A Practical Guide to ISO 10993: Part 1—Introduction to the Standards

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With so many versions of "harmonized" standards for the biological evaluation of medical devices, a fresh look at the basics might help clarify the issues. Note: this is the first installment of an ongoing series of articles dedicated to ISO 10993. Part 2, Materials Characterization, is also available for on-line reading.

ISO 10993

For nearly 10 years, Technical Committee 194 of the International Organization for Standardization (ISO) and its various working groups have been developing the documents known collectively as ISO 10993, a set of harmonized standards that address the biological evaluation of medical devices. During most of that period, the U.S. device industry has operated according to the Tripartite Guidance for medical device biocompatibility, which was introduced in 1987. That guidance was replaced in July 1995, when FDA issued its own version of ISO 10993-1, "Guidance on Selection of Tests" as a blue book memorandum. Currently, therefore, the status of globally harmonized standards for the biological evaluation of medical devices is as follows: those ISO 10993 standards that have been issued by ISO are used throughout Europe; the FDA version of ISO 10993-1 is used in the United States; and in Japan, even though ISO 10993 has been formally accepted, the "Japanese Guidelines for Basic Biological Tests of Medical Materials and Devices" favors certain test methods to evaluate specific categories of biological effects.

THE ISO 10993 STANDARDS

Technical Committee 194 meets annually in the spring to review progress made on the various 10993 standards and to chart the course for the coming year. Recent meetings were held in Stockholm in 1996 and in the UK city of York in 1997; the 1998 meeting will be held in the Washington, DC, area. To date, 12 ISO 10993 standards have been issued by the committee:
With the exception of 10993-2, all of the standards listed above are accepted European standards. Parts 3, 4, 5, 6, 10, and 11 have been published in the *Official Journal of the European Communities* and are considered harmonized standards, and it is expected that a recently revised version of ISO 10993-1 will also be accepted as a harmonized standard.

Two other standards are currently under review in draft form: ISO 10993-13, "Identification and Quantification of Degradation Products from Polymeric Medical Devices" and ISO 10993-16, "Toxicokinetic Study Design for Degradation Products and Leachables." In addition, Working Group 14 has written a preliminary draft document dealing with the characterization of materials, a subject that is expected to receive considerable attention in the coming year as it relates to biocompatibility evaluation. Working Group 15, on a strategic approach to biological assessment, was organized to provide overall guidance and advice to TC 194 and to promote internationally uniform application of the standards. Its goal is to minimize the amount of testing that is needed and to optimize the biological safety evaluation of medical devices. This working group is not charged with developing a standard.

The fundamental principles of toxicity evaluation expressed in ISO 10993-1 (and in the Tripartite Guidance) provide excellent guidelines for considering the safety of medical devices. These seven principles can be summarized as follows:

1. Materials should be characterized to provide an understanding of formulation, potential impurities, and extractables, and to provide the basis for specifications.

2. Leachable chemicals and degradation products should be considered in evaluating the toxicology of a device.

3. The availability of chemical extractables and degradation products to the patient when exposed to the device should be considered in designing testing programs.

4. Testing should be conducted according to good laboratory practices and evaluated by competent, informed persons.

5. Full experimental data should be made available to reviewing authorities.

6. Changes in the composition of materials, manufacturing practices, or intended use of the device should be evaluated with respect to possible changes in toxicological effects to patients.

7. All relevant data, including information from nonclinical sources, clinical studies, and postmarket
experiences, should be taken into account when evaluating a device.

**FDA'S BLUE BOOK MEMORANDUM**

In May of 1995, FDA issued blue book memorandum #G95-1, titled "Use of International Standard ISO 10993, 'Biological Evaluation of Medical Devices'—Part 1: Evaluation and Testing." The agency then began using this guidance in place of the Tripartite Guidance for all premarket approval and 510(k) submissions received on or after July 1, 1995. The blue book memorandum adopted ISO nomenclature for device categories, included an FDA-modified flowchart designating the type of testing needed for each device category, and made several modifications to the testing requirements outlined in ISO 10993-1, adding various requirements in several device categories.

Device manufacturers in the United States should use this blue book memorandum to determine which kinds of biological effects are of concern for the materials in a particular device, based on the nature and duration of the product's end use. Such effects can include sensitization, irritation, hemocompatibility, various other types of toxicity, and reproductive or developmental changes. In all, 12 categories of potential biological concerns are identified in both the memorandum and ISO 10993. Once categories of concern are determined, various sources of information can be used to confirm that each of the effects has been adequately addressed. Safety data from previously studied devices that used the same materials, data and literature obtained from vendors of raw materials or component parts, and data resulting from prospective studies of the device in question can all be drawn upon. If prospective testing is required, the various ISO 10993 standards can be used as a source of suitable laboratory test methods. These methods, their principles, and their use will be the subject of future articles in this continuing series.

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Continue to Part 2 of this series, ISO 10993-14: Materials Characterization [4].

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[1]