A Practical Guide to ISO 10993-11: Systemic Effects

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Created 07/01/1998 - 03:00

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Posted by mddiadmin on July 1, 1998

Systemic toxicity studies address the effects of chemicals that migrate from a device into a patient, where they may exert adverse effects on vital organs.

Note: This article is part of a continuing series on ISO 10993. Earlier articles discussed materials characterization[^6], cytotoxicity[^7], irritation testing[^8], and sensitization testing[^9].

Part 11 of the set of international biocompatibility standards known as ISO 10993 discusses methods for evaluating the potential adverse effects of medical devices on patient organs and tissues that are remote from the site of contact. It is concerned, for example, with the effects that any chemicals released from a device material may have on behavior, general health, and target organs such as the liver, heart, kidneys, and brain. The standard does not provide detailed protocols for studying systemic toxicity; instead it cites various methods, primarily for the study of chemicals, that have been published in other international standards, national standards, directives, and regulations by such organizations as the Organization for Economic Cooperation and Development, the American Society for Testing and Materials, the U.S. Environmental Protection Agency, the U.S. and European Pharmacopeias, the American National Standards Institute, and the U.S. FDA. The referenced methods that were written for drugs and other soluble chemicals must be modified for testing insoluble medical device materials.

For some types of devices, actual material or product samples may be evaluated, usually by implantation in test animals, but in most cases, tests are performed using appropriate fluid extracts. Mice and rats are generally used in systemic toxicity studies, although rabbits, dogs, and other species of laboratory animals may be used for specific products.
ISO 10993-11 identifies systemic toxicity test methods that call for various routes of sample administration: topical or dermal, inhalation, intravenous, intraperitoneal, and oral. The standard also categorizes adverse effects as acute, subacute, subchronic, and chronic. Acute effects occur within 24 hours after a single dose or repeated doses are delivered to the test animal, and subacute effects appear within 14 to 28 days of delivery. Longer-term studies that continue for 90 days or for up to 10% of an animal's life span are considered subchronic, and those that continue for longer than 10% of an animal's life span are considered chronic. The investigator must select both the route of administration, which should reflect the intended use of the device, and the duration of the study based on information taken from ISO 10993-1, "Guidance on Selection of Tests," which FDA has adapted as blue book memorandum #G95-1.

TESTS USING FLUID EXTRACTS

In practice, the test most commonly used to address acute systemic effects is the systemic toxicity test described in the USP and other pharmacopeias. This is a relatively simple test that depends upon visual observations of animals that have received a large dose of extraction fluid prepared under exaggerated conditions of surface area or weight to volume. Saline or oil extracts of the potential device material are prepared under standard conditions and single (50-ml/kg) doses are administered by intravenous (saline) or intraperitoneal (oil) injection to groups of five mice, which are then weighed. Control mice are injected with extraction fluids alone. For the next three days the mice are observed for adverse signs, such as convulsions or prostration, and may be weighed daily. Conclusions regarding the material's toxicity are based upon significant differences between the test and control groups.

Additional information can be obtained from acute systemic toxicity studies by adding steps to the protocol, such as collecting terminal blood samples and performing routine hematology and serum chemistry tests or collecting representative tissue samples for microscopic examination by a pathologist as part of a gross necropsy. These protocol additions are generally reserved for studies lasting longer than three days and involving repeated dosing or constant exposure to an extract or device.

Test methods used in longer-term systemic toxicity studies are much the same as acute toxicity tests, except larger groups of animals are exposed to the fluid extracts. Periodic measurements of body weight and blood tests are nearly always performed. Sometimes urine tests, gross and microscopic examinations of the implant site and of major organs, and ophthalmologic and other special exams are included as well. In a typical subacute study, groups of 10 rats are injected intravenously or intraperitoneally each day for 14 days with freshly prepared test-article extracts. Observations are made daily throughout the dosing period and at its termination.

Large numbers of acute systemic toxicity studies in mice have been conducted for medical device materials intended for many different applications. Spurred originally by the issuance of the Tripartite Guidance in 1987, manufacturers have also carried out increasing numbers of subacute systemic toxicity studies during the past 10 years. To date, however, there have been relatively few true subchronic or chronic systemic toxicity studies of medical device materials. Simple implant studies in which local tissue reactions are evaluated are not considered to be systemic toxicity studies regardless of how long the implants are in place.

IMPLANT TESTS

Although most systemic toxicity studies make use of fluid extracts of device materials, in some cases surgical implantation of the test article may be a better choice. Absorbable materials are particularly good candidates for implantation because over time tissue fluids will act on such materials, causing them to degrade, and the resulting breakdown products may cause adverse effects on various organs.

In order to ensure that there is a margin of safety built into any conclusion about a device's long-term
nontoxicity, implantation studies should use exaggerated amounts of material whenever possible. Consequently, it may be necessary for the investigator to calculate the maximum amount of material that would be implanted in a human patient and then implant multiples of that amount in experimental animals. Depending upon the amount of material to be implanted, and sometimes upon the anatomic site at which the device will ultimately be used, placement may be at intramuscular, subcutaneous, intraperitoneal, or other body sites.

PYROGEN TESTS

Some compounds derived from chemical or bacterial sources are capable of causing a fever when present in the body at sufficiently high doses. Called pyrogens, these compounds can be detected by the rabbit pyrogen test. This test consists of preparing fluid extracts of the test materials, administering the extracts intravenously to rabbits, and monitoring the animals' rectal temperatures over the course of several hours. A significant rise in temperature indicates the presence of pyrogens.

The *Limulus* amebocyte lysate (LAL) reagent test can also be used to detect bacterial endotoxins, but the rabbit pyrogen test is the standard method for detecting chemical, or material-mediated, pyrogenicity. In recent years, testing with LAL reagent has largely replaced the rabbit pyrogen test on individual production lots to confirm the absence of bacterial endotoxins on products intended for blood contact.

Bacterial endotoxins produced by gram-negative bacteria are the fever-causing chemicals most often found on medical devices. The most common source of such contaminants is the water used in the manufacturing process. Thus, it should be noted that the contamination of finished products with bacterial endotoxins is not a biocompatibility issue, but rather a manufacturing control issue.

CONCLUSION

Developed by the International Organization for Standardization to ensure the biocompatibility of medical devices, ISO 10993 consists of numbered sections that identify various techniques for the evaluation of materials. Section 11 addresses the issue of systemic toxicity and cites test methods that have been published by other organizations and governmental agencies. Depending on the nature and intended use of their devices, manufacturers can select fluid extraction tests for assessing short- (acute and subacute) and long-term (subchronic and chronic) toxicity, implantation tests, and pyrogen assays. Other sections of ISO 10993, covering such areas of concern as cytotoxicity, sensitization, and carcinogenicity, have been or will be discussed in other installments of this series of articles, which began in the January 1998 *MD&DI*.

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Continue to the next article in this series, ISO 10993-6: Implant Effects [10].

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