CFDA Announcement No. 13 in 2018, Issued on Jan. 18, 2018

接受医疗器械境外临床试验数据技术指导原则

Guidelines for Acceptance of Overseas Clinical Trial Data

To fulfill the clinical need of publics for medical devices, improve the innovation of medical device technology, this guideline is made according to the "Opinions on reforming the review and approval system to encourage the innovation of drugs and medical devices" by the General Office of the Central Committee of the CPC and the General Office of the State Council (GO [2017] No.42), and the relevant regulatory requirements of medical devices in China. This guideline is to provide technical guidance for applicants using overseas clinical trial data for registration and for authorities reviewing these data, to avoid or reduce redundancy of clinical trials and to facilitate medical devices marketing process in China.

I. Scope

This guideline is applicable to guide the work that applicants use overseas clinical trial data as clinical evaluation material during medical device (including in vitro diagnostic reagents) registration in China.

The overseas clinical trial data in this guideline refers to the research data generated completely or simultaneously in the overseas clinical trial sites fulfilling the requirements of the countries (regions), in the verification process for the safety and effectiveness of the medical device to be registered in China.

II. Principles of acceptance of overseas clinical trial data

(I) Ethic principles

Overseas clinical trial data shall follow the ethical principles of "Declaration of Helsinki". The applicant shall describe the norms and standards of ethics, laws and regulations in the countries (regions) where the clinical trial is conducted, or the international norms and standards.

(II) Principles according to the law

The overseas clinical trial should be conducted in the countries (regions) that have the quality management of clinical trials and meets the regulatory requirements for clinical trials of medical devices (including IVD reagents) in China. If the quality management regulations that the clinical trial complies are different from Medical Device Good Clinical Practices (GCP) in China, the differences shall be described in detail, and it shall be fully proved that the differences do not affect the authenticity, scientificity, reliability and traceability of trial data, and can guarantee the rights and interests of the subjects. The applicant and the clinical trial sites shall be supervised by the CFDA.

(III) Scientific principles

Overseas clinical trial data shall be authentic, scientific, reliable and traceable. The applicant shall provide the complete trial data, not the selected data.

The applicant shall ensure that the purpose of the overseas clinical trial is appropriate, the trial design is scientific and reasonable, the conclusion is clear, the rights and interests of the subject are protected, and the risks of other personnel are protected.

III. Requirements for the submission and the acceptance of overseas clinical trial data

The overseas clinical trial data submitted by the applicant shall at least include: clinical trial protocol, the ethic committee approval, and the clinical trial report. The clinical trial report shall include a complete analysis and conclusion of the clinical trial data.

According to the clinical evaluation path selected by the applicant, the overseas clinical trial data can be used as clinical trial material, also be used as verification material proving that the differences from the predicate device does not has negative effects on the safety and effectiveness of the product. The data generation process of the latter shall include: the data to be created in the overseas clinical trial for evaluating the differences from the predicate; the content that the previous overseas clinical trial that can cover the differential study after comparing the predicate.

If the overseas clinical trial data comply with the requirements of the product registration in China, and the data are scientific, complete and sufficient, it shall be accepted. If overseas trial data comply with the basic requirements in section II of this guideline, and part of materials shall be supplemented according to the requirements in China, the supplementary clinical trial can be conducted in China or overseas. If the comprehensive evaluation of supplementary trial data and overseas clinical trial data comply with the technical requirements in China, it shall be accepted.

If applicant uses the multi-center clinical trial data conduct simultaneously in China and out of China as registration material, the evidence of determining sample size in China shall be clarified, in order to evaluate further whether the data comply with the requirements for product registration in China.

For the devices in the “List of Class III Medical Device Requiring Approval for Conducting Clinical Trial”, the overseas clinical trial data can be submitted according to this guideline as well.

IV. Factors and technical requirements to accept overseas clinical trial material

(I) Differences in technical review requirements

The overseas clinical trial may comply with the technical review requirements in the country (region) where the clinical trial is conducted, but may not fully comply with the review requirements in China. For example, in the clinical trial design, the performance of the device only need to reach a certain endpoint in some countries, but the performance of device need to reach multiple endpoints in China and the safety of the device shall be supported by appropriate evidences. If a guideline for technical review for a certain device including the requirements of clinical trial has been issued by the CFDA, and the overseas review requirements are different from that in China, sufficient and adequate reasons and evidences shall be provided.

(II) Differences in subject cohort

Due to the difference in the working mechanism of medical device on the human body, the way and time of human body contact, and expected clinical effects, the safety effects and intervention levels of a certain device are different in different populations. The applicant should confirm that data studied on the overseas population can be deduced to the Chinese population.

Factors related to different subject cohorts that may influence clinical trial data include:

1. Internal factors: it refers to the factors based on human genetic characteristics or demographic characteristics, including race, ethnicity, age, gender, etc.

2. External factors: it refers to factors based on social environment, natural environment and culture, including dietary habits, religious beliefs, exposed environment, smoking, drinking, incidence of disease, rare or regional comorbidity, obesity, treatment concept, Social and economic conditions, education, medical compliance and so on.

Some of these factors above can be both internal and external, such as ethnic differences.

(III) Differences on clinical trial condition

Overseas clinical trial shall consider the impact of its difference from trial conditions in China on the trial data and the relevance of Chinese population. The differences in trial conditions include: the medical environment, the medical facilities, the ability of investigators (learning curve), the concept of treatment or guidelines, etc. Some factor may have a significant impact on the trial results, for example, the clinical practice method may not comply with relevant guidelines in China. In addition, differences in the level of medical facilities and investigators also have an impact on the trial data. For devices requiring higher operability, the ability of the investigators to use the device may have a direct effect on the trial results.

The impact factors of the above three aspects on a medical device clinical trial may exist solely or together. Although those factors are known to exist objectively and shall have some impacts on clinical trial, the impact level of various factors shall be determined with the characteristics of investigational medical device and the purpose of the clinical trial. According to the state of act of the medical device, the clinical experience, and the cognition of related diseases and treatment methods, it is not required to prove the impact factors one by one, if their impacts on the clinical trial data of most medical devices can be determined to have no clinical significance. If a certain factor has a clinically significant impact on the clinical trial data, or if it is difficult to determine whether a certain factor has a clinical significant impact on the clinical trial data or not, the applicant should clarify the method to reduce or eliminate the impact of various factors, for example, performing subgroup design of the study cohort or doing subgroup analysis of the existing clinical data.

For those factors, the clinically significant impact of which on the trial data can be clearly determined, the applicant can conduct a supplementary trial in China for this factor, and confirm the safety and the effectiveness of device in normal use in China in combination with the overseas clinical trial.

It is suggested that the applicant shall negotiate with the medical device review department before submitting the overseas clinical trial data, to have an agreement that the clinical evaluation materials are scientific, complete and sufficient.

Examples of factors with a determined clinical significance on clinical data are given as follows:

Example 1: Pulse oximeter utilizes the time-dependent change of tissue optical properties caused by pulsed blood flow through the interaction between optical signal and tissue, to measure SpO2 and Pulse Rate (PR). Because the working principle of the device involves the interaction between optical signal and tissue, the skin melanin deposition should be considered. There is a difference in skin color between the overseas population and the Chinese population, and the corresponding clinical research should be carried out.

Example 2: In vitro diagnostic reagents for gene test of genetic diseases: If there is a difference in genes of different ethnic groups, the selected genes of overseas products based on overseas populations may differ from those of Chinese population. The mutation loci and mutation frequencies and other influencing factor of related diseases in Chinese population should be considered and the corresponding clinical research should be carried out.

Example 3: In vitro diagnostic reagents for pathogen detection: The genotypes are different between in China and in other countries. For example, the distribution of hepatitis B virus subtypes varies in countries. The subtypes of B, C and D are common in China, and total 9 subtypes of A to I exist globally. The Hepatitis B virus genotyping reagents should demonstrate the genotype coverage and detectability through clinical evaluation.