How FDA's New Biocompatibility Testing Guidance Could Affect You

The new draft guidance is the most expansive presentation of testing standards for the medical device industry in over 18 years.

THOR ROLLINS

In April 2013, FDA released a draft guidance for industry and FDA staff titled "Use of International Standard ISO 10993, 'Biological Evaluation of Medical Devices Part 1: Evaluation and Testing.'" Meant to replace FDA's 1995 G95 document, the new draft guidance document is the most expansive presentation of testing standards affecting the medical device industry in over 18 years.

In the past, performing medical device testing was like checking off boxes. Neither the device type, type and duration of contact, nor materials mattered. While G95 was used as a kind of checklist, the new guidance teaches testing professionals how to change materials or how to view testing in a more scientific way. It puts more emphasis on scientific analysis, thus compelling professionals to have more knowledge and background about the tests they perform. In addition, it contains good ideas on how to justify biocompatibility testing—specifically animal testing—and presents ways for limiting the use of such tests for certain devices.

While many of the ideas contained in the new guidance document have appeared in FDA response letters over the past two years and more, it also incorporates changes that are new to the medical device industry.

Test for All Types of Exposures

The first such change is that devices subjected to multiple types of exposures should be tested for all of them. For example, if a short-term drug delivery device or IV bag features a long-term patient access port through which multiple devices might pass, both the port and the device itself should be evaluated.

In the past, some device manufacturers performed tests on long-term-contact devices that incorporate both short- and long-term components, relying on the worst-case scenario. But such tests are based on surface area, and the greater a device’s surface area, the more volume it has. By testing both short- and long-term components, the material’s testable surface area increases. If the short-term parts of the device are nontoxic and the long-term parts are toxic, the increased sur-
What It Covers
FDA’s new biocompatibility testing draft guidance document covers the following:

- Cover colorants and other chemical compounds.
- Test plans, final device approvals.
- Organ-specific devices.
- Master files.
- Good laboratory practices for in vivo and in vitro testing.
- Chronic toxicity and carcinogenicity testing for permanent devices.
- Representative coupon devices.
- Failure options.
- Sample preparation.
- Prolonged-contact devices.
- Cytotoxicity.
- Hemocompatibility.
- Implantation criteria.
- Testing justification.

For more detail about the guidance and what it will mean for medical device manufacturers, check out the article “How the New FDA Biocompatibility Guidance Could Affect You” on www.mddionline.com.

face area will skew the test results. Thus, it’s important to separate the two types of components so that the surface area of the safe materials does not obscure that of the toxic materials.

Conduct Extract Tests on All Components Separately
Another change in the new draft guidance document stipulates that if a device includes components that contact the body for different lengths of time, such as an implant and its delivery system, extract tests should be conducted on the components separately. For example, a stent delivery system cannot be tested together with the stent.

The document states that “implants, as well as sterile devices in contact directly or indirectly with the cardiovascular system, the lymphatic system, or cerebrospinal fluid, regardless of duration of contact,” should meet pyrogen limit specifications. In the past, guidance, especially from the U.S. Pharmacopeial Convention, stressed that such implantable devices should undergo limulus amebocyte lysate (LAL) testing. A pyrogenicity test, or a test for fever, the LAL test specifically looks for a pyrogen called endotoxin, a compound found in Gram-negative bacteria cell walls. Whether all implants—not just those that make contact directly or indirectly with the cardiovascular system, the lymphatic system, or cerebrospinal fluid—have to undergo LAL testing is still unclear.

In the subsection on pyrogenicity, the draft guidance recommends that, regardless of contact duration, material-mediated pyrogenicity should be assessed at 50°C or higher (except in the case of heat-labile or heat-sensitive materials) using the rabbit pyrogen test. While this statement makes sense from a scientific standpoint, why does FDA single out the rabbit pyrogen test if it wished to stress that devices should be extracted at 50°C where possible? Because testing involving prolonged contact at 50°C or higher is already addressed elsewhere in the document, it would appear to be redundant here unless FDA is concerned specifically about using higher temperatures in the rabbit pyrogen test.

Use the Mouse Lymphoma Test for Genotoxicity
In the past, FDA preferred that devices be tested for genotoxicity using the mouse micronucleus, Ames, mouse lymphoma, or chromosomal aberration assay. The new guidance document has settled on the mouse lymphoma test because it detects the broadest set of genotoxic mechanisms associated with carcinogenic activity. However, contradicting data suggest that the chromosome aberration test can detect a broader set of genotoxic mechanisms. In fact, Japanese experts presented data three years ago indicating that the chromosome aberration test might be the most sensitive genotoxicity test. Thus, more guidance is required in this area.

Devise a Meaningful Test Outline
Of all the changes, “Initial Evaluation Tests for Consideration,” Table 1 in the new guidance document, may have the greatest impact. In G95, the table contained dots to designate required tests and diamonds for others that may be applicable, enabling an FDA reviewer to require the additional tests, depending on the device.

Emphasizing the importance of the tests designated with diamonds, the new document states, “These additional evaluation tests should be addressed in the submission, either by inclusion of the testing or a rationale for its omission.” In the spirit of not treating the guidance document as a checklist, this table highlights the need to evaluate each one of these tests carefully, addressing them in the submission either by way of testing or by justifying the decision to forego testing. The new draft document puts greater emphasis than G95 did on the importance of knowing the scientific rationale behind the tests that are performed and devising a meaningful test outline for the device.

A Reference for Manufacturers
FDA’s new biocompatibility draft guidance marks the most comprehensive summary listing of testing standards affecting the medical device industry. By codifying these standards in a single document, FDA has enabled medical device manufacturers and testing facilities to reference them in order to perform such tasks as setting up a test design or evaluating the impact of a failure. While these ideas are familiar to many biocompatibility testing experts, their appearance in the draft guidance increases their impact.

Thor Rollins is in vivo biocompatibility section leader at Nelson Laboratories Inc. Email him at trollins@nelsonlabs.com.