Annex

Technical Guidelines for the Acceptance of Overseas Clinical Trial Data of Medical Devices

The Guidelines are formulated in accordance with general office of the central committee of the communist party of China, the state council general office *Opinions on Deepening the Review and Approval System Reform and Encouraging the Drug and Medical Device Innovation* (Ting Zi No. 2017 No. 42) and the requirements related to the registration management of medical devices in our country to better satisfy the clinical needs of the public for medical devices and promote the technical innovation of medical devices. The Guidelines aim to provide technical guidance for the registration application of the applicant with the data of the medical device clinical trial conducted overseas and for the technical review on such clinical trial data by the regulatory authority so as to avoid or reduce repetitive clinical trials, accelerate the marketing of medical devices in our country.

I. Scope of application

The Guidelines are applicable to guiding the acceptance of the overseas clinical trial data submitted by the applicant as the clinical evaluation data for the registration application of a medical device (an in vitro diagnostic reagent) in our country.

For the purpose of the Guidelines, the overseas clinical trial data refer to the study data generated during the validation of the safety and effectiveness of the medical device under the registration application in our country under the normal service conditions by all the clinical trial institutions or those equipped with the conditions required by the country (region) where the clinical trial is conducted at the corresponding period.

II. Basic principles for the acceptance of overseas clinical trial data

(I) Ethical principle

The overseas clinical trial shall follow the codes of ethics set forth in the World Medical Association Declaration of Helsinki. The applicant also needs to describe the norms and standards specified in the ethical rules, laws and regulations of the country (region) where the clinical trial is conducted, or international norms and standards.

(II) Legal principle

The overseas clinical trial shall be conducted in a country (region) where the clinical trial quality management is implemented and shall meet the regulatory requirements for the medical device (in vitro diagnostic reagent) clinical trial in our country. In case of any

difference between the clinical trial quality management document that a clinical trial complies with and the *Good Clinical Practice for Medical Devices* (GCP), the applicant shall describe the differences in detail and fully demonstrate that such differences will not affect authenticity, scientificity, reliability and traceability of trial results and the rights and interests of the subjects are protected. The applicant and the clinical trial institutions shall accept the supervisory inspection by CFDA.

(III) Scientific principle

The overseas clinical trial data shall be authentic, scientific, reliable and traceable. The applicant shall provide a complete set of trial data without screening.

The applicant shall ensure that the purpose of the clinical trial conducted overseas is appropriate; the trial design is scientific and reasonable; the trial conclusion is clear; the rights and interests of the subjects have been guaranteed; and other personnel have been protected from the possible risks.

III. Submission of overseas clinical trial data and acceptance criteria

Overseas clinical trial data of the medical device submitted by the applicant shall at least include: the clinical trial protocol, the opinions of the ethics, and the clinical trial report which includes the analysis on the complete clinical trial data and the conclusions.

Based on the clinical evaluation pathway selected by the applicant for registration application, the overseas clinical trial data may be used as clinical trial materials, or as the validation materials to prove that the difference with the similar medical device brings no adverse effect on product safety and effectiveness. The latter clinical trial data shall include: the data generated in the clinical trial conducted overseas which aims at the difference compared with the similar device; the overseas clinical trial data that the applicant already has owned that can cover the content of difference trial to be conducted after the comparison with the similar device.

The scientific, complete and sufficient overseas trial data that meets relevant requirements for the registration in our country shall be accepted. Where the overseas trial data meet the basic requirements specified in Section II of the Guidelines, but need supplement partial data according torelevant technical requirements for the registration in our country, a supplementary clinical trial may be conducted in our country or overseas. If the supplementary trial data and the previous overseas trial data meet relevant technical requirements for the registration in our country in the comprehensive evaluation, the data shall be accepted.

In case of using the data of a multi-center clinical trial conducted in our country and overseas at the same period as the registration submission material, the applicant shall also demonstrate the basis for the distribution of the cases undertaken by the institutions

in our country so as to further evaluate whether such data meet relevant requirements for the registration in our country.

For the medical device in the *List of Class III Medical Devices Requiring Clinical Trial Review and Approval*, the overseas clinical trial data may also be submitted according to the Guidelines.

IV. Considerations for the acceptance of overseas clinical trial data and technical requirements

(I) Difference in technical review requirements

A clinical trial conducted overseas may meet the technical review requirements of the country (region) where it has been conducted, but not necessarily fully meet the relevant technical review requirements in our country. For example, for the design of a clinical trial, the requirement in some countries is that the clinical trial can reach the conclusion that the performance of a medical device achieves one observation endpoint, but the requirement for registration application in our country is that the effectiveness can only be verified until the performance of a medical device achieves multiple observation endpoints and there is appropriate evidence supporting the safety of the medical device. If the guidelines for technical review of a specific medical device issued by CFDA specified relevant requirements for the clinical trial of the medical device, such requirements shall be considered for the overseas clinical trial of the medical device. In case of any inconsistency, sufficient and reasonable grounds and basis shall be provided.

(II) Difference in subjects

Medical devices differ in the mechanism of action on human body, the way and time for the contact with human body and expected clinical effect, therefore, some medical devices may be different in terms of safety and intervention degree among different populations. The applicant shall confirm that the data of the study population can be extrapolated to our country users.

The differences in subjects that may possibly influence the clinical trial data include:

1. Internal factors: the influence factors based on human genetic characteristics or demographic characteristics, such as race, ethnic lines, age and gender.
2. External factors: the influence factors based on social environment, natural environment and culture, such as dietary habit, religious belief, environment to be exposed to, smoking, drinking, incidence of diseases, rare or regional comorbidity, obesity, treatment concept, social and economic conditions, educational background and medical compliance.

Some of the above factors may be generated on the basis of both internal and external factors, such as ethnic difference.

(III) Difference in clinical trial conditions

For the overseas clinical trial, it is necessary to consider the influence of the differences from the trial conditions in our country on trial data and the relevance of the intended target population in our country. The differences in trial conditions include the differences in medical environment, medical facilities, investigator ability (learning curve), and the diagnosis and treatment concept or code. Some factors may have a significant influence on trial results. For example, due to different diagnosis and treatment concepts or criteria, the clinical practice may not comply with relevant guidelines for clinical operation in our country. In addition, the differences in medical facilities and investigator's abilities may also influence the trial data. For the medical device requiring higher operability, the ability of an investigator to use the device may have a significant influence on trial conclusions.

The influence factors generated from the above differences in three aspects may exist singly or may coexist during the generation process of the clinical trial data of a certain medical device. Although it is already known that such factors exist objectively and may have some influence on the clinical trial, the influence degree of such factors shall be judged in combination with the characteristics of the medical device under application and the purpose of the clinical trial. Where it is determined that such factors have no actual clinically significant influence on the clinical trial data of most medical devices according to the development status, the experience in clinical application as well as the cognition of related diseases and diagnosis and treatment methods, it is not required to prove them one by one. Where it is determined that or it is hard to determine whether some factors have clinically significant influence on the clinical trial data, the applicant shall explain the methods taken to reduce or eliminate the influence of each difference, for example, the applicant may consider to conduct subgroup design for the subjects or conduct subgroup analysis for the existing clinical trial data as needed.

For the factors that can be clearly defined to have clinically significant influence on trial data, the applicant may conduct a supplementary trial in our country on the difference factors, which can be used to validate the safety and effectiveness of such device under normal service conditions in our country jointly with the previous overseas clinical trial data.

It is recommended that the applicant make sound communication with the medical device evaluation authority in our country before submitting overseas clinical trial data so as to reach a consensus on the scientificity, completeness and sufficiency of the clinical evaluation data for the medical device under application.

Following are the examples for which it can be determined that different factors have clinically significant influence on their clinical data:

Example 1: A pulse oximeter device that uses a time-dependent change in the tissue optical properties caused by pulsatile blood flow through the interaction of optical signals with tissue for noninvasive measurement of pulse oxygen saturation (SpO_2) and pulse rate (PR). Because the operating principle involves the interaction between optical signals and tissues, the issue of skin melanin deposition shall be considered. There is a difference in the skin color between the overseas population and the our country population, and the corresponding clinical study shall be carried out.

Example 2: An in vitro diagnostic reagent for gene detection of genetic disease. If there is a difference in genetic genes of different ethnic groups, the detection genes selected for foreign products based on the overseas population may differ from those of the our country population, then it is necessary to conduct corresponding clinical study based on such influence factors as the mutation site, mutation frequency of genetic genes of relevant diseases in the Chinese population.

Example 3: An in vitro diagnostic reagent for pathogen detection. The genotypes prevalent in inner country and those prevalent overseas may differ, for example, there is a difference in the distribution of the genotypes of hepatitis B virus in different parts of the world, the common genotypes in our country are Types B, C and D while there are 9 genotypes currently found in the world from Type A to Type I. For a hepatitis B virus genotyping detection reagent, clinical evaluation shall be conducted to prove the genotype coverage and detection capability.