Appendix

Provisions for Drug Registration
(Revised)

Chapter I General Provisions

Article 1 These *Provisions for Drug Registration* ("***Provisions***"), formulated in accordance with the *Drug Administration Law of the People's Republic of China* ("***Drug Administration Law***"), *Administrative Permission Law of the People's Republic of China* ("***Administrative Permission Law***"), *Regulations for Implementation of the Drug Administration Law of the People's Republic of China* ("***Implementation Regulations for Drug Administration Law***") and *Opinions of the State Council on Reforming the Review and Approval System for Drugs and Medical Devices*, are adopted to help ensure the safety, efficacy and quality of drugs and to regulate drug registration.

Article 2 These *Provisions* are applicable to drug registration and its regulation and supervision in the territories of the People's Republic of China.

Article 3 The term "drug registration" refers to the process in which a food and drug regulatory authority ("**Food and Drug Authority**"), in response to a drug registration application filed by an applicant ("**Applicant**"), comprehensively evaluates the safety, efficacy, and quality controllability of the drug to be marketed and issues an administrative approval or rejection in accordance with statutory procedures and applicable requirements.

Drug registration applications include drug clinical trial applications ("**Clinical Trial Application**"), drug marketing applications ("**Marketing Application**"), post-marketing supplementary applications to change previously registered information, and renewal applications.

Article 4 The term "Applicant" refers to any domestic person or lawful foreign drug manufacturer who files for drug registration application and is able to assume civil liabilities.

Drug registration by any lawful foreign drug manufacturer must be performed by proxy through either its branch office in China or an agency in China.

Article 5 The China Food and Drug Administration ("**CFDA**") is the central regulator for drug registration in China. Food and Drug Authorities of the provinces, autonomous regions, and direct-controlled municipalities ("**Provincial Food and Drug Authority**") of China are to supervise drug registration-related matters within their respective jurisdictions in accordance with the law and to perform such other drug registration works as delegated by CFDA.

Article 6 Clinical value-driven drug innovations are encouraged. Drugs subject to accelerated review regime by law shall be given priority in the review process.

CFDA shall develop technical guidelines for drug research and guidelines for drug registration, strengthen communication, and provide guidance on drug development and drug registration activities.

Chapter II Basic Requirements

Article 7 CFDA shall establish a sound, structured, sophisticated and efficient review and approval system, timely assess and improve the related rules, norms, standards and administrative measures, and maintain the well-functioning of the drug registration system.

Article 8 Each Provincial Food and Drug Authority shall establish a technical support and supervisory system for drug registrations, supervise drug registration-related research and development activities of non-clinical trial institutions, clinical trial institutes, and drug manufacturers in its jurisdiction, and conduct on-site inspections and random checks with respect to the items in the registrations filed in its jurisdiction.

Article 9 Drug evaluation centers ("**Drug Evaluation Center**") shall be responsible for the review of drug registration applications.

Drug Evaluation Centers shall establish a review quality management system that is grounded in science and features clear, transparent, consistent, and foreseeable rules.

Article 10 CFDA shall establish a risk-based system for technical review, on-site inspection and registration testing. A Drug Evaluation Center may request on-site inspection and sample registration testing based on the specific risk factors of a product and technical review requirements, and issue technical review conclusions after consolidating the findings

from on-site inspection and sample registration testing reports. Day-to-day supervisory findings may also be considered in technical reviews.

Article 11 Each Drug Evaluation Center shall establish a communication system, specify the communication process and requirements, assign project contacts who shall be field organizers for communication and exchange activities, and keep records on the comments from such communication and exchange as part of the documentation for the review process.

Where an Applicant requests for information and discussion before applying for clinical trial for its innovative drugs, or before submitting the follow-up clinical trial protocol or substantial amendments, or before tendering in its Marketing Application, the Drug Evaluation Center under CFDA shall process the request within the prescribed timeline in so far as the request conforms to applicable requirements.

Article 12 Each Food and Drug Authority at or above the provincial level shall establish an expert consultation system. During its reviews, the Drug Evaluation Center may organize expert consultation meetings as necessary, provided the concerned Applicant is invited. Comments from the expert consultation meetings may have a key impact on the conclusions from technical reviews.

Article 13 CFDA shall establish a dispute resolution mechanism that utilizes expert consultations, re-reviews and administrative reviews to resolve any dispute arising from the review and approval process.

Article 14 CFDA shall publicly announce and hold hearings for any approval matters that have material impact on the public interests.

Article 15 CFDA shall accept public oversight and regularly release the progress and summaries on the acceptance, inspection, testing, review, and review and approval status of drug registration applications as well as the information of pertinent individuals.

Article 16 CFDA shall establish a priority review system in consideration of clinical needs and drugs' characteristics.

Article 17 Food and Drug Authorities, related organizations, and staff members participating in the drug registration works shall be bound by confidentiality obligations with respect to the trade secrets and data submitted by Applicants.

Article 18 Food and Drug Authorities shall carry out the acceptance and review and approval of applications in accordance with the time limits prescribed by the *Administrative Permission Law*. However, for any drug registration whose administrative approval, by law, requires hearings, inspections, testing or expert consultations, the time taken by such hearings, inspections, testing or expert consultations shall not be factored into the time limit for the said drug registration.

At the start of each year, each Drug Evaluation Center shall publish a summary report on the progress and time taken for the technical reviews, on-site inspections and drug registration testing it had performed for each kind of drug registration applications in the preceding year, as well as a projection on the current year's timeline for each phase of the technical review process with respect to each kind of drug registration applications.

Article 19 CFDA shall manage drug registration through the Origin Numbers. Each Applicant will be assigned an Origin Number following the acceptance of its Clinical Trial Application or Marketing Application, and shall display such number throughout all its subsequent drug registration materials. In principle, all indications involved in clinical trials are to be managed under the same Origin Number.

Article 20 Each Applicant shall, throughout the drug development and application process, be responsible for the compliance and evaluability of any data, materials, and samples used in drug registrations, irrespective of whether such data, materials, and samples are derived from internal development or commissioned development or are sourced from other parties. Each Applicant shall establish a quality management system appropriate for its drug research and sample trial production to ensure that such processes are standardized and fully traceable.

Where the Applicant commissions another organization to develop the drug or produce the samples, the Applicant shall either itself assess the qualities and the quality management system of the organization, or review the assessments issued by another third party. The organization so commissioned shall abide by applicable quality management rules and ensure that the drug development and sample trial production processes are standardized and fully traceable.

Article 21 Administrative decisions on drug marketing authorization shall be based on evaluations and conclusions drawn from current technologies and scientific understandings. Each Applicant shall continuously

analyze the safety, efficacy and quality controllability of its marketed drugs.

Article 22 Each Applicant shall designate a drug registration specialist who is to handle matters relating to the drug registration application and liaise with the Food and Drug Authority on behalf of the Applicant, and to help the Applicant develop drugs with compliant processes.

The drug registration specialist shall possess the necessary professional knowledge and is familiar with the laws, regulations, and technical requirements of drug registration.

Article 23 Each Applicant shall conduct drug research and development in accordance with the technical guidelines published by CFDA or other internationally accepted technical guidelines. The use of any other evaluation methodology and technologies shall be accompanied by documentation certifying their scientific basis.

Article 24 The organization that performs the technical review, on-site inspection, or drug registration testing shall notify the Applicant if it requires supplementary materials for its technical review, on-site inspection, or drug registration testing. The Applicant may state its positions if it would like to dispute the judgement; otherwise, it shall prepare the supplementary materials in response to the comments of the Drug Evaluation Center and submit them under the same Origin Number. The review process will be temporarily suspended when the Applicant is preparing the materials, and will be duly resumed once the Drug Evaluation Center has received all supplementary materials.

Article 25 Review and approval processes shall terminate upon the withdrawal of application by the Applicant during the drug registration process.

Article 26 Applicant shall pay applicable fees according to the national regulations on drug registration fees. An application will automatically be deemed to be withdrawn if the Applicant fails to pay such fees within 30 days of the application's acceptance.

Chapter III Drug Clinical Trials

Section 1 General Rules

Article 27 Under these *Provisions*, drug clinical trial ("**clinical trial**"), with respect to any study drug to be marketed or has already been marketed

in China, refers to the systematic studies on the study drug performed by the Applicant on human bodies (either patients or healthy volunteers) to substantiate or reveal the effects and adverse reactions of the study drug as well as its absorption, distribution, metabolism and excretion characteristics for the purpose of confirming its safety and efficacy.

Article 28 Supervisory measures for Clinical Trials include the review and approval, follow-up review and record-filing with respect to Clinical Trial Applications and risk management for Clinical Trials.

Article 29 In principle, a clinical trial consists of Phases I, II, III and IV and bioequivalence study.

Phase I is for preliminary clinical pharmacology and safety evaluation on human bodies; Phase II is for preliminary evaluation of therapeutic effects; Phase III is for confirmation of therapeutic effects; and Phase IV refers to the post-marketing research of the applications of a new drug.

Bioequivalence study refers to human subject research in which preparations of the same drug in identical or different dosage forms are compared using the methodology of bioavailability studies and under identical study conditions to check whether the extent and rate of absorption of its active ingredients, as measured by pharmacokinetic parameters, exhibit statistical differences.

Article 30 An Applicant shall determine whether or not to submit a Clinical Trial Application for its drug based on the novelty factor of the drug, available clinical trial data, and the known and unknown risks. A clinical trial may be conducted in order, i.e., Phase I followed by Phase II followed by Phase III, or feature cross or overlapping phases, or be modified appropriately based on existing clinical trial data.

Article 31 An Applicant shall register information pertaining to the start, suspension, resumption, early termination and conclusion of a clinical trial at the clinical trial registry established by CFDA as required and in a timely manner.

Article 32 A clinical trial protocol must conform to scientific and ethical requirements. Clinical trial protocol shall be developed in view of the characteristics of the drug and the objectives specific to each research and development phase, and must place its focus on the protection of

the safety and interests of human subjects, the quality of clinical trial studies, and the scientific assessment of the drug's safety and efficacy.

Each Applicant shall design its clinical trial protocol in accordance with applicable technical requirements and guidelines. The sample size shall be in line with the objective and requirements of the clinical trial; for rare and special diseases, the Applicant may apply through its Clinical Trial Application to reduce the number of patients in its clinical trial or to exempt itself from the clinical trial.

Article 33 Before conducting a clinical trial, the Applicant shall provide materials that can justify the clinical trial and, where necessary, materials relating to the safety and efficacy of the study drug taken from completed or ongoing clinical studies in other countries and regions. The Applicant shall additionally provide the investigational samples.

Any Applicant who applies for clinical trial for an overseas preventive-use biological product shall furnish the safety and efficacy data of the biological product during its use in the country of origin.

Article 34 Preclinical safety research shall conform to the requirements of *Good Laboratory Practice* (GLP) and conducted at a GLP-certified institution. Clinical trial shall comply with *Good Clinical Practice* (GCP) and conducted at an institute satisfying the administrative requirements for clinical trials. The manufacturing and preparation of the investigational medicinal product must comply with the *Good Manufacturing Practice* (GMP).

Article 35 A study drug shall only be used in clinical trials after it is tested. The testing of the study drug may be performed by the Applicant in accordance with its proposed quality control standards, or be delegated to drug testing institutes at or above the provincial level or other third party institutes with relevant accreditations and testing capabilities. Vaccine products, blood products and other biological products specified by CFDA shall be tested by a CFDA-designated drug testing institute.

Article 36 Each Applicant shall assess the institute and researchers administering the clinical trial to ensure that the requirements of the clinical trial are satisfied and the human subjects are duly protected.

Section 2 Review and Approval

Article 37 Any Applicant who, during the development its drug, wishes to conduct a clinical trial in anticipation of marketing the drug in China shall file a Clinical Trial Application with CFDA or make record filings for conducting bioequivalence study.

The clinical trial must be based on science. Before carrying out human subject research, the Applicant must thoroughly consider the objectives of and issues to be resolved by the research, and shall weigh the expected public health benefits against potential risks to human subjects. The expected benefits should exceed the potential damages. Additionally, the clinical trial protocol must conform to scientific requirements and all reasonable ethical requirements.

Article 38 Each Applicant shall determine the items in its Clinical Trial Application in accordance with the submission requirements of the Marketing Application and clinical trial materials in its possession.

Article 39 An Applicant shall submit the application dossier in accordance with the submission requirements of the Clinical Trial Application. The Applicant shall submit drug development and manufacturing materials and the clinical trial protocol, along with the basis, general investigational plan and investigator's brochure for the clinical trial, each developed in accordance with the principles of drug research and development.

Article 40 CFDA shall complete the conformance evaluation of the application dossier within the prescribed timeline, and issue a Notice of Acceptance for each conforming application dossier, and a Notice of Rejection, accompanied by an explanation for the rejection, for each nonconforming application dossier.

Article 41 The Drug Evaluation Center under CFDA shall organize a preliminary review of the application dossier and issue its preliminary review opinions within 30 days of the application's acceptance. Applications meeting the applicable requirements shall be allowed to enter the technical review phase and those that do not shall be rejected with a Notice on Review Opinions, accompanied by the reasons for the rejection.

Article 42 The Drug Evaluation Center under CFDA shall review the items submitted by the Applicant, including the clinical trial protocol, its supporting materials and data, and measures for the protection of

subjects and risk control, and prepare the technical review report. During this review, the Drug Evaluation Center may launch on-site inspection for nonclinical safety evaluations as needed by its review process.

CFDA shall, within the prescribed timeline, issue its review decision based on the technical review report and in accordance with applicable regulations. CFDA shall approve and issue an Approval Letter for Drug Clinical Trial for each qualified application dossier, and reject and issue a Notice on Review Opinions, accompanied by the reasons for the rejection, for each unqualified application dossier.

The technical review for a Clinical Trial Application shall focus on such items as the substance of the application, evaluation of existing treatment approaches for the concerned indication, the clinical value and the clinical trial protocol, as well as on the technical requirements in regard to the follow-up safety evaluation and pharmacological evaluation. In particular, the safety evaluation shall be conducted in view of the clinical trial protocol and the general research plan of the drug, and shall feature risk control measures.

Article 43 The Approval Letter for Drug Clinical Trial shall contain the following key items:

(1) Drug information, including the proposed non-proprietary names (both Chinese and English), the Origin Number, route of administration and items under application;

(2) Applicant information, including the name and registered address of the Applicant; and

(3) Review and approval information, covering the specifics of the approval for clinical trial.

Article 44 The Notice on Review Opinions shall contain the following items: non-proprietary names of the drug, the Origin Number, route of administration, items under application, formulation strength, name of the Applicant, substance of the application, conclusions from the review process, and notification items.

Section 3 Review and Record-Filing

Article 45 After receiving the Approval Letter for Drug Clinical Trial, the Applicant shall submit follow-up clinical trial protocols or substantial

amendments to the Drug Evaluation Center under CFDA in view of the progress of the clinical trial. The Drug Evaluation Center shall issue its review opinion to the Applicant in the prescribed timeline and, in case of a rejection, shall state its reasons.

Article 46 For any suspended clinical trial, once the conditions required for continuing the clinical trial are satisfied, the Applicant shall first obtain the approval of the Ethics Committee before submitting a written request to the Drug Evaluation Center under CFDA for resuming the suspended clinical trial. The Drug Evaluation Center shall determine whether or not to approve the request within the prescribed timeline, and inform the Applicant of its decision through a written notice.

Article 47 During the clinical trial, the Applicant shall report and assess any surfaced serious adverse event as required, and submit an assessment report and related materials to the Drug Evaluation Center under CFDA regarding such serious adverse events.

Upon the receipt of the assessment report, the Drug Evaluation Center shall timely launch a review on account of the process of the clinical trial. If its opinion is to suspend the clinical trial, it may first notify the Applicant via telephone or other expedient means of communication, followed by a written notice to the Applicant.

During the review proceedings, the Drug Evaluation Center may elect to conduct a more comprehensive review by launching on-site inspections on the clinical trial and performing random checks on clinical trial samples.

Article 48 The Applicant shall regularly collect information indicating changes in the safety, efficacy, and quality controllability of the drug from the drug development process, preclinical research and clinical trial, accept the supervisory information issued by Food and Drug Authorities, and evaluate the measures taken or to be undertaken in response. Such collected information and evaluation and analysis shall be submitted to the Drug Evaluation Center under CFDA in the form of annual reports on the clinical trial, with copies sent to the Provincial Food and Drug Authorities of where the Applicant and the concerned clinical trial institute are located. The Drug Evaluation Center may require the Applicant to adjust the reporting frequency as it deems necessary.

Article 49 Non-material changes during bioequivalence studies and clinical trials are managed by a record-filing regime. The Applicant shall make the record-filing as required through the clinical trial registry, and only

proceed with subsequent works after receiving the corresponding record number. The Drug Evaluation Center under CFDA shall make such records public.

Article 50 Where there has been a pharmacological change during clinical trial, the Applicant shall first perform technical studies on the change in accordance with applicable technical guidelines, then assess the effect of such change on the safety, efficacy, and quality controllability of the drug. The assessments may be submitted in the form of record-filing. If the pharmacological change requires a change to the clinical trial protocol, the Applicant shall submit the follow-up clinical trial protocol or other substantial amendments for review.

Section 4 Risk Management

Article 51 Each Applicant shall establish a clinical safety monitoring and assessment system, timely collect, analyze and assess all information collected on the safety of the study drug, and report its findings as required to a Food and Drug Authority at or above the provincial level.

Article 52 Before proceeding with clinical trial, the Applicant shall have obtained, as applicable, the review report from the Ethics Committee, the Approval Letter for Drug Clinical Trial, or the record number for the bioequivalence study. All clinical trial protocols and their modifications must be reviewed by the Ethics Committee before they are implemented.

Article 53 Where the Applicant discovers that the clinical trial institute or an investigator has violated applicable rules or deviated from the clinical trial protocol, it shall cause such institute or investigator to make corrections. In case of serious violation or deviation, the Applicant may suspend or terminate the institute or investigator from the clinical trial, and report the situation to CFDA and the competent Provincial Food and Drug Authority.

Article 54 Without the consent of the Applicant, the Ethics Committee, or both, no investigator may alter or deviate from the investigational plan, except in the circumstances where the investigator must take immediate actions to eliminate the harms to the subjects. The investigator shall record, archive, and justify any deviation from the clinical trial protocol, and inform the Applicant of the deviation and justification.

Article 55 An investigator shall timely notify the Applicant of any unexpected adverse event caused or may be caused by investigational medicinal product, and provide such follow-up information as required by the Applicant and the Ethics Committee. Serious adverse events must be reported immediately.

Article 56 The Ethics Committee shall establish an ethical review system, organize ethical reviews and continuing reviews, receive subjects' complaints, and ensure that the safety and interests of human subjects are duly protected. The Ethics Committee shall also regularly review the progress of a clinical trial and assess the risks and benefits to the subjects in view of the risk level of the particular trial.

Article 57 The Ethics Committee shall establish an emergency review mechanism to ensure that an emergency review may be held whenever the interests of subjects are threatened by a clinical trial and that their safety and interests are protected to the maximum extent possible.

Article 58 Each Provincial Food and Drug Authority shall develop annual inspection plans for the clinical trial projects running within its jurisdiction, carry out routine inspections on such projects and related institutions in accordance with the requirements of GCP, and hold extended inspections as necessary. Findings from routine inspections shall be timely aggregated and uncovered issues shall be reported to CFDA.

Article 59 Either the Applicant, the Ethics Committee, or the principal investigator may propose to suspend or terminate a clinical trial following the occurrence of an unexpected serious adverse event that threatens the safety of human subjects. Where a clinical trial is suspended or terminated following an assessment by the three parties, the Applicant shall report the decision and justifications to the Drug Evaluation Center under CFDA.

Article 60 A Food and Drug Authority may order the suspension of an ongoing clinical trial or even its termination if:

(1) the Applicant has failed to timely report a serious adverse event as required;

(2) the quality management system for the clinical trial contains significant defect which may threaten the safety of human subjects;

(3) with respect to any study drug designed to treat a serious life-threatening disease, another drug, whether marketed or to be

marketed and with the same design purpose and treats the same kind of patients, has demonstrated clear advantage in the benefit-to-risk ratio over the study drug; or

(4) there has been any other violation of GCP that has threatened the safety of human subjects.

Article 61 In principle, before ordering the suspension or termination of a clinical trial, the Food and Drug Authority shall hold a special meeting with the Applicant, investigators and clinical trial institute to hear their opinions. Under special circumstances, the Food and Drug Authority may hold such meeting within five days of the suspension or termination order.

Article 62 The Approval Letter for Drug Clinical Trial associated with a drug shall expire if all clinical trial projects for the drug have been suspended for over 18 months and no request for their resumption has been filed during that period. The Applicant shall re-apply for clinical trial if such trial is needed for the drug.

Article 63 Any modification to the clinical trial protocol designed to eliminate clear, direct harm to human subjects may be implemented by the Applicant concurrently with its submission of change materials to the Drug Evaluation Center under CFDA and the Ethics Committee.

Chapter IV Marketing Authorization

Section 1 General Rules

Article 64 Marketing authorization, in relation to any drug to be marketed in China, refers to the process in which CFDA issues an administrative approval or rejection with respect to the Marketing Application submitted by the Applicant following the Applicant's study and evaluation of the safety, efficacy and quality controllability of the drug.

Article 65 The research associated with marketing authorization shall be conducted in conformity with applicable technical requirements and guidelines; and the trial production of samples shall be commensurate with the production scale of the drug by the Applicant following marketing authorization. Clinical trial samples shall be consistent with the post-marketing drug in manufacturing process and quality control.

Article 66 Research materials and data supporting an application for marketing authorization shall comply with applicable evaluation principles and

guideline requirements and may be produced by any research institute or laboratory that conforms to the regulations of China and internationally accepted principles. If the Applicant does not hold ownership rights to these materials and data, it shall further provide documentation certifying that the owner has consented to their use by the Applicant.

Article 67 Any Applicant who intends to use clinical trial data in its application for marketing authorization in China shall submit all research materials relating to the clinical trial. The number of Chinese subjects participating in the trial should be sufficient for evaluating the safety and efficacy of the study drug among Chinese patients.

For preventive-use biological products, the Applicant shall ensure that its application is supported by protected epidemiological data and clinical data from China, except in the case that there has been no occurrence of the concerned epidemics in China.

Section 2 Application and Acceptance

Article 68 The Applicant shall submit the application dossier for the Marketing Application in accordance with relevant requirements, and provide lawful evidential documents as well as adequate, reliable research materials that demonstrate the safety, efficacy, and quality controllability of the drug. The contents and format of the application dossier should conform to the specific requirements of the application type and applicable guidelines.

Article 69 Where multiple persons intend to submit a Marketing Application for a drug they have been co-developing, they shall designate one person as the Applicant and list the other co-developing institutions. Such other persons may not submit Marketing Applications of their own.

Article 70 Before submitting a Marketing Application, the Applicant shall fully evaluate its application and ensure that its innovative drug demonstrates clear clinical values, improved new drug demonstrates clear clinical advantages over the original drug varieties, and generic drug is consistent with the original drug in quality and therapeutic effect.

Before submitting a Marketing Application for an innovative drug, the Applicant may inquire at the Drug Evaluation Center under CFDA and submit materials as required.

Article 71 Any Applicant intending to market a drug shall submit application materials to CFDA. CFDA shall complete the conformance evaluation of the application dossier within the prescribed timeline, and issue a Notice of Acceptance for each conforming application dossier, and a Notice of Rejection, accompanied by an explanation for the rejection, for each nonconforming application dossier.

Article 72 Once a new traditional Chinese medicine has been designated by its application as a protected variety as part of its marketing authorization process, other Marketing Applications for the same drug variety will no longer be accepted.

Article 73 Where the application is solely for the marketing of a pharmaceutical preparation, the bulk drug substances used in the relevant studies must have the Approval Letter for Drug Registration and must be sourced from lawful channels. Bulk drug substances without the accompanying Approval Letter for Drug Registration must be approved by CFDA.

Article 74 Where an Applicant intends to apply for marketing of a bulk drug substance, the bulk drug substance must be applied under the Marketing Application or supplementary application of the pharmaceutical preparation containing such bulk drug substance. Marketing Application solely for a bulk drug substance will not be accepted.

Section 3 Review and Approval

Article 75 The Drug Evaluation Center under CFDA shall develop the key points and standards for its review in consideration of the requirements for technical evaluations, review the Marketing Applications submitted by Applicants, and issue standardized, clear review conclusions.

CFDA shall examine the level of compliance and fairness of the review procedures before issuing its review and approval decisions. If such examination reveals obvious deficiencies with the review procedures or the conclusions drawn therefrom are vague or requiring further clarifications, the case will be returned to the Drug Evaluation Center under CFDA for revision of its technical review conclusions.

Article 76 Through such means as on-site inspections and registration testing, the Drug Evaluation Center under CFDA shall perform comprehensive evaluation of the safety, efficacy and quality controllability of the drug

under consideration with particular weight given to the evaluation of its post-marketing risks and benefits, clinical needs, and the technical reviews, and shall be responsible for the contents under review as well as for the quality, process and conclusions of its reviews.

Article 77 The review of a Marketing Application shall focus on:

(1) with respect to an innovative drug, its clinical value;

(2) with respect to an improved new drug, its technological creativity and clinical advantage;

(3) with respect to a generic drug, its similarity with the original drug in terms of quality and therapeutic effect;

(4) with respect to a biosimilar drug, its consistency with the original drug in terms of quality and therapeutic effect;

(5) with respect to any renowned compound preparation of traditional Chinese medicine from ancient classical texts, its consistency with its classical applications in terms of manufacturing process, route of administration and main functions, as well as its nonclinical safety;

(6) with respect to any product intended for scale production, the stability and quality controllability of the product; and

(7) with respect to the package insert, its scientific soundness, conformance, and readability.

Article 78 The Drug Evaluation Center under CFDA shall organize a preliminary review of the application dossier for Marketing Application and issue its preliminary review opinions within 30 days of the application's acceptance. Marketing Applications meeting the applicable requirements shall be allowed to enter the technical review phase and those that do not shall be rejected with a Notice on Review Opinions, accompanied by the reasons for the rejection.

Article 79 The Drug Evaluation Center under CFDA shall hold a technical review on the application dossier, prepare a list of questions to be sent to the Applicant for response, and may, if it deems it necessary, notify a verification agency to perform on-site inspections and sampling.

Article 80 After performing the on-site inspection and sampling, the verification agency shall submit the samples to a designated drug testing institute for registration testing.

Article 81 The Drug Evaluation Center under CFDA shall finalize its conclusions for the technical review after receiving the supplementary materials from the Applicant in response to the questions list and on account of the reported findings from on-site inspections and registration testing.

Article 82 During its technical review, the Drug Evaluation Center under CFDA shall seek confirmation of the Chinese Pharmacopoeia Commission ("**Pharmacopoeia Commission**") on any new non-proprietary drug name. The Drug Evaluation Center shall submit the recommended name to the Pharmacopoeia Commission within seven days of the start of technical review, and the Pharmacopoeia Commission should form its decision and notify the Drug Evaluation Center of its decision within 30 days.

Article 83 The Drug Evaluation Center shall confirm with the Applicant of the specifications, labeling, package insert and manufacturing process to be registered. The Applicant shall be responsible for the scientific soundness, conformance, and accuracy of the package insert and labeling.

Article 84 The Drug Evaluation Center under CFDA shall, in view of the characteristics of non-prescription drugs, develop the technical requirements for their registration and perform the registration procedures in accordance with the requirements on the administration and review and approval of non-prescription drugs.

Article 85 China adopts a linked review and approval regime in which the drug is reviewed and approved along with its packaging materials and excipients.

China adopts a linked review and approval regime in relation to the Marketing Application for bulk drug substances, the Marketing Application for drug preparations and, with respect to marketed preparations, their supplementary applications.

Article 86 CFDA shall, within the prescribed timeline, issue its review decision based on conclusions from the technical review and in accordance with applicable regulations. CFDA shall approve and issue an Approval Letter for Drug Registration for each qualified application, and reject and issue a Notice on Review Opinions, accompanied by the reasons for the rejection, for each unqualified application. For any drug whose Marketing Application is to be approved, CFDA shall at the time of approval also verify the specifications, manufacturing process, labeling

and package inserts of the drug. The verified manufacturing process shall be sent to the Applicant only.

Article 87 The Approval Letter for Drug Registration shall contain the following key items:

(1) Information about the drug, including its non-proprietary names (Chinese name, English name, and trade name), the Origin Number, dosage form, strength (formulation strength), expiration date, indications/main functions, approval number/Imported Drug Registration Certificate number/Pharmaceutical Product Registration Certificate information, New Drug Certificate information, registration specification number, and the expiry date of the registration approval;

(2) Information about the manufacturer, including its name and address of the production plant; and

(3) Information about the Applicant receiving marketing authorization, including its name and registered address.

For any drug approved with qualifications, the Approval letter shall also include conditions such as the post-marketing studies that need to be completed within a specified period.

Article 88 The list of items in the registration specification and the determination of their testing methods shall conform to the essential requirements of the *Chinese Pharmacopoeia*, technical guidelines published by CFDA, and any national guidelines on the preparation of drug specifications. The specifications for biological products should include such items as the manufacturing process, testing methods and quality indicators.

Article 89 Labeling and package inserts shall be in compliance with the *Drug Administration Law* and its related rules.

Article 90 The review and approval authority shall reject an application in accordance with the law if:

(1) the application dossier shows there exists significant deficiency in the safety, efficacy, or quality controllability of the drug under consideration;

(2) the research materials and data submitted by different Applicants are either identical or similar and without reasonable explanations;

(3) the application dossier is found to contain untrue information during the registration process and the Applicant is unable to prove its truthfulness;

(4) the design and implementation of various studies cannot support an evaluation on the safety, efficacy, and quality controllability of the drug under consideration;

(5) a bulk drug substance is not procured from a compliant source;

(6) with respect to any registration application for a drug with modified dosage form, acid radical, alkali base, route of administration, etc. from the original drug, the Applicant is unable to demonstrate both the presence of innovative technologies and a clear advantage in clinical value over the original drug, except for registration applications for pediatric drugs with modified dosage form or strength;

(7) with respect to any registration application for a drug that, compared with a biological product already marketed in China, shows a slightly modified structure or features modified clinical properties, formulation properties, cell substrates, etc., the Applicant is unable to demonstrate both the presence of innovative technologies and a clear advantage in clinical value over the existing drug;

(8) a same-category biological product has already been marketed in China and the registration specification of the biological product under consideration is lower than that of the marketed product after a comprehensive assessment;

(9) the prescription for the new traditional Chinese medicine contains medicinal materials from endangered species such that the resources for the medicine are unsustainable;

(10) the relevant drug approval documents should be revoked pursuant to the *Drug Administration Law*;

(11) supplementary materials were not submitted within the prescribed timeframe;

(12) result from on-site inspection or sample testing fails to meet applicable requirements; or

(13) there exists any other situation that fails to meet the requirements for risks and benefits evaluation.

Article 91 Any drug preparation whose Marketing Application has been approved shall be issued a strength-specific drug approval number or Imported

Drug Registration Certificate number and Pharmaceutical Product Registration Certificate number.

Article 92 The registration classification and technical requirements of a drug whose Marketing Application is undergoing the review and approval process shall not be affected by the domestic or overseas marketing authorization of a preparation with identical active ingredients.

Article 93 In principle, no change to manufacturing, quality control, or usage conditions may be introduced once the Marketing Application has entered the review and approval phase. If such changes are necessary, the Applicant shall terminate the original Marketing Application and submit a new Marketing Application after it has completed the modification study. During the review process, the Applicant may submit an application dossier containing supplementary materials for the modification of any item in the registration form except the prescription, raw materials and excipients, and specification.

Chapter V Post-Marketing Change and Renewal

Article 94 Post-marketing change management refers to the administration of the changes to the information specified on an Approval Letter for Drug Registration and its appendices or of the changes to the manufacturing, quality control or usage condition of an approved drug, carried out by a Food and Drug Authority through such means as supplementary applications, record-filing and annual reports.

Article 95 An Applicant shall submit a supplementary application if it intends to change any item specified on the approval documents of a marketed drug or their appendices. If the manufacturing, quality control and usage condition of a marketed drug has changed, the Applicant shall, in accordance with applicable technical requirements and guidelines, systematically assess the effect of such change on the safety, efficacy and quality controllability of the drug, and either submit a supplementary application or make record-filing depending on its assessments. Additionally, all changes must be consolidated into the annual reports.

Article 96 Changes are classified into three categories depending on their impact on the safety, efficacy, and quality controllability of the drug:

(1) Type I changes are minor changes that have essentially no impact on the safety, efficacy, and quality controllability of the drug;

(2) Type II changes are moderate changes that require corresponding studies to demonstrate the absence of impact on the safety, efficacy, and quality controllability of the drug;

(3) Type III changes are major changes that require a series of studies to demonstrate the absence of adverse impact on the safety, efficacy, and quality controllability of the drug.

Refer to the corresponding technical and management guidelines for the specific scenarios for the modification studies.

Article 97 An Applicant shall submit supplementary applications and truthful materials to the competent Food and Drug Authority to make the desired changes. The Food and Drug Authority shall issue a Notice of Acceptance for each conforming application, and a Notice of Rejection, accompanied by an explanation for the rejection, for each nonconforming application.

Article 98 The Drug Evaluation Center shall organize a preliminary review of the application dossier for the supplementary application and issue its preliminary review opinions within 30 days of the application's acceptance. Applications not meeting the applicable requirements shall be rejected with a Notice on Review Opinions, accompanied by the reasons for the rejection; applications meeting the requirements and needing technical reviews shall enter in the technical review phase; applications meeting the requirements but not needing technical reviews shall be issued a review report and enter into the review and approval phase.

Article 99 During the technical review phase, the Drug Evaluation Center may, if it deems it necessary for the technical review, notify a verification agency to perform on-site inspection and sampling. After performing the on-site inspection and sampling, the verification agency shall submit the samples to a designated drug testing institute for registration testing. The Drug Evaluation Center shall finalize its conclusions for the technical review based on the reported findings from the on-site inspection and sample registration testing.

Article 100 The Drug Evaluation Center shall, within the prescribed timeline, issue its review decision based on conclusions from the technical review and in accordance with applicable regulations. The Drug Evaluation Center shall approve and issue an Approval Letter for Supplements for each qualified application, and reject and issue a Notice on Review Opinions, accompanied by the reasons for the rejection, for each unqualified application.

Article 101 To renew an expiring Approval Letter for Drug Registration, an application for its renewal shall be filed three months before its expiry. The competent Food and Drug Authority determines whether or not to approve the renewal before the expiry of the Approval Letter, but an Approval Letter shall be deemed as renewed if no decision has been issued by the expiry of the Approval Letter.

Article 102 If the drug approval documents require an Applicant to complete certain studies before a prescribed time, the Applicant shall submit results from such studies, in the form of a supplementary application, before applying for renewal of its Approval Letter for Drug Registration.

Article 103 Once a Food and Drug Authority determines to renew an Approval Letter for Drug Registration, it may also determine its new term of validity based on the effectiveness of its risk control measures.

Article 104 Where the original drug approval documents are not to be replaced following the approval of a supplementary application, the original drug approval documents shall remain valid.

Article 105 CFDA adopts the record-filing regime for changes that have no impact on the efficacy, safety, and quality controllability of a drug.

Article 106 An Applicant shall timely file and publish, in accordance with applicable requirements, any information that is related to a change and for which record-filing is required.

Article 107 An Applicant shall submit the information that is required to be filed on a change through the platform hosted by CFDA and as required. CFDA will publish the said information on the public platform if the Applicant has made no change to the information in the five days following its submission.

Article 108 Each Applicant who has received marketing authorization shall, for each year that its Approval Letter for Drug Registration remains valid, submit an annual report to the competent Drug Evaluation Center containing aggregated information, along with the Applicant's assessment and analysis, on the changes to its drug and on the drug's post-marketing safety-related events from the preceding year, with a copy sent to the Provincial Food and Drug Authority of where the Applicant is located. The interval between such annual reports may not be longer than one year.

Article 109 Each annual report shall contain: a summary and analysis of all the changes to the efficacy, safety, and quality controllability of the drug and to the package inserts and labeling from the preceding year, as well as the measures that have been or will be taken in response; information on post-marketing studies, manufacturing and sales; specimens of previous package inserts and labeling; progress on the mandatory post-marketing studies and information on other post-marketing research projects; and a log tracking the supervisory instructions received from the Food and Drug Authorities.

Article 110 Each Applicant shall submit its annual reports as required and through the material submission platform of the Drug Evaluation Center under CFDA.

Chapter VI Supervision and Administration

Article 111 Each Food and Drug Authority shall establish a professional inspection system staffed primarily by a team of dedicated inspectors; conduct on-site inspections on the drug research and development sites, on-site inspections on the manufacturing sites before marketing approval, as well as sampling where necessary, to verify the truthfulness, accuracy and completeness of application dossiers. Forms of on-site inspections include risk-driven supervisory inspections, review-driven routine inspections, and "for cause" inspections motivated by other factors.

Registration-related testing shall be performed by the National Institutes for Food and Drug Control, the drug control institutes of the provinces, autonomous regions or direct-controlled municipalities of China, or other third party institutes with relevant accreditations and testing capabilities.

Article 112 Each Food and Drug Authority shall establish a platform for the record-filing and publishing of information relating to clinical trials.

Article 113 Where an Applicant is required to submit physical materials, such materials shall contain the same information as the electronic materials previously submitted and registered.

Article 114 To confirm the truthfulness, accuracy, and completeness of an application dossier, a Drug Evaluation Center may, at any such time as it deems necessary during its reviews, require a traceback inspection on the data in the application dossier.

Article 115 To facilitate the trackback inspection of Food and Drug Authorities, each Applicant shall be responsible for the safekeeping of all the raw data relating to all its materials and data.

Article 116 If during routine supervision it is discovered that certain fact is inconsistent with the information previously filed for a bioequivalence study, CFDA shall, upon the receipt of the routine supervision report, revoke the record number corresponding to the study. If the discrepancy indicates that the original information was false, CFDA shall reject the corresponding registration application.

If during routine supervision it is discovered that the package inserts or labeling is inconsistent with the information on record, CFDA shall, upon the receipt of the routine supervision report, revoke the corresponding information on record.

Article 117 After obtaining marketing authorization for its drug, the Applicant shall produce the drug with the manufacturing process previously verified by CFDA.

The competent Food and Drug Authority shall supervise and inspect the post-marketing production of the Applicant in accordance with the manufacturing process and quality standard previously verified by CFDA.

Article 118 After obtaining marketing authorization, the Applicant shall voluntarily conduct post-marketing research and report its work to Food and Drug Authority.

Article 119 If an organization involved in the manufacturing, sales, use, testing, or supervision of drug discovers that a marketed drug has a severe efficacy or safety issue, it shall promptly report its discovery to the Provincial Food and Drug Authority, who shall then immediately organize an investigation and report the incident to CFDA.

Article 120 CFDA will aggregate information from various reports and feedbacks from public monitoring organizations to propose recommendations or impose requirements on a marketed drug in regard to revising its package inserts.

For any marketed drug with a confirmed safety issue, CFDA may withdraw the drug from the market and suspend the acceptance and review of its generic versions.

For any marketed drug with severe adverse effects, CFDA shall require the Applicant with the marketing authorization to take such measures as limiting the drug's usage, suspending its sales, halting its production or conducting recalls. If necessary, CFDA may cancel the approval number of the drug.

Article 121 For any Applicant with marketing authorization for its drug but who withholds information about a severe adverse effect or who did not take certain measures as ordered, CFDA may revoke the corresponding drug approval number and hold the Applicant legally liable in accordance with the law.

Article 122 Innovative traditional Chinese medicines and natural medicines may by application automatically acquire the status of protected traditional Chinese medicine at the same time as their marketing authorization.

Article 123 Any Drug Evaluation Center that decides pursuant to its procedures and criteria to not approve an application at the technical review phase shall provide the reasons for its decision. Its conclusions shall be published for 60 days, and the Drug Evaluation Center shall information the Applicant that it may request for a re-review in accordance with the law.

Article 124 Where the Applicant objects to the Drug Evaluation Center's decision on not approving its application in the technical review phase, it may request at the Drug Evaluation Center for a re-review within 60 days of the publication of the conclusions and state its reasons for the re-review.

The scope of the re-review shall be limited to the items in the original application and the original application dossier.

Article 125 Each Drug Evaluation Center shall establish a re-review expert committee which is responsible for the re-review of any review conclusion under dispute.

Article 126 Drug Evaluation Center shall organize a meeting of the re-review expert committee within 50 days of the receipt of a re-review request, and shall hear from the review experts and the Applicant in open discussions. The final re-review opinions shall be formed by a simple majority and sent to the Applicant. If the original decision was upheld in the re-review, the Drug Evaluation Center will not accept any further request for re-review.

Article 127 If the re-review process requires another technical review, CFDA shall organize specialized technical staff to conduct and complete the technical review in a timeframe no lengthier than that for the original application.

Article 128 Where an Applicant objects to CFDA's decision of suspending its clinical trial, it may request for a repeal in accordance with the applicable rules for re-review.

Article 129 An Applicant may submit a Marketing Application for a drug to which another person holds the patent right in China. CFDA will evaluate the drug in accordance with these *Provisions* and issue the Approval Letter for Drug Registration if the drug is judged to be compliant.

Article 130 An Applicant shall describe the Chinese patents and their ownership status for the drug it is applying for marketing or for the drug's prescription, manufacturing process, purpose, etc., regardless of whether such patent and ownership rights rest with the Applicant or another person. Where another person holds a relevant Chinese patent, the Applicant shall submit a statement guaranteeing that its drug will not infringe upon the patent right of that person. The Food and Drug Authority shall publish the description and the statement on the website of the administrative body. Any dispute involving patent rights shall be resolved pursuant to patent laws and regulations.

Article 131 In view of its mission to protect public health, CFDA may set a monitoring period for any new drug variety that has been approved for marketing. The monitoring period shall start on the day the new drug is approved for marketing, and last for a maximum of five years.

Starting from the day that the new drug enters the monitoring period, CFDA will no longer accept any Marketing Application from another Applicant on the same drug variety. CFDA may accept Marketing Applications from Applicants on the same drug variety after the expiry of the monitoring period.

Article 132 If a new drug with monitoring period requirement is not sold on the market within two years following the marketing authorization, CFDA may accept Marketing Applications on the same drug variety from other Applicants and restart the monitoring program.

Article 133 As of the date that a new drug enters the monitoring period, any Marketing Applications for the same drug that have already been

accepted by a Drug Evaluation Center may continue with their review proceedings and review and approval process even if they are from other Applicants. CFDA will approve the marketing of such new drug if it is compliant with applicable rules, and shall monitor the new drug along with the first new drug.

Chapter VII Legal Liabilities

Article 134 Upon the occurrence of any of the circumstances specified under Article 69 of the *Administrative Permission Law*, CFDA may, based on the request of a stakeholder or in accordance with its own power and authority, revoke the relevant drug approval documents.

Article 135 If a Food and Drug Authority or one of its staff members has violated these *Provisions* and is implicated in one of the following circumstances, its superior administrative body or supervisory body shall order the offender to rectify; in the case of a serious violation, the manager with direct oversight responsibilities and other individuals who are directly responsible for the violation shall be imposed with an administrative penalty in accordance with the law:

(1) refusing to accept a drug registration application that by statutory criteria should be accepted;

(2) failing to publicly display a material in the application acceptance area that by law should be displayed;

(3) failing to fulfill its statutory notification obligation to the Applicant or other stakeholders during the application acceptance, review, and review and approval process;

(4) failing to inform the Applicant in one setting of all the contents that it must additionally provide with respect to its incomplete or non-conforming application dossier;

(5) failing to state the reason or reasons for not accepting or not approving a drug registration application in accordance with the law; or

(6) failing to hold a hearing that by law should be held.

Article 136 Any Food and Drug Authority or any of its staff members that solicits or accepts bribes or seeks illegitimate benefits during the drug registration process shall either be prosecuted for criminal offense if such solicitation, acceptance or pursuit constitutes a criminal conduct,

or be imposed with an administrative penalty if the action is not severe enough to be deemed criminal.

Article 137 If a Food and Drug Authority has been involved in one of the following circumstances during the drug registration process, its superior administrative body or supervisory body shall order the offender to rectify; in the case of a serious violation, the manager with direct oversight responsibilities and other individuals who are directly responsible for the violation shall be imposed with an administrative penalty in accordance with the law; in the case of a criminal offence, the offender shall be prosecuted for the criminal offence:

(1) approving a registration application that does not comply with statutory criteria or approving it by overstepping the relevant statutory power and authority;

(2) not approving a registration application despite its compliance with statutory criteria or approving it after the statutory timeframe has passed; or

(3) violating the confidentiality obligation under Article 17 of these *Provisions*.

Article 138 Where a drug testing institute has issued a false testing report while performing the requisite testing works for the drug review and approval process, it shall be punished in accordance with Article 86 of the *Drug Administration Law*.

Article 139 Any Food and Drug Authority that demands unauthorized fees and charges or does not collect fees and charges in accordance with the statutory billable items list and fee schedule shall be ordered by its superior administrative body or supervisory body to return the illegal proceeds, and the manager with direct oversight responsibilities and other individuals who are directly responsible for the violation shall be imposed with an administrative penalty in accordance with the law.

Article 140 Any person who does not implement GLP, GCP or GMP as required during drug registration shall be punished in accordance with Article 78 of the *Drug Administration Law*. Where the initial application for clinical trial has already been approved, the corresponding Approval Letter for Clinical Trial shall be revoked.

Article 141 Where an Applicant has submitted false application dossier or samples during drug registration, the Food and Drug Authority shall refuse to accept the registration application or reject the application if it was

already accepted, issue a warning to the Applicant, and refuse to accept for one year any registration application the said Applicant intends to file with respect to the same drug. Where the initial application for clinical trial has already been approved, the corresponding Approval Letter for Clinical Trial shall be revoked, and the Applicant shall be fined no less than RMB 10,000 and no more than RMB 30,000, and no such Clinical Trial Application from the Applicant shall be accepted for three years. Where the concerned drug is already approved for marketing, the corresponding drug approval documents shall be revoked, and no application from the Applicant be accepted in five years, and the Applicant shall be fined no less than RMB 10,000 and no more than RMB 30,000.

Food and Drug Authorities shall establish and publish a misconduct record with respect to the Applicants and registration specialists who have submitted false materials and samples.

Article 142 CFDA shall cancel the corresponding drug approval number and announce its decision if:

(1) the Applicant has voluntarily applied for the cancellation of the drug approval number while it is still valid;

(2) the Applicant did not submit a supplementary application requesting to update the validity period of the approval documents when they expired, or such application was rejected;

(3) the corresponding Drug Manufacturing License has been revoked or cancelled in accordance with the law;

(4) the corresponding approval documents have been revoked in accordance with Article 42 of the *Drug Administration Law* and Article 41 of the *Implementation Regulations for Drug Administration Law* due to the drug having a major adverse effect or other harmful effect on human health;

(5) the drug approval documents have been revoked in accordance with the law; or

(6) there has been any other circumstance where the cancellation of the corresponding drug approval documents is warranted by law.

Chapter VIII Supplementary Provisions

Article 143 Separate rules will be provided with respect to: the application dossier and requirements for the Clinical Trial Application, Marketing

Application, and supplementary application of traditional Chinese medicines, natural medicines, chemical drugs and biological products; the materials and requirements for the follow-up clinical trial protocols and substantial amendments, and for the application for resuming suspended clinical trials, regular assessment reports and annual reports; the record-filing rules and requirements for bioequivalence studies, package inserts and labeling.

Article 144 The drug approval number has the format of Guo Yao Zhun Zi H (or Z, S, J) + 4-digit year number + 4-digit sequence number, where "H" denotes a chemical drug, "Z" denotes a traditional Chinese medicine, "S" denotes a biological product, and "J" denotes a repackaged import drug.

The Imported Drug Registration Certificate number has the format of H (or Z, S) + 4-digit year number + 4-digit sequence number; the Pharmaceutical Product Registration Certificate number has the format of H (or Z, S) C + 4-digit year number + 4-digit sequence number, where, in each case, "H" denotes a chemical drug, "Z" denotes a traditional Chinese medicine, and "S" denotes a biological product. If the same registration certificate for the large package version of a drug is also used for its repackaged version in China, a letter "B" will be prefixed to the original registration certificate number.

The new drug certificate number has the format of Guo Yao Zheng Zi H (or Z, S) + 4-digit year number + 4-digit sequence number, where "H" denotes a chemical drug, "Z" denotes a traditional Chinese medicine, and "S" denotes a biological product.

Article 145 In addition to complying with the rules under these *Provisions*, registration applications for narcotic drugs, psychotropic substances, toxic drugs for medical use, and radioactive drugs shall also comply with other applicable national rules.

Article 146 CFDA will separately provide the rules governing the registration of Chinese herbal medicines, prepared slices of Chinese crude drugs, and imported Chinese herbal medicines that are managed by approval numbers.

Article 147 These *Provisions* shall come into force on [*] [*], 20[*]. The Provisions for Drug Registration (State Food and Drug Administration Order No. 28), as promulgated by the then State Food and Drug Administration on July 10, 2007, shall expire on the same date.