A Practical Guide to ISO 10993-11: Designing Subchronic and Chronic Systemic Toxicity Tests

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Systemic toxicity tests must be designed carefully to ensure that medical device components will have no adverse effects on internal organs.

The International Organization for Standardization (ISO) has provided guidelines for the selection of toxicity tests under section ISO 10993-11: "Tests for Systemic Toxicity" of its harmonized standards for the biological evaluation of medical devices. In addition, the standards' introductory section, ISO 10993-1, contains general information on the conduct of acute, subchronic, and chronic toxicity studies (studies of short, medium, and long duration, respectively). However, these sections provide only limited guidance on the actual conduct of such studies, instead referring manufacturers to specific information provided in the Organization for Economic Cooperation and Development guidelines and other documents, which were written without medical devices in mind. An earlier installment in this series described the fluid extract, implant, and pyrogen tests that can be used for acute systemic toxicity studies; this article focuses on the overall design of test protocols for evaluating subchronic and chronic systemic effects of medical devices and their materials.
TEST ARTICLE CHARACTERIZATION

Although it is often overlooked, characterization of test articles is an important first step for device manufacturers to take before committing to longer-term toxicity testing programs. ISO 10993-1 notes, although it does not mandate, "If appropriate, identification and quantification of extractable chemical entities of the final product should precede biological evaluation." In some cases, chemical analysis of material extracts may preclude the necessity for systemic toxicity testing if it can be shown that the material does not give up significant quantities of extractables. In other instances, when specific extracted chemicals can be positively identified, the scientific literature can provide valuable information regarding their known toxicity profiles or lack of toxicity.

SELECTING TEST PARAMETERS

When designing chronic and subchronic toxicity studies, selection of exposure duration; species and number, age, and sex of test animals; and dosage size and dosing intervals all require careful consideration. In general, the exposure duration for a subchronic study would be less than 10% of the life span of the species tested, while the duration of a chronic study would be longer than 10% of the animal's life span.

The rat is normally chosen as the rodent species used in such test protocols and the dog as the nonrodent species because of the large historical databases available for these animals. Both laboratory rats and dogs are readily available worldwide, and the size of each species provides ease of handling and facilitates data collection. In some cases, species selection may be driven by such factors as the maximum number of devices that can be implanted into an animal. For example, the dog would be preferable to the rat for testing a catheter device simply because of its size. Animals of both sexes should be included in the protocol unless the clinical end use predetermines the need to test in only one sex. To limit test variables, the female animals should not have reproduced and should not be pregnant. The number of animals tested should be based on the minimum required to provide meaningful data. Enough animals must remain at the termination of the study to ensure proper statistical evaluation of the results.

The ISO standards generally provide little information about the dosage levels or number of doses to employ. One exception is ISO 10993-3, "Test for Genotoxicity, Carcinogenicity, and Reproductive Toxicity," which includes a guideline for dose selection in carcinogenicity studies. The maximum implantable dose, or MID, is defined there as the maximum amount of material (dose) that a test animal can tolerate without adverse physical or mechanical effects, and it is suggested that three groups of test animals be used: those exposed to the MID, those exposed to a fraction of the MID (usually one-half), and a control group. For systemic studies in which the test article is implanted, this recommendation may be useful. However, in most studies the animals are dosed at intervals with fluid extracts of the test articles. Normally, they are dosed daily for the duration of the study with no allowable recovery period between exposures, although dosing schedules may vary depending upon the clinical end use of the product and the toxicokinetic data available for extractables from the test article.

COLLECTING AND EVALUATING DATA
Data collected during the course of a systemic toxicity study and at its end points must enable researchers to assess the overall impact that the treatment regimen had on the test animals' organ systems. Observations of the animals must be made at intervals during treatment to ensure all toxicologic effects are detected. Clinical tests performed during the in-life phase often include measurements of body weight and food consumption, blood and urine analyses, and eye examinations.

Clinical pathology measurements consist of two major components: hematology and clinical chemistry. Urinalysis may also be a component of the clinical pathology screen. Blood samples should be analyzed individually and not pooled. Recommended test parameters are hematocrit, hemoglobin, erythrocyte counts, and total and differential leukocyte counts. Platelet counts and measurements of clotting time, prothrombin time, and thromboplastin time are optional but are frequently performed. Clinical chemistry tests are normally done using serum that has been separated from whole blood, but they may also be performed on plasma. The list of possible clinical chemistry tests is extensive and their selection requires careful consideration. At a minimum, the protocol should include assays that test proper electrolyte balance, carbohydrate metabolism, and liver and kidney function. Additional tests may be included depending on the specific requirements of the study, which in turn depend on the device being evaluated.

Clinical pathology testing is easily performed for such species as the rat and dog, which provide adequate blood volumes for analysis. Smaller species such as the mouse may not provide adequate blood volume from an individual animal for both hematology and clinical chemistry assays and, thus, mice are not usually selected for chronic and subchronic studies. Samples for clinical pathology tests should be collected periodically from the living animals, so that changes in each individual animal's organ systems can be monitored over the entire course of study.

Postmortem analyses include gross observations at necropsy, organ weighing, and a microscopic examination of selected tissues. The types of tissues collected can be quite extensive and can vary from a few select organs to all types of tissues and organs and the entire animal carcass. It is important to be able to correlate microscopic findings with the clinical condition of the individual animal.

CONCLUSION

The purpose of systemic toxicity studies is to evaluate the potential adverse effects of chemical extractables from medical devices on organ systems throughout the body. The ISO 10993-11 standard permits considerable freedom in the design of studies intended to explore such effects. Study protocols should be based on those taken from classical toxicology evaluation of drugs and other chemicals but must be modified to accommodate the solid components of medical devices. Considerable care must be given to the design of subchronic and chronic studies to make certain that they provide assurance of the device's safety. In general, it is anticipated that those medical device materials that have been tested appropriately will produce no significant adverse effects on organ systems.

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