A Sensible Approach to Biocompatibility Testing

Proving that medical products will remain biologically inert during use doesn't have to be complicated.

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In the early 1980s, implantable devices designed to replace and repair damaged temporomandibular lower jaw joints were introduced. Some of these devices were coated with a Teflon-carbon or Teflon-aluminum oxide fiber composite, known commercially as Proplast, to provide smooth articulation. They came to market through the 510(k) clearance process.

It was soon discovered that Proplast tended to fragment in the patient's jaw over time. The resultant powderlike debris lodged permanently in the patient's body and caused a wide range of painful and debilitating complications. Both the device manufacturer and FDA issued safety alerts in May and December 1990, the inevitable product liability suits were filed, and the manufacturer went bankrupt. To this day, some patients still suffer complications from Proplast devices.

After the Proplast debacle, FDA became more vigilant about biocompatibility issues. Within internationally recognized standards and guidance documents, the agency has defined a long list of detailed tests that manufacturers should conduct. Yet, despite the importance that FDA places on proof of biocompatibility, the agency does not require or even encourage companies to conduct unnecessary testing.

During product reviews, FDA often accepts a combination of existing information and limited new testing. It will only utilize this approach, however, when the manufacturer provides a device's materials of manufacture; patient and user contact routes (and durations); previous use in other, similar devices; and information about how the manufacturer's specific production process might affect the materials differently from other manufacturers'.

What Is Biocompatibility Testing?

The issue of biocompatibility comes down to whether a device is likely to remain biologically inert the entire time it is in contact with patients or users. One concern is whether the device materials or any substance that could leach out. If a substance could leach out, would it have an adverse effect on either the patient or user?

These assessments include tests to determine whether the device's materials contain substances that are toxic to cells, including blood cells; irritate the tissues they touch; cause unexpected immunological or allergic reactions; affect the patient's physiological systems; or increase risks of cellular mutations or cancer. Briefly stated, manufacturers need to provide evidence that their devices do not contain materials or substances that could harm patients during initial use or over time.

For many devices, like permanently implanted temporomandibular joint replacements or cardiac pacemakers, FDA also requires that manufacturers test whether the patient's body could interact with the device in a way that affects its performance or harms the patient. Even if the device does not contain substances directly harmful to patients, the patient's body might produce cells or substances that degrade the device or oxidize electrical connections.

There is also the potential to destroy bone surrounding the device. Such interactions between the patient and the device may limit the device's useful life, increase risks to patients by requiring

more surgeries, and cause a patient's original medical condition to recur or worsen.

To help manufacturers understand device biocompatibility and testing requirements, FDA relies on two documents. The first is an internationally recognized standard, ISO Standard ISO-10993-1:1997, "Biocompatibility Evaluation of Medical Devices—Part 1: Evaluation and Testing." The second is the May 1, 1995, Blue Book Memorandum #G95-1, "Required Biocompatibility Training and Toxicology Profiles for Evaluation of Medical Devices." Both documents specify a long list of biocompatibility tests and a variety of different "exposure conditions" that manufacturers should evaluate in determining which biocompatibility tests to perform.

These documents, however, do not entirely reflect FDA's actual practice. Despite the daunting list of required tests, it is possible to obtain FDA's agreement to omit some or all of them if the necessary information already exists. The steps discussed below may help in negotiating reduced testing requirements with FDA.

What You Need to Know

To understand what biocompatibility tests or information FDA will require, as outlined in the ISO standard and FDA's Blue Book Memorandum, manufacturers need to know

- The identity of the patient- and user-contact materials.
- The length of time that the device will be in contact with the patient and user.
- The tissue, organs, or structures of the body that the device will touch.
- The likelihood of reexposure of the patient to the device in the future.

For example, if a manufacturer is developing a new kind of suture clip or stent for placement in the intestines using a laparoscope, that company needs to decide which materials will be used to make the clip or stent (e.g., metals or plastics) and also what materials will be used to make the laparoscope. If the laparoscope has an eyepiece through which the surgeon looks, the eyepiece likely will contact the surgeon.

CERTIFICATION OF THE BIOCOMPATIBILITY OF *[MATERIAL]* (A SAMPLE)

I certify that *[component]* of *[Company's name and the new product name]* is constructed of *[material]*, which, to the best of my knowledge, is the same material that is used in the *[component]* of *[the name of at least one device with the same intended use that has received 510(k) premarket clearance and the name of the manufacturer]*. I also certify that, to the best of my knowledge, the *[material]* that is used to construct the *[component]* of *[new device name]* is processed and manufactured in the same manner as the *[material]* that is used in *[component]* of *[predicate device identified above]*. Thus, the biocompatibility of *[material]* has been demonstrated by the premarket clearance of *[the 510(k) cleared product identified above and its 510(k) number]*.

In this example, the manufacturer also will need to understand the length of time that the patient (and user) will be in contact with the device. If a worst-case estimate is that the procedure takes two hours to complete, the duration of exposure to the laparoscope will be two hours. However, if the clip is intended as a permanent implant, the patient will be exposed to its materials for the remainder of his or her life. The organs and tissues exposed to this sample device would include the user's skin surrounding the eye (contacting the eyepiece); the patient's skin, musculature, fascia, and peritoneum (for the laparoscope); and the intestinal mucosa (for the clip). If the population of patients receiving this treatment has a high likelihood of retreatment, the manufacturer also will need to incorporate multiple device exposures into the biocompatibility testing plan.

Armed with this information, the manufacturer can review the ISO standard and Blue Book Memorandum to identify what information FDA will require. For example, FDA defines three different routes of exposure: external contact devices that touch the surface of the skin, mucosa, or "breached or compromised surfaces;" external communicating devices that touch the blood pathway indirectly, through either tissue/bone/dentin or circulating blood; and implant devices that touch either tissue/bone or blood.

Similarly, FDA defines exposure duration within the categories of limited exposure (i.e., exposure of less than 24 hours), prolonged exposure (i.e., exposure between 24 hours and 30 days), and permanent exposure (i.e., longer than 30 days). Within each of these categories, specific tests are listed for which FDA expects manufacturers to provide information. It is important to note, however, that "providing information" does not necessarily mean that a manufacturer must conduct new, independent testing.

In lieu of certification, FDA often allows manufacturers making new devices from materials with long histories of use in similar devices to conduct a limited set of biocompatibility tests.

Reducing the Testing Burden

One approach that may limit new testing requirements is biocompatibility certification. This approach is not spelled out in the Blue Book Memorandum. Nonetheless, FDA will often accept a certification to the biocompatibility of human-contact materials where the manufacturer can show that identical materials with identical manufacturing processes have been used in other legally marketed devices for the same exposure routes and dura-

tion of contact. This is in lieu of biocompatibility testing in accordance with the Blue Book Memorandum and ISO 10993.

FDA has not issued any recommended or required certification format. The certification presented in the sidebar is a format that we developed and have used successfully in past 510(k) submissions.

Clearly, this approach requires manufacturers to have detailed knowledge of the device materials, their processing, and their previous use in similar devices. Not all manufacturers will have this knowledge, especially with regard to the exact manufacturing processes used for other companies' devices. For example, coronary stents manufactured of 316L-grade stainless steel can undergo a wide range of annealing, passivation, electropolishing, and cleaning processes. While the underlying material can clearly be identified, the exact surface chemistry, likelihood of surface corrosion, and durability of the device over a prolonged period of time can differ significantly depending on the specific processing and finishing steps. But this knowledge gap does not mean that each new stent manufacturer must ignore years of accumulated biocompatibility data for this material and repeat all possible biocompatibility tests.

In lieu of certification, FDA often allows manufacturers making new devices from materials with long histories of use in similar devices (but with differences in manufacturing processes) to conduct a limited set of biocompatibility tests. These include tests for cytotoxicity, sensitization, and implantation. The agency's scientific rationale appears to be that cytotoxicity, sensitization, and implantation tests are likely to detect differences in material reactivity caused by manufacturing process changes. Any change in the expected reactivity of materials detected in these initial tests likely will lead FDA to request additional testing using the entire spectrum of identified biocompatibility tests.

FDA also has stated that manufacturers following an abbreviated testing approach need to clearly document their justification for using it. For example, manufacturers should document any bench testing conducted to assess electropolishing or passivation of the stent materials (e.g., corrosion testing or surface analysis). They should also spell out similarities between the new device and the approved devices. If the manufacturer documents the company's rationale for limited testing, demonstrates that the company's stent materials conform to specifications for the limited tests, and provides the rationale and test results to FDA in appropriate regulatory submissions, then limited biocompatibility testing can be a viable approach.

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Another approach that may be acceptable to FDA is for manufacturers to justify why one or two tests only may be sufficient in place of a broad battery of tests. For example, for some materials' routes and durations of exposure, manufacturers are required to assess the potential for genetic toxicity and carcinogenicity. Such tests typically include a battery of at least three in vitro tests and one or more in vivo assessments. (Examples of these are the Ames reverse mutation test, the mouse lymphoma forward mutation test, the Chinese hamster ovary chromosomal aberration test, and the in vivo rodent micronucleus test.)

Depending, however, on the materials being tested and the manufacturer's knowledge about the reactivity of the raw materials, FDA may accept even more limited testing. For example, if the manufacturer uses materials that have been tested by their supplier and shown to comply with appropriate specifications, (e.g., *U.S. Pharmacopeia*, Monograph <88>, specifications for Class VI implantable plastics), FDA may agree to limit testing to the three in vitro tests. Similarly, a manufacturer can argue that a long history of use for the device material, together with acceptable genetic toxicity test results, reduces the need for formal carcinogenicity testing. Again, with detailed knowledge and a sound scientific justification, manufacturers can seek to persuade FDA to accept more limited testing.

Finally, if data about similar materials are not available, or if the material is novel, it is a good idea to meet with FDA to discuss a biocompatibility testing proposal. The company will have to justify the proposed program based upon information about the materials' physical and chemical characteristics and the device's intended route and duration of exposure. The point of meeting with FDA is to ensure that the proposed testing is acceptable to the agency. Otherwise, the company risks losing time and money in conducting tests that FDA does not believe are relevant or adequate to demonstrate the device's biocompatibility.

Conclusion

Understanding the characteristics of a device's materials and the ways in which those materials interact with the human body allows manufacturers to rationally select specific kinds of biocompatibility tests. While FDA's default position may be to require the broadest possible biocompatibility testing, a company's knowledge of its materials and careful scientific justification can help persuade FDA to accept a reduced testing program. By consulting with FDA in advance about the acceptability of a proposed testing program, a manufacturer can reduce regulatory uncertainty and the cost of bringing a new device to market. ■