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Preclinical animal study of medical devices - Part 1: General considerations

医疗器械临床前动物研究 第 1 部分：通用要求

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Preclinical animal study of medical devices - Part 1: General considerations

1 Scope

This Part of YY/T 1754 specifies the general considerations for preclinical animal study of medical devices.

This Part applies to the design of animal test and the acquisition of data for preclinical medical devices.

Note: This Part does not replace the technical documents, which are related to the biological evaluation of medical devices, such as GB/T 16886 series standards. For the biocompatibility of medical devices which is evaluated through animal test, refer to the GB/T 16886 series standards and other relevant technical documents related to biological evaluation.

2 Normative references

The following documents are indispensable for the application of this document. For dated references, only the dated version applies to this document. For undated references, the latest edition (including all amendments) applies to this document.

GB/T 16886.1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process

GB/T 16886.2, Biological evaluation of medical devices - Part 2: Animal welfare requirements

3 Terms and definitions

Terms and definitions determined by GB/T 16886.1 and GB/T 16886.2 are applicable to this document.

4 General principles

4.1 The purpose of preclinical animal study of medical devices is to provide evidence of the safety of medical devices, including safety-related performance and manipulation, and to evaluate the effectiveness and feasibility of the medical devices. It is advisable to choose an animal model that has been scientifically demonstrated. For certain types of medical devices, which may not

The selection of preclinical animal models of medical devices should simulate the clinical use of medical devices as much as possible. The selected animal model should be analyzed, including but not limited to:

a) The similarities and differences between the animal model and the human body in the use of medical devices. For drug-device combination products, consideration should also be given to the differences in drug metabolism between the animal model and the human body.

b) Compare the size of the test medical device and/or delivery system with the final product which is expected to be used in the human body, taking into account the potential limitations of matching the size of the medical device with the animal model.

c) The anatomical structures of animals and humans at the surgical entrance and comparison of the used surgical techniques, when testing the location and route of medical device placement and surgical placement,

6.2 Study objectives

6.2.1 Safety of medical devices

6.2.1.1 Physiological response

Medical devices can generate mechanical or biological stress; therefore, it is advisable to identify the key biological response variables in the area where the medical device is used, including the area adjacent to the implantation site (if applicable) and the area along all implantation paths or use paths, so as to formulate an effective method for studying the effects of medical devices on the body.

6.2.1.2 Unexpected morbidity and death

It is advisable to fully describe the number of observed animal diseases and deaths and explain whether these cases are related to medical devices; keep corresponding evidence, records and reports. If the medical device may indirectly cause animal death or disease, the cause should be analyzed. It is advisable to develop key assessment methods for the systemic effects of medical devices in use. These assessment methods include clinicopathological examinations immediately after surgery, in mid-term study and at study endpoint, including but not limited to: blood biochemical, hematology and coagulation indicators with laboratory reference range values; imaging reports; case report forms for specific evaluation, such as electrophysiological, behavioral, and neurological assessments.

6.2.1.3 Downstream and systemic effects

c) Analysis of all removed tissues;

d) Preparation of tissue;

e) Formulation and issuance of the final written report.

6.4 Test samples and control samples

All test samples and control samples which are used in the study shall be fully characterized. It is recommended to use test samples that can represent the final clinical design for animal study. If the final design product is not used, reasons should be provided as to why the final clinical design product does not create new risks when it is compared with the design samples in animal study. The test and control samples should be delivered to the research site by using the same packaging, sterilization and transportation methods as the clinical products. Researchers should develop and follow a method to trace the entire process.

6.5 Medical devices and medical device accessories

Certain test samples are usually used in conjunction with specific medical device accessories. When these accessories are indispensable in the use of test samples, they should be described as part of the test model system. The researcher should declare: whether all the medical device accessories that are used in the animal study are completely provided separately from the test sample, or whether the medical device accessories are purchased together with the test sample; and whether the final label of the medical device includes the selection or instructions for use of medical device accessories.

6.6 Animal test system

The final study report shall include a description of the animal test system. When it is applicable, a description of the factors that may affect the animal test system should be provided, so that the influence of these factors on the study results can be reasonably assessed. It mainly includes: environmental factors, such as temperature, light and facility structure; animal nutritional status; animal body homeostasis control, including electrolytes, blood sugar, sterile maintenance and bleeding control; auxiliary diagnostic tools; and materials and methods which are used to specify or describe test samples or the interaction between the control sample and the animal.

7 Personnel

Key researchers should be listed in each test report. The personnel should include a qualified veterinarian, to be able to detect and deal with undesirable results and to ensure animal welfare requirements.

Procedures for animal identification, grouping, and processing or configuration information tables for studying animals should be established, so that a complete traceability chain can be formed for all animals which are used in the test group or control group.

9.4 Animal quarantine and conditions

The quarantine of animals shall comply with the corresponding national standards and guidelines; the corresponding standard operating procedures shall be formulated.

9.5 Animal groups and numbers

A control group should be included in the animal study design; or an explanation for not setting up a control group should be given. The number of animals and the gender of animals should be confirmed on the basis of scientific argumentation; the principle of replacement, reduction and refinement (3R) should be followed; the animal welfare requirements in GB/T 16886.2 should be fully considered. For high-risk medical devices, due to the high level of complex operation technology and the expected animal mortality, it may be necessary to appropriately increase a certain number of animals to ensure the scientific nature of animal test study. The number of animals should be reasonably determined according to the characteristics of the product. At the same time, consider whether it is possible to reasonably study one or more test samples and/or control samples in one animal.

9.6 Food, water and basic feeding conditions

The feeding of animals should in compliance with the corresponding national standards and guidelines, so as to ensure that researchers can monitor the animals' food intake and water intake, as well as urination and defecation activities. The long-term research on animal parasitic infections should also be considered.

9.7 Observation period

9.7.1 General

Specific animal monitoring procedures should be developed together with the veterinarian, to fully explain the effects of medical devices on animals. Important monitoring contents that need to be considered include but are not limited to:

a) Respiratory rate, type and depth;

b) Blood pressure;

c) Heart sounds and pulse characteristics;

A comprehensive and systematic animal autopsy should be included in the study protocol, including tissue collection and possible processing and preservation, for histopathological examination to obtain result information. If an animal died unexpectedly, evidence should be provided to explain the cause of the accidental death.

9.8 Image inspection and evaluation method after animal execution (when applicable)

9.8.1 Retrieved object image

Before performing histomorphological analysis on the retrieved object, it is advisable to consider the use of imaging techniques, such as radiological imaging, micro-computerized tomography, and the like, to analyze whether the structural integrity of the medical device is helpful to determine the safety of the medical device.

9.8.2 Scanning electron microscope (SEM)

After taking out the medical device from the animal, use a scanning electron microscope to fully characterize the surface of the medical device implant.

9.8.3 Histomorphological analysis

It is recommended that the animal pathologists or the clinical pathologists perform the histomorphological analysis, and score and analyze all the observed tissues with damage and inflammation. Attentions should be paid to inflammation, vascularization, calcification, proteoglycan/collagen, and fibrin/thrombosis. Record any non-standard tools and methods which are used to collect tissue, including medical devices, as well as methods of fixation, sectioning, and staining. Graphical illustration to indicate the location of the implant should also be included in the report. Describe the sectioning method, including tissue and medical device positioning, in details. When discussing study results, the report should include high-resolution color images; indicate animal number, study group, tissue section, magnification, staining, and other important identifying information in each image.

9.8.4 Local and downstream issue assessment

Most medical devices in contact with the blood system have the possibility of forming embolic particles or microthrombi from the structural components or coatings of the medical device, causing observable adverse effects in the surrounding or upstream/downstream tissues, such as compressive necrosis and inflammation. If there is a risk of forming an upstream thrombus, the skull should be cut for brain tissue sectioning. If it is identified in the risk analysis that the medical device has this potential risk, it is recommended to include a descriptive evaluation of the upstream/downstream and surrounding tissue

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