug's therapeutic effectiveness and safety on patients with target indications, to evaluate the overall benefit-risk relationships of the drug, and ultimately to provide sufficient evidence for the review of drug registration application. Phase IV refers to a new drug's post-marketing study to assess therapeutic effectiveness and adverse reactions when the drug is widely used, to evaluate the overall benefit-risk relationships of the drug when used among the general population or specific groups and to adjust the administration dose.

Pursuant to the Several Policies Circular, the CDE grants a one-time approval for clinical trial applications for new drugs and does not require separate declarations, reviews or approvals for the subsequent phases of clinical trials. The CDE review focuses on the scientific nature of the clinical trial protocols and the control of safety risks to ensure patient safety. Applicants must promptly communicate with the CDE, to resolve problems during clinical trials and make a supplementary report on the latest research materials as the relevant reviewer requires. Upon the completion of Phase I and Phase II clinical trials, the applicant must submit trial results and the clinical trial protocol for the next phase in a timely manner. Where there is no safety problem, applicants can proceed to Phase III clinical trials after discussion with the CDE. The applicants must report serious adverse events that occur during the clinical trials and submit annual research reports. Where clinical trial risks cannot be controlled, the clinical trials must be stopped immediately.

On June 2, 2016, the CFDA promulgated the Administrative Measures for Communication on the Research, Development and Technical Evaluation of Drugs (trial) (藥物研發與技術審評溝通交流管理辦法(試行)), or the Communication Measure, which provides that communication meetings between the applicants and the CDE can be classified into three types. Type I communication meetings are convened to address key safety issues in clinical trials of drugs and key technical issues in the research and development of breakthrough therapeutic drugs. Type II communication meetings are convened in key research and development periods of innovative drugs, mainly including (i) meetings before the application for Phase I clinical trials, (ii) meetings upon the completion of Phase II trials and before the Phase III trial begins, (iii) meetings before submitting a marketing application for a new drug and (iv) meetings for risk evaluation and control. Type III communication meetings refer to other kinds of meetings. Pursuant to the Communication Measure, applicants must prepare meeting minutes promptly, and after the technical review project leader reviews and confirms the meeting minutes, project management personnel must send the meeting minutes to the drug registrar of the CDA within 30 days after the meeting. The minutes of the meeting are archived as important documents and serve as an important basis for drug development, review and approval.

On July 24, 2018, the CDA promulgated the Announcement on Adjusting the Evaluation and Approval Procedures for Drug Clinical Trials(關於調整藥物臨床試驗審評審批程序的公告), which provides that, within 60 days after acceptance of and charging the fees for clinical trial application,

the applicant may conduct clinical trial in accordance with the clinical trial protocol submitted if no negative or questioned opinion is received from the CDE. The minutes of the communication meetings between the applicants and the CDE are archived as review and approval documents and serve as a reference for review and approval.

We have conducted four Type II meetings with the CDE in May 2016, November 2016, December 2016, and October 2017 after we completed our Phase II clinical trial. See "Business—Material Communications with the CFDA."

We have already completed seven Phase I trials and one Phase II trial in China for Dorzagliatin and we are currently enrolling patients for two Phase III trials in China with Dorzagliatin as a monotherapy and in combination with metformin.

Sampling and Collecting Human Genetic Resources Filing

On June 10, 1998, the Ministry of Science and Technology and the Ministry of Health promulgated the Interim Administrative Measures on Human Genetic Resources (人類遺傳資源管理暫行辦法), which established the rules for protecting and utilizing human genetic resources in the PRC. On July 2, 2015, the Ministry of Science and Technology issued the Service Guide for Administrative Licensing Items concerning Examination and Approval of Sampling, Collecting, Trading or Exporting Human Genetic Resources, or Taking Such Resources out of the PRC (人類遺傳資源採集、收集、買賣、出口、出境審批行政許可事項服務指南), which became effective on October 1, 2015 according to the Circular on Implementing the Approval of Sampling, Collecting, Trading or Exporting Human Genetic Resources (關於實施人類遺傳資源採集、收集、買賣、出口、出境行政許可的通知), which clarified that the sampling and collection of human genetic resources though clinical trials by a foreign-invested sponsor shall be required to be filed with the China Human Genetic Resources Management Office through the online system. On October 26, 2017, the Ministry of Science and Technology promulgated the Circular on Optimizing the Administrative Examination and Approval of Human Genetic Resources (關於優化人類遺傳資源行政審批流程的通知) simplifying the approval of sampling and collecting human genetic resources for the purpose of listing a drug in the PRC.

We and our clinical trial institutions have filed with the China Human Genetic Resources Management Office for our ongoing Dorzagliatin Phase III trials.

Drug Clinical Practice Certification and Compliance with GCP

To improve the quality of clinical trials, the CFDA promulgated the Administration of Quality of Drug Clinical Practice (藥物臨床試驗質量管理規範), or GCP Administration, in August 2003, which aims to ensure standard clinical trial which will deliver scientific and reliable results, and protect the rights, interests and safety of human subjects. In February 2004, the CFDA issued the Circular on Measures for Certification of Drug Clinical Practice (Trial) (藥物臨床試驗機

構資格認定辦法(試行)), which provides that the CFDA is responsible for certification of clinical trial institutions, and that the National Health and Family Planning Commission of the PRC, formerly known as the Ministry of Health, is responsible for certification of clinical trial institutions within its duties. Under the Circular on Measures for Certification of Drug Clinical Practice (trial), the CFDA and the NHFPC will decide whether an institution is qualified for undertaking pharmaceutical clinical trials upon the evaluation of the institution's organizational administration, its research personnel, its equipment and facilities, its management system and its standard operational rules. If all requirements are met, a GCP Certification will be issued by the CFDA and the result will be published on the CFDA's website. Pursuant to the Deepening Reform Opinions, the accreditation of the institutions for drug clinical trials shall be subject to record-filing administration. The conduct of clinical trials must adhere to the GCP and the protocols approved by the ethics committees of each study site.

To date, we have only used CFDA certified GCP clinical trial institutions to conduct trials following GCP based on CFDA requirements.

On July 17, 2018, the SAMR released the Revised Administration of Quality of Drug Clinical Practice (Draft for Comments) (藥物臨床試驗質量管理規範(修訂草案徵求意見稿)) (the "New Practice") to seek comments from the public, which as compared to current GCP Administration, mainly includes the following key highlights:

- GCP Administration is applicable to the clinical trial of drugs for registration purposes, and clinical trials for other purposes may refer to GCP Administration;
- the rights and safety of the subjects shall be the primary factor to be considered, giving priority over scientific and social benefits;
- ethical review and informed consent shall be the main measures to protect the rights of the subjects;
- a quality management system shall be established for clinical trial purposes; and
- investigators and their family members (including spouse and children) shall avoid the following material conflicts of interests: receiving a fee of more than RMB20,000 which are not directly related to clinical trials from the sponsor within one year or in the next year, holding shares or stocks in the sponsor, holding the intellectual property of the clinical trial products or technology, or holding senior positions in the sponsor.

The consultation period ended on August 16, 2018. If implemented, the New Practice will replace the current GCP Administration.

Drug Clinical Trial Registration

Pursuant to the Administrative Measures for Drug Registration, upon obtaining approval of its CTA and before conducting a clinical trial, an applicant shall file a registration form with the CFDA containing various details, including the clinical study protocol, the name of the principal researcher of the leading institution, names of participating institutions and researchers, an approval letter from

the ethics committee, and a sample of the Informed Consent Form, with a copy sent to the competent provincial administration departments where the trial institutions will be located. On September 6, 2013, the CFDA published the Announcement on Drug Clinical Trial Information Platform (關於藥物臨床試驗信息平台的公告), providing that, instead of the aforementioned registration filed with the CFDA, all clinical trials approved by the CFDA and conducted in China shall complete a clinical trial registration and publish trial information through the Drug Clinical Trial Information Platform. The applicant shall complete the trial pre-registration within one month after obtaining the approval of CTA in order to obtain the trial's unique registration number and complete registration of certain follow-up information before the first subject's enrollment in the trial. If the registration is not completed within one year after the approval of CTA, the applicant shall submit an explanation, and if the first submission is not completed within three years, the approval of CTA shall automatically expire.

We have completed clinical trial registrations through the Drug Clinical Trial Information Platform for our eight clinical trials conducted in China.

Good Manufacturing Practice

Pursuant to the Administrative Measures for Drug Registration, all facilities and techniques used in the manufacture of drug samples for clinical trial use in the PRC must conform to GMP guidelines as established by the CFDA. The drug samples for our Dorzagliatin clinical trials have been manufactured by Shanghai SynTheAll Pharmaceuticals Co., Ltd. and Shanghai Desano Bio-Pharmaceutical Co., Ltd., the CFDA certified GMP manufacturers.

New Drug Application

Pursuant to the Administrative Measures for Drug Registration, when Phases I, II and III of clinical trials have been completed, the applicant may apply to the CFDA for approval of a new drug application, or the NDA. The CFDA then determines whether to approve the application according to the comprehensive evaluation opinion provided by the CDE of the CFDA. We must obtain approval of an NDA before our drugs can be manufactured and sold in the China market.

International Multi-Center Clinical Trials Regulations

On January 30, 2015, the CFDA promulgated the Notice on Issuing the International Multi-Center Clinical Trial Guidelines (Trial) (國際多中心藥物臨床試驗指南(試行)), or the Multi-Center Clinical Trial Guidelines, effective as of March 1, 2015, to provide guidance for the regulation of application, implementation and administration of international multi-center clinical trials in China. Pursuant to the Multi-Center Clinical Trial Guidelines, international multi-center clinical trial applicants may simultaneously perform clinical trials in different centers using the same clinical trial protocol. Where the applicant plans to make use of the data derived from the international multi-center clinical trials for application to CFDA for approval of an NDA, such international multi-center clinical trials shall satisfy, in addition to the requirements set forth in the PRC Drug Administration Law and its implementation measures, the Administrative Measures for Drug Registration and relevant laws and regulations.

Pursuant to the Deepening Reform Opinions, the clinical trial data obtained from foreign centers may be used to apply for registration in China if they meet the relevant requirements for the registration of drugs and medical devices in China. The applicant for new drug registration shall provide the clinical trial data on racial difference, if any.

Pilot Plan for the Marketing Authorization Holder System

Pursuant to the Reform Opinions in 2015, the State Council published a policy of carrying out a pilot plan for the drug marketing authorization holder mechanism, or the MAH System. Under the authorization of the Standing Committee of the National People's Congress, the State Council issued the Pilot Plan for the Drug Marketing Authorization Holder Mechanism (藥品上市許可持有人制度試點方案) on May 26, 2016, which provides a detailed pilot plan for the MAH System, for drugs in 10 provinces in China. Under the MAH System, domestic drug research and development institutions and individuals in the pilot regions are eligible to be holders of drug registrations without having to become drug manufacturers. The marketing authorization holders may engage contract manufacturers for manufacturing, provided that the contract manufacturers are licensed and GMP-certified, and are also located within the pilot regions. Drugs that qualify for the MAH System are: (1) new drugs (including Category 1 and 2 drugs under the Reform Plan) approved after the implementation of the MAH System; (2) generic drugs approved as Category 3 or 4 drugs under the Reform Plan; (3) previously approved generics that have passed equivalence assessments against original drugs; and (4) previously approved drugs whose licenses were held by drug manufacturers originally located within the pilot regions, but which have moved out of the pilot regions due to corporate mergers or other reasons.

On August 15, 2017, the CFDA issued the Circular on the Matters Relating to Promotion of the Pilot Program for the Drug Marketing Authorization Holder System (關於推進藥品上市許可持有人制度試點工作有關事項的通知), or the MAH Circular, which clarified the legal liability of the marketing authorization holder, who is responsible for managing the whole manufacturing and marketing chain and the whole life cycle of drugs and assumes the full legal liability for non-clinical drug study, clinical trials, manufacturing, marketing and distribution and adverse drug reaction monitoring. The marketing authorization holder is permitted to entrust several drug manufacturers under the drug quality management system established by the marketing authorization holder. Pursuant to the MAH Circular, the holder shall submit a report of drug manufacturing, marketing, prescription, techniques, pharmacovigilance, quality control measures and other situations to the CFDA within 20 working days after the end of each year.

On October 24, 2016, the CFDA granted us a market authorized holder certification for Dorzagliatin, for which the entrusted drug manufacturers are Shanghai STA Pharmaceutical Co, Ltd and Shanghai Desano Bio-Pharmaceutical Co, Ltd.

Administrative Protection and Monitoring Periods for New Drugs

According to the Administrative Measures for Drug Registration, the Implementing Regulations of the Drug Administration Law and the Reform Plan, the CFDA may, for the purpose of protecting public health, provide for an administrative monitoring period of five years for new Category 1 drugs approved to be manufactured, commencing from the date of approval, to continually monitor the

safety of those new drugs. During the monitoring period of a new drug, the CFDA will not accept other applications for new drugs containing the same active ingredient. This results in an effective five-year exclusivity protection for Category 1 new drugs. The only exception is that the CFDA will continue the regular examination process if, prior to the commencement of the monitoring period, the CFDA has already approved the applicant's clinical trial for a similar new drug. If such application meets the relevant requirements, the CFDA may approve such applicant to manufacture or import the similar new drug.

Packaging of Pharmaceutical Products

Pursuant to the Administration of Quality of Drug Clinical Practice, the applicant shall be responsible for the proper packaging and labeling of drugs for clinical trials and, in double-blind clinical trials, the test drug shall be consistent with the control drug or placebo in appearance, odor, packaging, labeling, and other features. According to the Measures for The Administration of Pharmaceutical Packaging (藥品包裝管理辦法) effective on September 1, 1988, pharmaceutical packaging must comply with national and professional standards. If there is no national or professional standard available, an applicant can formulate and implement its own standards after obtaining the approval of the provincial administration or bureau of standards. The applicant must reapply if it needs to change its own packaging standards. Drugs that have not been developed and approved for packaging standards must not be sold or marketed in PRC (except for drugs for the military).

Healthcare System Reform

The PRC government recently promulgated several healthcare reform policies and regulations to reform the healthcare system. On March 17, 2009, the Central Committee of the PRC Communist Party and the State Council jointly issued the Guidelines on Strengthening the Reform of Healthcare System (關於深化醫藥衛生體制改革的意見). On December 27, 2016, the State Council issued the Notice on the Issuance of the 13th Five-year Plan on Strengthening the Reform of Healthcare System (關於印發"十三五"深化醫藥衛生體制改革規劃的通知). On April 25, 2017, the General Office of the State Council issued the Main Tasks of Healthcare System Reform in 2017 (深化醫藥衛生體制改革2017年重點工作任務). Highlights of these healthcare reform policies and regulations include the following:

(1) One of the main objectives of the reform is to establish a basic healthcare system to cover both urban and rural residents and provide the Chinese people with safe, effective, convenient and affordable healthcare services. By 2020, a basic healthcare system covering both urban and rural residents shall be established.

(2) Another main objective of reform is to improve the healthcare system, through the reform and development of a graded hierarchical healthcare system, modern hospital management, basic medical insurance, drug supply support and comprehensive supervision.

(3) The reforms aim to promote orderly market competition and improve the efficiency and quality of the healthcare system to meet the various medical needs of the Chinese population.

From 2009, basic public healthcare services such as preventive healthcare, maternal and child healthcare and health education were to be provided to urban and rural residents. In the meantime, the reforms also encourage innovations by pharmaceutical companies to eliminate pharmaceutical products that fail to prove definite efficacy and positive risk-benefit ratio.

Chronic Diseases Prevention and Treatment

Pursuant to the Guiding Opinion of the General Office of the State Council on Promoting the Construction of the Hierarchical Healthcare System (國務院辦公廳關於推進分級診療制度建設的指導意見), or the Hierarchical Healthcare System Opinion, issued by the General Office of the State Council on September 8, 2015, and the Notice on Promoting Pilot Work for Hierarchical Healthcare System (關於推進分級診療試點工作的通知) promulgated by the NHFPC and the State Administration of Traditional Chinese Medicine on August 19, 2016, the hierarchical healthcare system is expected to be gradually improved and the framework for division and coordination among medical and health institutions shall be substantially established by 2017, and a diagnosis and treatment model featuring the objectives, such as initial diagnosis of common diseases and frequent diseases at primary hospitals and separate treatment of acute and chronic diseases, are expected to be gradually established. According to the Hierarchical Healthcare System Opinion, several chronic diseases, including hypertension, diabetes, cancer and cardiovascular and cerebrovascular diseases, are pilot diseases under the hierarchical healthcare system. Primary healthcare institutions, rehabilitation hospitals, and nursing institutions can provide treatments, rehabilitation and nursing services for patients with chronic diseases, patients in stable conditions, elderly patients, and advanced cancer patients who have clear diagnosis and stable disease conditions.

On January 22, 2017, the General Office of the State Council promulgated the Mid and Long-Term Plan for Chronic Disease Prevention and Treatment in China (2017-2025) (中國防治慢性病中長期規劃(2017-2025)), or the Chronic Disease Plan, which sets up the objective of the diabetes patients management with target involvement of 35 million diabetics by 2020 and 40 million diabetics by 2025 in chronic disease management. The Chronic Disease Plan reaffirms that the hierarchical healthcare system of chronic diseases, such as diabetes, shall be promoted, and encourages the initial diagnosis of common diseases and frequent diseases at primary hospitals. It also encourages, social participation in regional medical services, health managements and chronic disease prevention services, as well as investments in the field of chronic disease prevention by social capital.

PRC coverage and reimbursement

Historically, most Chinese healthcare costs have been borne by patients out-of-pocket, which has limited the growth of more expensive pharmaceutical products. However, in recent years, the number of people covered by government and private insurance has increased. According to the PRC National Bureau of Statistics, as of December 31, 2017, 1.1 billion employees and residents in China were enrolled in the national medical insurance program, including those who were enrolled in a new rural co-operative medical system. The PRC government has announced a plan to provide every person in China access to basic healthcare by 2020.

Reimbursement under the national medical insurance program

The national medical insurance program was first adopted pursuant to the Decision of the State Council on the Establishment of the Urban Employee Basic Medical Insurance Program (國務院關於建立城鎮職工基本醫療保險制度的決定) issued by the State Council on December 14, 1998, under which all employers in urban cities are required to enroll their employees in the basic medical insurance program and the insurance premium is jointly contributed by the employers and employees. The national medical insurance program was further developed according to the Guiding Opinions of the State Council about the Pilot Urban Resident Basic Medical Insurance (國務院關於開展城鎮居民基本醫療保險試點的指導意見) on July 10, 2007, under which urban residents of the pilot district, rather than urban employees, may voluntarily join Urban Resident Basic Medical Insurance. In addition, on January 3, 2016, the Opinions on Integrating the Basic Medical Insurance Systems for Urban and Rural Residents (國務院關於整合城鄉居民基本醫療保險制度的意見) issued by the State Council required the integration of the urban resident basic medical insurance and the new rural cooperative medical care system and the establishment of a unified basic medical insurance system, which will cover all urban and rural residents other than rural migrant workers and persons in flexible employment arrangements who participate in the basic medical insurance for urban employees.

Medical Insurance Catalogue

Participants of the national medical insurance program and their employers, if any, are required to contribute to the payment of an insurance premium on a monthly basis. Program participants are eligible for full or partial reimbursement of the cost of medicines included in the medical insurance catalogue. The Notice Regarding the Tentative Measures for the Administration of the Scope of Basic Medical Insurance Coverage for Pharmaceutical Products for Urban Employee (關於印發城鎮職工基本醫療保險用藥範圍管理暫行辦法的通知), or the Medical Insurance Coverage Notice, jointly issued on May 12, 1999 by several authorities including, among others, the Ministry of Labor and Social Security and the Ministry of Finance, provides that a pharmaceutical product listed in the medical insurance catalogue must be clinically necessary, safe, effective, reasonably priced, easy to use, available in sufficient quantity, and must meet the following requirements: (1) be set forth in the pharmacopoeia of the PRC, (2) satisfy the standards promulgated by the CDA, and (3) be approved by the CDA for imported pharmaceutical products.

The National Drug Catalog for Basic Medical Insurance, Work-related Injury Insurance and Maternity Insurance (國家基本醫療保險、工傷保險和生育保險藥品目錄), or the National Reimbursement Drug List, or the NRDL, sets forth the payment standard for pharmaceutical products under the basic medical insurance, work-related injury insurance and maternity insurance funds. The Ministry of Human Resources and Social Security of the PRC, together with other government authorities, have the power to determine which medicines are listed in the NRDL. In order for any drug to be listed in the NRDL, it must be included in the National Essential Drug List that is promulgated and revised by the MOH. Medicines listed in the NRDL are divided into two parts, List A and List B. List A drugs are widely used clinical treatments with good efficacy and lower prices compared to similar drugs, while List B drugs are clinical treatments with good efficacy and slightly higher prices compared to List A drugs.

In February 2017, the Ministry of Human Resources and Social Security of the PRC released the 2017 NRDL, the scope of which was expanded to cover 2,535 drugs in total, including 339 newly added drugs. In July 2017, the Ministry of Human Resources and Social Security of the PRC announced that the 2017 NRDL would be expanded to include an additional 36 innovative drugs, classified as List B medicines. The 2017 NRDL reflects an emphasis on innovative drugs and drugs that treat cancer and other serious diseases. For instance, most of the innovative chemical drugs and biological products approved in China between 2008 and the first half of 2016 have been included in the 2017 NRDL or its candidate list. As the PRC government has started to include more innovative drugs in the NRDL, Dorzagliatin, may be accepted by the Ministry of Human Resources and Social Security of the PRC or any of its local counterparts for inclusion in the NRDL or provincial or local medical insurance catalogues, which may increase the demand for Dorzagliatin.

According to the Deepening Reform Opinions, in order to support the clinical application of new drugs, (1) the dynamic adjustment mechanism applicable to the catalogue of drugs by medical insurance will be improved, (2) the establishment of a negotiation mechanism regarding payment standards for drugs covered by medical insurance will be explored, (3) new drugs will be promptly incorporated according to applicable provisions into the payment scope covered by basic medical insurance, and (4) research and development of new drugs will be supported. An evaluation steering group composed of the members of Ministry of Labor and Social Security of the PRC and other authorities is responsible for (i) evaluating the drugs to be included in or deleted from the NRDL, (ii) reviewing the list of members of the drug selection expert panel and consulting group, and (iii) coordinating the evaluation and implementation of the Provincial Reimbursement Drug List, or PRDL. A drug selection expert panel composed of clinical and pharmacy specialists with higher professional skills is responsible for selecting drug candidates fulfilling the required criteria to be listed in the NRDL.

Pursuant to the Medical Insurance Coverage Notice, a PRDL must be established by the labor administration departments of the provincial governments in the PRC. As with the NRDL, provincial evaluation institutions and expert groups have been established to select the drugs to be listed in the PRDL. Provincial governments are required to include all Part A medicines listed on the NRDL in their provincial medical insurance catalogue, but have discretion to adjust upwards or downwards by no more than 15% the number of Part B medicines listed in the NRDL to be listed in the PRDL based on local economic levels, medical demands, and medication practices. As a result, the contents of Part B of the provincial medical insurance catalogues may differ from region to region in the PRC.

Pursuant to the Medical Insurance Coverage Notice, patients purchasing medicines included in Part A of the NRDL are entitled to reimbursement of the entire amount of the purchase price through the basic medical insurance program. Patients purchasing medicines included in Part B of the NRDL are required to pay a certain percentage of the purchase price and obtain reimbursement for the remainder of the purchase price through the basic medical insurance program. The percentage of reimbursement for Part B medicines differs from region to region in the PRC. Similarly, patients purchasing drugs included in List A catalogue of the PRDL are entitled to reimbursement of the entire amount of the purchase price through the basic medical insurance program. Patients purchasing drugs included in List B catalogue of the PRDL are required to pay a certain percentage (approximately 10%-30%) of the purchase price and obtain reimbursement for the remainder of the purchase price (about 70%-90%), through the basic medical insurance program. The percentage of reimbursement for List B drugs differs from region to region in the PRC.

According to the Medical Insurance Coverage Notice, the National Essential Drug List must be adjusted every two years in principle, and the provincial Essential Drug List must be adjusted based on the adjustment of the National Essential Drug List. The PRDL can only be adjusted according to the respective adjustment of the NRDL, and all adjustments to the List A drugs in the NRDL are required to be made in the PRDL. The National Essential Drug List is permitted to be expanded for new drugs once every year, while provincial governments are not permitted to expand the provincial Essential Drug List for new drugs.

The Opinions on Promoting Drug Pricing Reform (推進藥品價格改革的意見), which was promulgated by the NDRC, the National Health and Family Planning Commission, CDA, Ministry of Commerce and certain other departments on May 4, 2015, and came into effect on the same day, set forth that from June 1, 2015, except for narcotic drugs and Class I psychotropic drugs, the restrictions on the prices of the drugs that were subject to government pricing will be cancelled. The medical insurance regulatory authority shall, along with other competent departments, draw up provisions in relation to the standards, procedures, basis and methods of the payment of drugs paid by medical insurance funds. The prices of patent drugs and exclusively produced drugs are set through transparent and public negotiation among multiple parties. The prices for blood products not listed in the Medical Insurance Drugs List, immunity and prevention drugs that are purchased by the government in a centralized manner, and AIDS antiviral drugs and contraceptives provided by the government for free, shall be set through tendering purchase or negotiation. Except as otherwise mentioned above, the prices for other drugs may be determined by manufacturers and operators on their own on the basis of production or operation costs and market supply and demand. In addition, the 2017 NRDL proposed to explore the development of a negotiation mechanism for drugs to be listed in the NDRL. The Ministry of Human Resource and Social Security will negotiate with drug manufacturers for the drugs proposed to be negotiated as determined by experts upon review in accordance with the relevant criteria. Those eligible will be included in the payment scope of the medical insurance fund.

Intellectual Property Rights

China became a member of the World Trade Organization and a party to the Agreement on Trade-Related Aspects of Intellectual Property Rights (與貿易有關的知識產權協定) on December 11, 2001. In addition, China has entered into several international conventions on intellectual property rights, including without limitation, the Paris Convention for the Protection of Industrial Property (保護工業產權巴黎公約), the Madrid Agreement Concerning the International Registration of Marks (商標國際註冊馬德里協議) and the Patent Cooperation Treaty (專利合作公約).

Patents

Pursuant to the Patent Law of the PRC (中華人民共和國專利法) promulgated by the SCNPC on March 12, 1984, as amended on September 4, 1992, August 25, 2000 and December 27, 2008, and effective from October 1, 2009 and the Implementation Rules of the Patent Law of the PRC (中華人民共和國專利法實施細則), promulgated by the State Council on June 15, 2001 and as amended on January 9, 2010, there are three types of patents in the PRC: invention patents, utility model patents and design patents. The protection period is 20 years for an invention patent and 10 years for a utility model patent and a design patent, commencing from their respective application dates. Any individual or entity that utilizes a patent or conducts any other activity in infringement of a patent without prior

authorization of the patent holder shall pay compensation to the patent holder and is subject to a fine imposed by relevant administrative authorities and, if constituting a crime, shall be held criminally liable in accordance with the law. According to the PRC Patent Law, for public health purposes, the State Intellectual Property Office of the PRC may grant a compulsory license for manufacturing patented drugs and exporting them to countries or regions covered under relevant international treaties to which PRC has acceded. In addition, pursuant to the Patent Law, any organization or individual that applies for a patent in a foreign country for an invention or utility model patent established in China is required to report to the State Intellectual Property Office for confidentiality examination.

Trade Secrets

Pursuant to the PRC Anti-Unfair Competition Law (中華人民共和國反不正當競爭法), as amended in November 2017, promulgated by the SCNPC in September 1993, the term "trade secrets" refers to technical and business information that is unknown to the public, has utility, may create business interests or profits for its legal owners or holders, and is maintained as a secret by its legal owners or holders. Under the PRC Anti-Unfair Competition Law, business persons are prohibited from infringing others' trade secrets by: (1) obtaining the trade secrets from the legal owners or holders by any unfair methods such as theft, solicitation or coercion; (2) disclosing, using or permitting others to use the trade secrets obtained illegally under item (1) above; or (3) disclosing, using or permitting others to use the trade secrets, in violation of any contractual agreements or any requirements of the legal owners or holders to keep such trade secrets in confidence. If a third party knows or should have known of the above-mentioned illegal conduct but nevertheless obtains, uses or discloses trade secrets of others, the third party may be deemed to have committed a misappropriation of the others' trade secrets. The parties whose trade secrets are being misappropriated may petition for administrative corrections, and regulatory authorities may stop any illegal activities and fine infringing parties.

Trademarks

Pursuant to the Trademark Law of the PRC (中華人民共和國商標法), promulgated by the SCNPC on August 23, 1982, amended on February 22, 1993, October 27, 2001 and August 30, 2013 and effective from May 1, 2014, the period of validity for a registered trademark is 10 years, commencing from the date of registration. Upon expiry of the period of validity, the registrant shall go through the formalities for renewal within twelve months prior to the date of expiry, if intending to continue to use the trademark. Where the registrant fails to do so, a grace period of six months may be granted. The period of validity for each renewal of registration is 10 years, commencing from the day immediately after the expiry of the preceding period of validity for the trademark. In the absence of a renewal upon expiry, the registered trademark shall be canceled. Industrial and commercial administrative authorities have the authority to investigate any behavior in infringement of the exclusive right under a registered trademark in accordance with the law. In case of a suspected criminal offense, the case shall be timely referred to a judicial authority and decided according to law.

Domain names

Domain names are protected under the Measures on Administration of Domain Names for the Chinese Internet (中國互聯網絡域名管理辦法) promulgated by the Ministry of Industry and Information Technology, or the MIIT, on November 5, 2004 and effective from December 20, 2004,

which was replaced by the Administrative Measures on the Internet Domain Names (互聯網域名管理辦法) issued by the MIIT as of November 1, 2017, and the Implementing Rules on Registration of Domain Names (中國互聯網絡信息中心域名註冊實施細則) issued by China Internet Network Information Center on May 28, 2012, which became effective on May 29, 2012. The MIIT is the main regulatory body responsible for the administration of PRC internet domain names. Domain name registrations are handled through domain name service agencies established under the relevant regulations, and the applicants become domain name holders upon successful registration.

Product Liability

The Product Quality Law of the PRC (中華人民共和國產品質量法), promulgated by the SCNPC on February 22, 1993 and amended on July 8, 2000 and August 27, 2009, is the principal governing law relating to the supervision and administration of product quality. According to the Product Quality Law, manufacturers shall be liable for the quality of products produced by them and sellers shall take measures to ensure the quality of the products sold by them. A manufacturer shall be liable to compensate for any bodily injuries or damage to property other than the defective product itself resulting from the defects in the product, unless the manufacturer is able to prove that: (1) the product has never been circulated; (2) the defects causing injuries or damage did not exist at the time when the product was circulated; or (3) the science and technology at the time when the product was circulated were at a level incapable of detecting the defects. A seller shall be liable to compensate for any bodily injuries or damage to property of others caused by the defects in the product if such defects are attributable to the seller. A seller shall pay compensation if it fails to indicate neither the manufacturer nor the supplier of the defective product. A person who is injured or whose property is damaged by the defects in the product may claim for compensation from the manufacturer or the seller.

Pursuant to the General Principles of the Civil Law of the PRC (中華人民共和國民法通則) promulgated by the National People's Congress on April 12, 1986, amended and became effective on August 27, 2009, both manufacturers and sellers shall be held liable where relevant defective products result in damage to property of others or bodily injuries. Pursuant to the Tort Liability Law of the PRC (中華人民共和國侵權責任法), promulgated by the SCNPC on December 26, 2009 and effective on July 1, 2010, manufacturers shall assume tort liability where the defects in relevant products cause damage to others. Sellers shall assume tort liability where the defects in relevant products causing damage to others are attributable to the sellers. The aggrieved party may claim for compensation from the manufacturer or the seller of the relevant product in which the defects have caused damage.

Environmental Protection

According to the Environmental Protection Law of the PRC (中華人民共和國環境保護法), promulgated by the SCNPC on December 26, 1989 and amended on April 24, 2014, the Environmental Impact Assessment Law of the PRC (中華人民共和國環境影響評價法), promulgated by the SCNPC on October 28, 2002 and amended on July 2, 2016, the Administrative Regulations on the Environmental Protection of Construction Project (建設項目環境保護管理條例), promulgated by the State Council on November 29, 1998 and amended on July 16, 2017, and other relevant environmental laws and regulations, enterprises which plan to construct projects shall engage qualified professionals

to provide the assessment reports, assessment form, or registration form on the environmental impact of such projects. The assessment reports, assessment form, or registration form shall be filed with or approved by the relevant environmental protection bureau prior to the commencement of any construction work.

Enterprises generating environmental pollution in the PRC must comply with the Law of the PRC on the Prevention and Control of Water Pollution (中華人民共和國水污染防治法) effective from November 1, 1984 and most recently amended on June 27, 2017, the Law of the PRC on the Prevention and Control of Atmospheric Pollution (中華人民共和國大氣污染防治法) effective from June 1 1988 and most recently amended on August 29 2015, the Law of the PRC on the Prevention and Control of Pollution from Environmental Noise (中華人民共和國環境噪聲污染防治法) effective from March 1,1997, and the Law of the PRC on the Prevention and Control of Environmental Pollution of Solid Waste (中華人民共和國固體廢物污染環境防治法), effective from April 1, 1996 and most recently amended on November 7, 2016. These laws regulate extensive issues in relation to environmental protections including waste water discharge, air pollution control, noise emission and solid waste pollution control. Pursuant to these laws, all the enterprises that may cause environmental pollution in the course of their production and business operation shall introduce environmental protection measures in their plants and establish a reliable system for environmental protection.

Our CMOs are subject to and must comply with above environmental laws and regulations.

Foreign Exchange Control

The PRC State Council promulgated the PRC Regulation for the Foreign Exchange (中華人民共和國外匯管理條例), or the Foreign Exchange Regulations, on January 29, 1996, which was then amended in January 1997 and in August, 2008. On June 20, 1996, the People's Bank of China further promulgated the Regulation on the Administration of the Foreign Exchange Settlement, Sales and Payment (結匯、售匯及付匯管理規定), or the Settlement Regulations, which came into effect on July 1, 1996. Pursuant to the Foreign Exchange Regulation and the Settlement Regulations, foreign exchanges required for distribution of profits and payment of dividends may be purchased from designated foreign exchange banks in the PRC upon presentation of a board resolution authorizing distribution of profits or payment of dividends. The Settlement Regulations remove the previous restrictions on convertibility of foreign exchange in respect of current account items, including the distribution of dividends, interest and royalty payments, trade and service-related foreign exchange transactions, while foreign exchange transactions in respect of capital account items, such as direct investment, loan, securities investment and repatriation of investment remain subject to the approval of SAFE.

On November 19, 2012, SAFE promulgated the Operating Rules for Foreign Exchange Issues with Regard to Direct Investment under Capital Account (資本項目直接投資外匯業務操作規程), an appendix to the Circular of SAFE on Further Improving and Adjusting the Foreign Exchange Policies on Direct Investment (國家外匯管理局關於進一步改進和調整直接投資外匯管理政策的通知), or SAFE Circular 59, which became effective on December 17, 2012 and amended on May 4, 2015. According to SAFE Circular 59, (i) the opening of and payment into foreign exchange accounts under direct investment accounts are no longer subject to approval by the SAFE; (ii) reinvestment with legal income of foreign investors in China is no longer subject to approval by SAFE; (iii) the procedures

for capital verification and confirmation that foreign-funded enterprises need to go through are simplified; (iv) purchase and external payment of foreign exchange under direct investment accounts are no longer subject to approval by SAFE; (v) domestic transfer of foreign exchange under direct investment account is no longer subject to approval by SAFE; and (vi) the administration over the conversion of foreign exchange capital of foreign-funded enterprises is improved. In addition, on February 13, 2015, SAFE issued the Circular on Further Simplifying and Improving Foreign Exchange Administration Policies in Respect of Direct Investment (關於進一步簡化和改進直接投資外匯管理政策的通知), which became effective on June 1, 2015 and provides that the bank instead of SAFE can directly handle the foreign exchange registration and approval under foreign direct investment while SAFE and its branches indirectly supervise the foreign exchange registration and approval under foreign direct investment through the bank.

On May 11, 2013, SAFE promulgated the Provisions on the Administration of Foreign Exchange in Foreign Direct Investments by Foreign Investors (外國投資者境內直接投資外匯管理規定), or FDI Provisions, and the relevant supporting documents which regulate and clarify the administration over foreign exchange administration in foreign direct investments. The FDI Provisions became effective on May 13, 2013.

On March 30, 2015, SAFE released the Circular on the Reform of the Management Method for the Settlement of Foreign Exchange Capital of Foreign-invested Enterprises (國家外匯管理局關於改革外商投資企業外匯資本金結匯管理方式的通知), or SAFE Circular 19, which came into force and superseded SAFE Circular 142 from June 1, 2015. On June 9, 2016, SAFE further promulgated the Circular on the Reform and Standardization of the Management Policy of the Settlement of Capital Projects (關於改革和規範資本項目結匯管理政策的通知), or SAFE Circular 16. SAFE Circular 19 has made certain adjustments to some regulatory requirements on the settlement of foreign exchange capital of foreign-invested enterprises, and some foreign exchange restrictions under SAFE Circular 142 are lifted. Under SAFE Circular 19 and SAFE Circular 16, the settlement of foreign exchange by foreign invested enterprises shall be governed by the policy of foreign exchange settlement on a discretionary basis. However, SAFE Circular 19 and SAFE Circular 16 also reiterate that the settlement of foreign exchange shall only be used for its own operation purposes within the business scope of the foreign invested enterprises and following the principles of authenticity. Considering that SAFE Circular 19 and SAFE Circular 16 are relatively new, it is unclear how they will be implemented, and there exists high uncertainties with respect to their interpretation and implementation by authorities. For example, under SAFE Circular 19 and SAFE Circular 16, we may still not be allowed to convert foreign currency-registered capital of our PRC subsidiaries which are foreign-invested enterprises into RMB capital for securities investments or other finance and investment except for principal-guaranteed bank products. Further, SAFE Circular 19 and SAFE Circular 16 restrict a foreign-invested enterprise from using Renminbi converted from its registered capital to provide loans to a its non-affiliated company.

SAFE promulgated the Circular on Relevant Issues Concerning Foreign Exchange Control on Domestic Residents' Offshore Investment and Financing and Roundtrip Investment through Special Purpose Vehicles (關於境內居民通過特殊目的公司境外投融資及返程投資外匯管理有關問題的通知), or SAFE Circular 37, on July 4, 2014. SAFE Circular 37 requires PRC residents to register with local branches of SAFE in connection with their direct establishment or indirect control of an offshore entity, for the purpose of overseas investment and financing, with such PRC residents' legally owned

assets or equity interests in domestic enterprises or offshore assets or interests, referred to in SAFE Circular 37 as a "special purpose vehicle". SAFE Circular 37 further requires an amendment to the registration in the event of any significant changes with respect to the special purpose vehicle. Failure to comply with the SAFE registration requirements under SAFE Circular 37 could result in liability under PRC law for evasion of foreign exchange controls. On February 13, 2015, SAFE issued the Circular on Further Simplifying and Improving Foreign Exchange Administration Policies in Respect of Direct Investment (關於進一步簡化改進直接投資外匯管理政策的通知), effective June 1, 2015, which provides that the local bank instead of SAFE can directly handle the initial foreign exchange registration and amendment registration under SAFE Circular 37.

Labor and Social Insurance

Pursuant to the PRC Labor Law (中華人民共和國勞動法), which was promulgated by the SCNPC on July 5, 1994 and became effective on January 1, 1995 and subsequently amended on August 27, 2009, the PRC Labor Contract Law (中華人民共和國勞動合同法), which was promulgated by the SCNPC on June 29, 2007 and subsequently amended on December 28, 2012 and became effective on July 1, 2013, and the Implementing Regulations of the Employment Contracts Law of the PRC (中華人民共和國勞動合同法實施條例), which was promulgated by the State Council and became effective on September 18, 2008, labor contracts in written form shall be executed to establish labor relationships between employers and employees. In addition, wages cannot be lower than local minimum wage. The employers must establish a system for labor safety and sanitation, strictly abide by State rules and standards, provide education regarding labor safety and sanitation to its employees, provide employees with labor safety and sanitation conditions and necessary protection materials in compliance with State rules, and carry out regular health examinations for employees engaged in work involving occupational hazards.

Under applicable PRC laws, including the Social Insurance Law of PRC (中華人民共和國社會保險法), which was promulgated by the SCNPC on October 28, 2010 and became effective on July 1, 2011, the Interim Regulations on the Collection and Payment of Social Security Funds (社會保險費徵繳暫行條例), which was promulgated by the State Council and became effective on January 22, 1999, and the Regulations on the Administration of Housing Provident Funds (住房公積金管理條例), which was promulgated by the State Council and became effective on April 3, 1999 and amended on March 24, 2002, employers are required to contribute, on behalf of their employees, to a number of social security funds, including funds for basic pension insurance, unemployment insurance, basic medical insurance, occupational injury insurance, maternity insurance and to housing provident funds. These payments are made to local administrative authorities and any employer who fails to contribute may be fined and ordered to make good the deficit within a stipulated time limit.

Dividend Distribution

Pursuant to the PRC Company Law and the Foreign-Owned Enterprise Law of PRC, as amended on October 31, 2000 and September 3, 2016 respectively, and the Implementing Rules for the Foreign-Owned Enterprise Law of the PRC, as amended on April 12, 2001 and February 19, 2014, foreign-invested enterprises in the PRC may pay dividends only out of their accumulated profits as determined in accordance with PRC accounting standards and regulations. In addition, a foreign-invested enterprise is required to set aside at least 10% of its respective accumulated profits

each year to fund certain reserve funds, until the accumulative amount of such fund reaches 50% of its registered capital. These wholly foreign-owned companies may also allocate a portion of their after-tax profits based on PRC accounting standards to staff welfare and bonus funds. Amounts allocated to these reserve funds and staff welfare and bonus funds reduce the amount distributable as cash dividends. Upon approval of the competent governmental authorities, foreign investors may utilize RMB dividends to invest or re-invest in enterprises established in China.

On January 26, 2017, SAFE issued the Notice on Improving the Check of Authenticity and Compliance to Further Promote Foreign Exchange Control (國家外匯管理局關於進一步推進外匯管理改革完善真實合規性審核的通知), or SAFE Circular 3, which stipulates several capital control measures with respect to the outbound remittance of profit from domestic entities to offshore entities, including the requirements that (i) under the principle of genuine transaction, banks shall check board resolutions regarding profit distribution, the original version of tax filing records and audited financial statements; and (ii) domestic entities shall hold income to account for previous years' losses before remitting the profits. Moreover, pursuant to SAFE Circular 3, domestic entities shall make detailed explanations of sources of capital and utilization arrangements, and provide board resolutions, contracts and other proof when completing the registration procedures in connection with an outbound investment.

Employee Stock Incentive Plan

On February 15, 2012, SAFE promulgated the Notices on Issues Concerning the Foreign Exchange Administration for Domestic Individuals Participating in Stock Incentive Plans of Overseas Publicly Listed Companies (國家外匯管理局關於境內個人參與境外上市公司股權激勵計劃外匯管理有關問題的通知), or the Stock Option Rules, which replaced the Application Procedures of Foreign Exchange Administration for Domestic Individuals Participating in Employee Stock Ownership Plans or Stock Option Plans of Overseas Publicly Listed Companies (境內個人參與境外上市公司員工持股計劃和認股期權計劃等外匯管理操作規程) issued by SAFE on March 28, 2007. In accordance with the Stock Option Rules and relevant rules and regulations, PRC citizens or non-PRC citizens residing in China for a continuous period of not less than one year, who participate in any stock incentive plan of an overseas publicly listed company, subject to a few exceptions, are required to register with SAFE through a domestic qualified agent, which could be a PRC subsidiary of such overseas listed company, and complete certain procedures and handle matters in connection with their exercise of stock options, the purchase and sale of corresponding stocks or interests and fund transfers. In addition, the agent is required to amend the SAFE registration with respect to the stock incentive plan if there is any material change to the stock incentive plan. In addition, the Stock Option Rules provide that PRC residents who participate in a share incentive plan of an overseas unlisted special purpose company may register with SAFE or its local branches before exercising rights.

Taxation

Because we carry out our PRC business operations through operating subsidiaries organized under the PRC law, our PRC operations and our operating subsidiaries in China are subject to PRC tax laws and regulations, which indirectly affect your investment in our shares. Pursuant to the Enterprise Income Tax Law of the PRC (中華人民共和國企業所得税法), or the EIT Law, promulgated by the National People's Congress on March 16, 2007, which became effective on January 1, 2008 and

was amended on February 24, 2017, the income tax rate for both domestic and foreign-invested enterprises is 25% commencing on January 1, 2008 with certain exceptions. In order to clarify certain provisions of the EIT Law, the State Council promulgated the Implementation Rules of the Enterprise Income Tax Law of the PRC (中華人民共和國企業所得税法實施條例) on December 6, 2007, which became effective on January 1, 2008. Under the EIT Law and the EIT Implementation Rules, enterprises are classified as either "resident enterprises" or "non-resident enterprises". Pursuant to the EIT Law and the EIT Implementation Rules, besides enterprises established within the PRC, enterprises established outside China whose "de facto management bodies" are located in China are considered "resident enterprises" and subject to the uniform 25% enterprise income tax rate for their global income. In addition, the EIT Law provides that a non-resident enterprise refers to an entity established under foreign law whose "de facto management bodies" are not within the PRC but which have an establishment or place of business in the PRC, or which do not have an establishment or place of business in the PRC but have income sourced within the PRC.

The EIT Implementation Rules provide that, since January 1, 2008, an income tax rate of 10% will normally be applicable to dividends declared to non-PRC resident enterprise investors that do not have an establishment or place of business in the PRC, or that have such establishment or place of business but the relevant income is not effectively connected with the establishment or place of business, to the extent such dividends are derived from sources within the PRC. The income tax on the dividends may be reduced pursuant to a tax treaty between China and the jurisdictions in which our non-PRC shareholders reside.

Pursuant to an Arrangement Between the Mainland of China and the Hong Kong Special Administrative Region for the Avoidance of Double Taxation on Income (內地和香港特別行政區關於對所得避免雙重徵税和防止偷漏税的安排) and other applicable PRC laws, if a Hong Kong resident enterprise is determined by the competent PRC tax authority to have satisfied the relevant conditions and requirements under such Double Tax Avoidance Arrangement and other applicable laws, the 10% withholding tax on the dividends the Hong Kong resident enterprise receives from a PRC resident enterprise may be reduced to 5%. However, based on the Circular on Certain Issues with Respect to the Enforcement of Dividend Provisions in Tax Treaties issued on February 20, 2009 (關於執行税收協定股息條款有關問題的通知) by the state administration of taxation, if the relevant PRC tax authorities determine, in their discretion, that a company benefits from such reduced income tax rate due to a structure or arrangement that is primarily tax-driven, such PRC tax authorities may adjust the preferential tax treatment; and based on the Announcement on Certain Issues with Respect to the "Beneficial Owner" in Tax Treaties (國家税務總局關於税收協定中"受益所有人"有關問題的公告), issued on February 3, 2018 and effective on April 1, 2018, if an applicant's business activities do not constitute substantive business activities, it could result in the negative determination of the applicant's status as a "beneficial owner", and consequently, the applicant could be precluded from enjoying the above-mentioned reduced income tax rate of 5% under the Double Tax Avoidance Arrangement.

Overview of U.S. Regulations

U.S. regulation of pharmaceutical product development and approval

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and its implementing regulations. The process of obtaining approvals and the subsequent compliance with appropriate federal, state and local rules and regulations requires the expenditure of substantial time and financial resources. Failure to comply with the applicable U.S. regulatory requirements at any time during the product development process, approval process or after approval may subject an applicant and/or sponsor to a variety of administrative or judicial sanctions, including refusal by FDA to approve pending applications, withdrawal of an approval, imposition of a clinical hold, issuance of warning letters and other types of letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement of profits, or civil or criminal investigations and penalties brought by FDA and the Department of Justice, or DOJ, or other governmental entities. Drugs are also subject to other federal, state and local statutes and regulations.

Our drug candidates must be approved by the FDA through the NDA process before they may be legally marketed in the United States. The process required by the FDCA and FDA regulations before a drug may be marketed in the United States generally involves the following:

- completion of extensive pre-clinical studies, sometimes referred to as pre-clinical laboratory tests, pre-clinical animal studies and formulation studies all performed in compliance with applicable regulations, including the FDA's GLP regulations;

- submission to the FDA of an investigational new drug application, or IND, which must become effective before human clinical trials may begin and must be updated annually;

- approval by an independent IRB representing each clinical site before each clinical trial may be initiated;

- performance of adequate and well-controlled human clinical trials in accordance with applicable good clinical practices, or GCPs and other clinical trial-related regulations , to establish the safety and efficacy of the proposed drug product for its proposed indication;

- preparation and submission to the FDA of an NDA;

- a determination by the FDA within 60 days of its receipt of an NDA to file the NDA for review and review by an FDA advisory committee, where appropriate or if applicable;

- satisfactory completion of an FDA pre-approval inspection of the manufacturing facility or facilities at which the API and finished drug product are produced to assess compliance with the FDA's cGMP;

- potential FDA audit of the pre-clinical and/or clinical trial sites that generated the data in support of the NDA;

- payment of user fees and FDA review and approval of the NDA prior to any commercial marketing or sale of the drug in the United States; and

- compliance with any post-approval requirements, including Risk Evaluation and Mitigation Strategies, or REMS, and post-approval studies required by FDA.

Preclinical studies

The data required to support an NDA is generated in two distinct development stages: pre-clinical and clinical. For new chemical entities, or NCEs, the pre-clinical development stage generally involves synthesizing the active component, developing the formulation and determining the manufacturing process, evaluating purity and stability, as well as carrying out non-human toxicology, pharmacology and drug metabolism studies in the laboratory, which support subsequent clinical testing. The conduct of the pre-clinical tests must comply with federal regulations, including GLPs. The sponsor must submit the results of the pre-clinical tests, together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical protocol, to the FDA as part of the IND. An IND is a request for authorization from the FDA to administer an investigational drug product to humans. The central focus of an IND submission is on the general investigational plan and the protocol(s) for human trials. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA raises concerns or questions regarding the proposed clinical trials and places the IND on clinical hold within that 30-day time period. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns or questions before the clinical trial can begin. Some long-term preclinical testing, such as animal tests of reproductive adverse events and carcinogenicity, may continue after the IND is submitted. The FDA may also impose clinical holds on a drug candidate at any time before or during clinical trials due to safety concerns or non-compliance. Accordingly, submission of an IND does not guarantee the FDA will allow clinical trials to begin, or that, once begun, issues will not arise that could cause the trial to be suspended or terminated.

Clinical studies

The clinical stage of development involves the administration of the drug product to human subjects or patients under the supervision of qualified investigators, generally physicians not employed by or under the trial sponsor's control, in accordance with GCPs, which include the requirement that all research subjects provide their informed consent in writing for their participation in any clinical trial. Clinical trials are conducted under written study protocols detailing, among other things, the objectives of the clinical trial, dosing procedures, subject selection and exclusion criteria, and the parameters to be used to monitor subject safety and assess efficacy. Each protocol, and any subsequent amendments to the protocol, must be submitted to the FDA as part of the IND. Further, each clinical trial must be reviewed and approved by each institution at which the clinical trial will be conducted. An IRB is charged with protecting the welfare and rights of trial participants and considers such items as whether the risks to individuals participating in the clinical trials are minimized and are reasonable in relation to anticipated benefits. The IRB also generally reviews and approves the informed consent form that must be provided to each clinical trial subject or his or her

legal representative and must monitor the clinical trial until completed. There are also requirements governing the reporting of ongoing clinical trials and completed clinical trial results to public registries. For example, information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health for public dissemination on their ClinicalTrials.gov website.

Clinical trials are generally conducted in three sequential phases that may overlap or be combined, known as Phase I, Phase II and Phase III clinical trials.

- Phase I: The drug is initially introduced into a small number of healthy volunteers who are initially exposed to a single dose and then multiple doses of the drug candidate. The primary purpose of these clinical trials is to assess the metabolism, pharmacologic action, side effect tolerability and safety of the drug.

- Phase II: The drug is administered to a limited patient population with the disease or condition under study to determine dose tolerance and optimal dosage required to produce the desired benefits. At the same time, safety and further pharmacokinetic and pharmacodynamic information is collected, as well as identification of possible adverse effects and safety risks and preliminary evaluation of efficacy.

- Phase III: The drug is administered to an expanded number of patients, generally at multiple sites that are geographically dispersed, in well-controlled clinical trials to generate enough data to demonstrate the efficacy of the drug for its intended use, its safety profile, and to establish the overall benefit/risk profile of the drug and provide an adequate basis for drug approval and labeling of the drug product. Phase III clinical trials may include comparisons with placebo and/or other comparator treatments. The duration of treatment is often extended to mimic the actual use of a drug during marketing. Generally, two adequate and well-controlled Phase III clinical trials are required by the FDA for approval of an NDA. A pivotal study is a clinical study that adequately meets regulatory agency requirements for the evaluation of a drug candidate's efficacy and safety such that it can be used to justify the approval of the drug. Generally, pivotal studies are also Phase III studies but may be Phase II studies if the trial design provides a well-controlled and reliable assessment of clinical benefit, particularly in situations where there is an unmet medical need.

- Post-approval trials, sometimes referred to as Phase IV clinical trials, may be conducted after initial marketing approval. These trials are used to gain additional experience from the treatment of patients in the intended therapeutic indication. In certain instances, FDA may mandate the performance of Phase IV clinical trials.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA, and more frequently if serious adverse events occur. Written IND safety reports must be submitted to the FDA and the investigators for serious and unexpected adverse reactions or any finding from tests in laboratory animals that suggests a significant risk to human subjects. The FDA, the IRB, or the clinical trial sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. The FDA will typically inspect one or more clinical sites to assure compliance with GCP and the

integrity of the clinical data submitted. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution, or an institution it represents, if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected serious harm to patients. Additionally, some clinical trials are overseen by an independent group of qualified experts organized by the clinical trial sponsor, known as a data safety monitoring board or committee. This group provides authorization for whether or not a trial may move forward at designated check points based on access to certain data from the trial. Concurrent with clinical trials, companies usually complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the drug as well as finalize a process for manufacturing the drug in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the drug candidate and, among other things, cGMPs impose extensive procedural, substantive and recordkeeping requirements to ensure and preserve the long term stability and quality of the final drug product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the drug candidate does not undergo unacceptable deterioration over its shelf life.

NDA submission and FDA review process

Following trial completion, trial results and data are analyzed to assess safety and efficacy. The results of pre-clinical studies and clinical trials are then submitted to the FDA as part of an NDA, along with proposed labeling for the drug, information about the manufacturing process and facilities that will be used to ensure drug quality, results of analytical testing conducted on the chemistry of the drug, and other relevant information. The NDA is a request for approval to market the drug and must contain adequate evidence of safety and efficacy, which is demonstrated by extensive pre-clinical and clinical testing. The application may include negative or ambiguous results of pre-clinical and clinical trials as well as positive findings. Data may come from company-sponsored clinical trials intended to test the safety and efficacy of a use of a drug, or from a number of alternative sources, including studies initiated by investigators. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety and efficacy of the investigational drug product to the satisfaction of the FDA. Under federal law, the submission of most NDAs is subject to the payment of an application user fees; a waiver of such fees may be obtained under certain limited circumstances. FDA approval of an NDA must be obtained before a drug may be offered for sale in the United States.

Under the Prescription Drug User Fee Act, or PDUFA, as amended, each NDA must be accompanied by an application user fee. The FDA adjusts the PDUFA user fees on an annual basis. According to the FDA's fee schedule, effective through September 30, 2015, the user fee for an application requiring clinical data, such as an NDA, is $2,335,200. PDUFA also imposes an annual product fee for human drugs ($110,370) and an annual establishment fee ($569,200) on facilities used to manufacture prescription drugs. Fee waivers or reductions are available in certain circumstances, including a waiver of the application fee for the first application filed by a small business.

The FDA reviews all NDAs submitted before it accepts them for filing and may request additional information rather than accepting an NDA for filing. The FDA conducts a preliminary review of an NDA within 60 days of receipt and informs the sponsor by the 74th day after FDA's receipt of the submission to determine whether the application is sufficiently complete to permit substantive review. Once the submission is accepted for filing, the FDA begins an in-depth review of the NDA. Under the goals and policies agreed to by the FDA under PDUFA, the FDA has ten months from the filing date in which to complete its initial review of a standard NDA and respond to the applicant, and six months from the filing date for a "priority review" NDA. The FDA does not always meet its PDUFA goal dates for standard and priority review NDAs, and the review process is often significantly extended by FDA requests for additional information or clarification.

After the NDA submission is accepted for filing, the FDA reviews the NDA to determine, among other things, whether the proposed drug is safe and effective for its intended use, and whether the drug is being manufactured in accordance with cGMP to assure and preserve the drug's identity, strength, quality and purity. The FDA may refer applications for novel drugs or drug candidates that present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions. The FDA may re-analyze the clinical trial data, which can result in extensive discussions between the FDA and us during the review process.

Before approving an NDA, the FDA will conduct a pre-approval inspection of the manufacturing facilities for the new drug to determine whether they comply with cGMPs. The FDA will not approve the drug unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the drug within required specifications. In addition, before approving an NDA, the FDA may also audit data from clinical trials to ensure compliance with GCP requirements. After the FDA evaluates the application, manufacturing process and manufacturing facilities where the drug product and/or its API will be produced, it may issue an approval letter or a Complete Response Letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. A Complete Response Letter indicates that the review cycle of the application is complete and the application is not ready for approval. A Complete Response Letter usually describes all of the specific deficiencies in the NDA identified by the FDA. The Complete Response Letter may require additional clinical data and/or an additional pivotal clinical trial(s), and/or other significant, expensive and time-consuming requirements related to clinical trials, pre-clinical studies or manufacturing. If a Complete Response Letter is issued, the applicant may either resubmit the NDA, addressing all of the deficiencies identified in the letter, or withdraw the application. Even if such data and information is submitted, the FDA may ultimately decide that the NDA does not satisfy the criteria for approval. Data obtained from clinical trials are not always conclusive and the FDA may interpret data differently than we interpret the same data.

If a drug receives marketing approval, the approval may be limited to specific diseases and dosages or the indications for use may otherwise be limited. Further, the FDA may require that certain contraindications, warnings or precautions be included in the drug labeling or may condition the approval of the NDA on other changes to the proposed labeling, development of adequate controls and specifications, or a commitment to conduct post-market testing or clinical trials and surveillance to monitor the effects of approved drugs. For example, the FDA may require Phase 4 testing which involves clinical trials designed to further assess a drug's safety and effectiveness and may require testing and surveillance programs to monitor the safety of approved drugs that have been commercialized. The FDA may also place other conditions on approvals including the requirement for a Risk Evaluation and Mitigation Strategy, or REMS, to ensure that the benefits of a drug or biological product outweigh its risks. If the FDA concludes a REMS is needed, the sponsor of the NDA must submit a proposed REMS. The FDA will not approve the NDA without an approved REMS, if required. A REMS could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. Any of these limitations on approval or marketing could restrict the commercial promotion, distribution, prescription or dispensing of drugs. Drug approvals may be withdrawn for non-compliance with regulatory requirements or if problems occur following initial marketing.

Special FDA expedited review and approval programs

The FDA has various programs, including Fast Track Designation, accelerated approval, priority review and Breakthrough Therapy Designation, that are intended to expedite or simplify the process for the development and FDA review of drugs that are intended for the treatment of serious or life threatening diseases or conditions and demonstrate the potential to address unmet medical needs. The purpose of these programs is to provide important new drugs to patients earlier than under standard FDA review procedures.

Fast track designation

To be eligible for a Fast Track Designation, the FDA must determine, based on the request of a sponsor, that a drug is intended to treat a serious or life threatening disease or condition and demonstrates the potential to address an unmet medical need for the disease or condition. Diabetes is explicitly identified as an example of a serious condition. Under the fast track program, the sponsor of a drug candidate may request FDA to designate the product for a specific indication as a fast track product concurrent with or after the filing of the IND for the drug candidate. The FDA must make a fast track designation determination within 60 days after receipt of the sponsor's request.

In addition to other benefits, such as the ability to use surrogate endpoints and have greater interactions with FDA, FDA may initiate review of sections of a fast track product's NDA before the application is complete. This rolling review is available if the applicant provides, and FDA approves, a schedule for the submission of the remaining information and the applicant pays applicable user fees. However, FDA's time period goal for reviewing a fast track application does not begin until the last section of the NDA is submitted. In addition, the fast track designation may be withdrawn by FDA if FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

Priority review

The FDA may give a priority review designation to drugs that offer significant improvements in treatment, or provide a treatment where no adequate therapy exists. A priority review means that the goal for the FDA to review an application is six months, rather than the standard review of ten months under current PDUFA guidelines. These six and ten month review periods are measured from the "filing" date rather than the receipt date for NDAs for new molecular entities, which typically adds approximately two months to the timeline for review and decision from the date of submission. Most products that are eligible for Fast Track Designation are also likely to be considered appropriate to receive a priority review.

Breakthrough therapy designation

Under the provisions of the new Food and Drug Administration Safety and Innovation Act, or FDASIA, enacted by Congress in 2012, a sponsor can request designation of a drug candidate as a "breakthrough therapy." A breakthrough therapy is defined as a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. Drugs designated as breakthrough therapies are also eligible for accelerated approval. The FDA may take certain actions, such as holding timely meetings and providing advice, intended to expedite the development and review of an application for approval of a breakthrough therapy.

Accelerated approval

FDASIA also codified and expanded on FDA's accelerated approval regulations, under which FDA may approve a drug for a serious or life-threatening illness that provides meaningful therapeutic benefit over existing treatments based on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit. This determination takes into account the severity, rarity or prevalence of the disease or condition and the availability or lack of alternative treatments. As a condition of approval, the FDA may require a sponsor of a drug receiving accelerated approval to perform Phase IV or post-marketing studies to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical endpoint, and the drug may be subject to accelerated withdrawal procedures. In addition, FDA may require that all promotional materials for drug candidates approved under accelerated regulations are subject to prior review by the FDA.

Even if a product qualifies for one or more of these programs, the FDA may later decide that the product no longer meets the conditions for qualification or decide that the time period for FDA review or approval will not be shortened. Furthermore, Fast Track Designation, priority review, accelerated approval and Breakthrough Therapy Designation, do not change the standards for approval and may not ultimately expedite the development or approval process.

Post-marketing requirements

Following approval of a new drug, a pharmaceutical company and the approved drug are subject to continuing regulation by the FDA, including, among other things, monitoring and recordkeeping activities, reporting to the applicable regulatory authorities of adverse experiences with the drug, providing the regulatory authorities with updated safety and efficacy information, drug sampling and distribution requirements, and complying with applicable promotion and advertising requirements, which include, among others, standards for direct-to-consumer advertising, restrictions on promoting drugs for uses or in patient populations that are not described in the drug's approved labeling (known as "off-label use"), limitations on industry-sponsored scientific and educational activities, and requirements for promotional activities involving the internet. Although physicians may legally prescribe drugs for off-label uses, manufacturers may not market or promote such off-label uses. Modifications or enhancements to the drug or its labeling or changes of the site of manufacture are often subject to the approval of the FDA and other regulators, which may or may not be submitted to FDA or may result in a lengthy review process.

Prescription drug advertising is subject to federal, state and foreign regulations. In the United States, the FDA regulates prescription drug promotion, including direct-to-consumer advertising. Prescription drug promotional materials must be submitted to the FDA in conjunction with their first use. Any distribution of prescription drugs and pharmaceutical samples must comply with the U.S. Prescription Drug Marketing Act, or the PDMA, a part of the FDCA.

In the United States, once a drug is approved, its manufacture is subject to comprehensive and continuing regulation by the FDA. The FDA regulations require that drugs be manufactured in specific approved facilities and in accordance with cGMP. Applicants may also rely on third parties for the production of clinical and commercial quantities of drugs, and these third parties must operate in accordance with cGMP regulations. cGMP regulations require among other things, quality control and quality assurance as well as the corresponding maintenance of records and documentation and the obligation to investigate and correct any deviations from cGMP. Drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with cGMP and other laws. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance. These regulations also impose certain organizational, procedural and documentation requirements with respect to manufacturing and quality assurance activities. NDA holders using third party contract manufacturers, laboratories or packagers are responsible for the selection and monitoring of qualified firms, and, in certain circumstances, qualified suppliers to these firms. These firms and, where applicable, their suppliers are subject to inspections by the FDA at any time, and the discovery of violative conditions, including failure to conform to cGMP, could result in enforcement actions that interrupt the operation of any such facilities or the ability to distribute drugs manufactured, processed or tested by them. Discovery of problems with a drug after approval may result in restrictions on a drug, manufacturer, or holder of an approved NDA, including, among other things, recall or withdrawal of the drug from the market, and may require substantial resources to correct.

The FDA also may require post-approval testing, sometimes referred to as Phase IV testing, risk minimization action plans and post-marketing surveillance to monitor the effects of an approved drug or place conditions on an approval that could restrict the distribution or use of the drug. Discovery of previously unknown problems with a drug or the failure to comply with applicable FDA requirements can have negative consequences, including adverse publicity, judicial or administrative enforcement, warning letters from the FDA, corrective advertising or communications with doctors, and civil or criminal penalties, among others. Newly discovered or developed safety or effectiveness data may require changes to a drug's approved labeling, including the addition of new warnings and contraindications, and also may require the implementation of other risk management measures. Also, new government requirements, including those resulting from new legislation, may be established, or the FDA's policies may change, which could delay or prevent regulatory approval of our drugs under development.

Other U.S. regulatory matters

Manufacturing, sales, promotion and other activities following drug approval are also subject to regulation by numerous regulatory authorities in addition to the FDA, including, in the United States, the Centers for Medicare & Medicaid Services, other divisions of the Department of Health and Human Services, the Drug Enforcement Administration for controlled substances, the Consumer Product Safety Commission, the Federal Trade Commission, the Occupational Safety & Health Administration, the Environmental Protection Agency and state and local governments. In the United States, sales, marketing and scientific/educational programs must also comply with state and federal fraud and abuse laws. Pricing and rebate programs must comply with the Medicaid rebate requirements of the U.S. Omnibus Budget Reconciliation Act of 1990 and more recent requirements in the Health Care Reform Law, as amended by the Health Care and Education Affordability Reconciliation Act, or ACA. If drugs are made available to authorized users of the Federal Supply Schedule of the General Services Administration, additional laws and requirements apply. The handling of any controlled substances must comply with the U.S. Controlled Substances Act and Controlled Substances Import and Export Act. Drugs must meet applicable child-resistant packaging requirements under the U.S. Poison Prevention Packaging Act. Manufacturing, sales, promotion and other activities are also potentially subject to federal and state consumer protection and unfair competition laws.

The distribution of pharmaceutical drugs is subject to additional requirements and regulations, including extensive record-keeping, licensing, storage and security requirements intended to prevent the unauthorized sale of pharmaceutical drugs.

The failure to comply with regulatory requirements subjects firms to possible legal or regulatory action. Depending on the circumstances, failure to meet applicable regulatory requirements can result in criminal prosecution, fines or other penalties, injunctions, recall or seizure of drugs, total or partial suspension of production, denial or withdrawal of product approvals, or refusal to allow a firm to enter into supply contracts, including government contracts. In addition, even if a firm complies with FDA and other requirements, new information regarding the safety or efficacy of a product could lead the FDA to modify or withdraw product approval. Prohibitions or restrictions on sales or withdrawal of future products marketed by us could materially affect our business in an adverse way.

U.S. patent term restoration and marketing exclusivity

Depending upon the timing, duration and specifics of the FDA approval of our drug candidates, some of our U.S. patents may be eligible for limited patent term extension under the Hatch-Waxman Act. The Hatch-Waxman Act permits a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally one-half the time between the effective date of an IND and the submission date of an NDA plus the time between the submission date of an NDA and the approval of that application. Only one patent that covers the approved drug (and to only those patent claims covering the approved drug, a method for using it, or a method for manufacturing it) is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent. The United States Patent and Trademark Office, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration.

Marketing exclusivity provisions under the FDCA can also delay the submission or the approval of certain marketing applications. The FDCA provides a five-year period of non-patent marketing exclusivity within the United States to the first applicant to obtain approval of an NDA for a NCE. A drug is a NCE if the FDA has not previously approved any other new drug containing the same active moiety, which is the molecule or ion responsible for the action of the drug substance. During the exclusivity period, the FDA may not accept for review an ANDA, or a 505(b)(2) NDA submitted by another company for another drug based on the same active moiety, regardless of whether the drug is intended for the same indication as the original innovator drug or for another indication, where the applicant does not own or have a legal right of reference to all the data required for approval. However, an application may be submitted after four years if it contains a certification of patent invalidity or non-infringement to one of the patents listed with the FDA by the innovator NDA holder. Specifically, the applicant must certify with respect to each relevant patent that: the required patent information has not been filed; the listed patent has expired; the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration, or the listed patent is invalid, unenforceable or will not be infringed by the new product. A certification that the new product will not infringe the already approved product's listed patents or that such patents are invalid or unenforceable is called a Paragraph IV certification. If the applicant does not challenge the listed patents or indicate that it is not seeking approval of a patented method of use, the ANDA application will not be approved until all the listed patents claiming the referenced product have expired. If the ANDA applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days after the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA until the earlier of 30 months after the receipt of the Paragraph IV notice, expiration of the patent, or a decision in the infringement case that is favorable to the ANDA applicant.

The FDCA also provides three years of marketing exclusivity for an NDA, or supplement to an existing NDA if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant are deemed by the FDA to be essential to the approval of the application, for example new indications, dosages or strengths of an existing drug. This three-year exclusivity covers only the modification for which the drug received approval on the basis of the new clinical investigations and does not prohibit the FDA from approving ANDAs for drugs containing the active agent for the original indication or condition of use. Five-year and three-year exclusivity will not delay the submission or approval of a full NDA. However, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the pre-clinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and effectiveness.

Rest of the world regulation of pharmaceutical product development and approval

For other countries outside of China and the United States, such as countries in Europe, Latin America or other parts of Asia, the requirements governing the conduct of clinical trials, drug licensing, pricing and reimbursement vary from country to country. In all cases the clinical trials must be conducted in accordance with GCP requirements and the applicable regulatory requirements and ethical principles.

If we fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.