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A Practical Guide to ISO 10993-6: Implant Effects

Richard F. Wallin
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An *MD&DI* August 1998 Column

Implant tests can be used to assess the local effects of device material on living tissue at both the macroscopic and microscopic levels.

Note: This article is part of a continuing series on ISO 10993. Earlier articles outlined [cytotoxicity](#) [5], [sensitization](#) [6], [irritation](#) [7], and [systemic effects](#) [8] testing.

Implanting a test article inside the body of a laboratory animal is the most direct means of evaluating a medical device material's potential effects on the surrounding living tissue. Samples are cut to size, if necessary; sterilized; and implanted aseptically. Then, after a period of time ranging from weeks to months, the implant sites are examined. Attention is focused entirely on local effects that occur in response to the presence of the test material that has been in intimate contact with living tissue. Part six of the biocompatibility standards developed by the International Organization for Standardization, ISO 10993-6, "Tests for Local Effects after Implantation," presents the general considerations that must be taken into account when conducting such implant studies. It describes the selection of species, appropriate tissues for implantation, the length of time implants should remain in place, implantation methods, and the evaluation of biological responses.

THE RABBIT TEST MODEL

Although ISO 10993-6 mentions the use of mice, rats, and guinea pigs, the rabbit, because of its size and ease of handling, has long been the animal of choice for implant testing. Indeed, the rabbit model described in the standard is similar to that called for in several national pharmacopoeias. In this model,

test and control materials are cut into approximately 1 x 10-mm strips and placed in the lumens of 15–19-gauge needles. The samples may be sterilized either before or after they are loaded into needles, but the method of sterilization should be the same as that used on the final product to ensure that effects of the sterilization process on the material are taken into account.

After the rabbits are anesthetized and their skin shaved and prepared, four test samples are implanted in the paralumbar muscle on one side of the back and four plastic negative control (known nonreactive) samples are placed in the muscle on the opposite side. To evaluate materials used for short-term implants, local tissue response is assessed after 1, 4, and 12 weeks. For long-term-use tests, intervals of 12, 26, 52, and 78 weeks are specified. Three or more animals are required for each test interval. Guinea pigs or other small rodents may be used in place of rabbits; however, in order to have enough sites to evaluate in small species, more than three animals per test interval may be required. Recommended intervals may also vary somewhat if species other than rabbits are used.



Figure 1. Low-power micrograph of an intramuscular implant site showing minimal irritant response to a negative control material.

At the end of each specified interval, each implant site is examined with the aid of a low-power lens and the size of the capsule surrounding the implant is recorded. Reactive materials may produce a capsule that extends for 2 to 4 mm, while negative control materials generally produce no visible capsule at all (Figure 1). The implant is then removed (in most cases) and the tissues processed for histopathological examination. At the microscopic level, the nature and extent of cellular reaction to implants can be evaluated and scored. Severe reactions are marked by the increased presence of inflammatory cells and the death of muscle cells surrounding the implant (Figure 2). Evaluations should take into account the relative reactivity of the test and control materials.



Figure 2. Low-power micrograph of an intramuscular implant site showing a severe irritant response marked by cellular death and the presence of numerous inflammatory cells.

ALTERNATIVE TECHNIQUES

Most material samples are implanted in skeletal muscle, but ISO 10993-6 also recognizes that, because of their size and shape or the device's intended use, some samples may be implanted in subcutaneous tissue or in bone. Although such a requirement is not mentioned in the standard, it can also be useful to implant materials in or adjacent to the specialized tissues with which they will be in contact in clinical use. Thus, cerebral shunt materials could be implanted in the central nervous system and intraocular lenses in the eyes of laboratory animals.

For most materials, it is not necessary to include a positive control in the implant test protocol. However, some materials induce an intense foreign-body response that is considered quite "normal" for that material. In such cases, test results should be evaluated in light of the intended clinical application and in comparison with the response to a similar product already in clinical use. The standard recommends that a reference control, such as an appropriate metal, ceramic, or fabric, be implanted in the test animals in addition to the standard plastic negative control.

Another frequently used option is surgical implantation rather than the needle placement method described above. This approach is needed when it is not possible to trim a test article small enough to place it within a needle. During the surgery, small pockets are made by blunt dissection into muscle or subcutaneous tissue, the sample is introduced, and the layers of tissue closed in a routine fashion.

As mentioned earlier, the implanted materials are usually removed before local tissues are prepared histologically for microscopic examination. This is done because the microtome blades used to cut thin sections of samples embedded in paraffin are unable to cut hard, dense plastic or metallic implant materials. For some implants, however, especially those in bone, the material-tissue interface is of special interest, and this area may be lost during implant removal. For such cases, methods are available for embedding tissues and implants in a dense plastic matrix, cutting the embedded sample with a diamond saw, and then grinding the sample until a suitable thin section is obtained with the tissue-material interface preserved (Figure 3).



Figure 3. Low-power micrograph of a dental implant in bone. The specimen, including metallic implant, was embedded in plastic, cut with a diamond saw, and then ground to a thin section.

Implant tests are most often performed using solid samples. If a medical device material is in the form of a powder, gel, or paste, it may be possible to coat an inert reference plastic or stainless steel with the substance and use the standard test model. Such test materials can also be injected—with a dose of 1 ml per site, for example—and USP strips implanted using needle placement to aid in locating the test sites. As an alternative, some of the test material can be placed within an inert tube, which is then implanted, and tissue reactions can be scored at the ends of the tube where the test sample contacts living tissue.

CONCLUSION

The test procedures described above and detailed in ISO 10993-6 are for evaluating the local tissue response around a medical implant, not the potential systemic effects of the device material. While implantation may sometimes be the selected dosing route for systemic studies, such tests require a completely different protocol, which was discussed in our recent article on [ISO 10993-11](#) ^[8] (*MD&DI*, July 1998).

Richard F. Wallin, DVM, PhD, is the company president and Paul J. Upman, PhD, is a senior scientist at NAMSA (Northwood, OH).

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