Most medical device manufacturers must first receive approval from the U.S. Food and Drug Administration (FDA) before they can market a medical device. Device manufacturers must demonstrate that their device is safe and effective for the intended application. The tests that must be performed vary with the device, application of the device, and components of the device, such as coatings, as well as the length of time that the device may be used in a patient. To prevent delays in the FDA review process, manufacturers must ensure that they complete the necessary tests and avoid wasting time on tests that are not required or do not add to the assurance of safety of the product.

The best strategy to streamline FDA approval begins by formulating a detailed testing plan, then having the FDA review the plan. This approach permits the agency to offer guidance, if necessary. A provider of full, life-cycle testing services for medical devices, such as Nelson Laboratories of Salt Lake City, UT, can help formulate this plan to determine which tests a specific type of device may need. Many medical devices are unique and could require individualized or niche testing to get to market. The tests listed in this article are some of the most widely used.

**Biocompatibility**

Biocompatibility analyses consist of several defined tests including: sensitization, cytotoxicity, hemocompatibility, irritation, and systemic toxicity. These preclinical biocompatibility tests provide a degree of confidence about how a device will react when used in the human body. Sensitization: The sensitization test evaluates whether or not the device, or a device extract, will elicit an immune system reaction from repeated exposures. The test uses guinea pigs, the animal model that most closely mirrors the reaction of humans to an immunizing substance. The test is performed by repeatedly exposing the animals to device or device extracts followed by a rest period to allow antibody production, and then a challenge to determine the presence of antibodies. Examples of materials that can cause allergic reactions from second or subsequent exposures include detergents, solvents, adhesives, and biodegradable polymers. Initial exposure produces no response, but after the body has been exposed to an allergen, it makes an antibody that can cause dangerous, even life-threatening reactions from subsequent exposures.

Cytotoxicity: Cytotoxicity is arguably the most sensitive of the biocompatibility tests. It is a basic in vitro test that uses mammalian cells in culture to respond to any cytotoxic material present in the device or that can be extracted from the device. Cytotoxicity tests may include elution tests, which employ device extracts, or may be performed directly on cells with the agar overlay procedure. The cytotoxicity test is used as a finished device test as well as a device component screen, and is often used for monitoring each incoming lot of raw material.

Irritation: Irritation tests are performed on rabbits. Extracts of the device are injected into the skin and monitored for irritation reactions, typically redness, swelling, or both. This test allows manufacturers to determine if any toxic materials are leaching off their devices at levels that can be detected in a live mammalian system.

Hemocompatibility: If a device is designed for direct or indirect contact with circulating blood, it needs to be tested for blood compatibility. Hemolysis tests are performed by exposing the device or device extract to mammalian (typically human or rabbit) red blood cells. Blood cells and test samples are incubated together for sufficient time to allow any hemolysis to occur. The cell
containing liquid is then analyzed for the presence of hemoglobin that cannot be removed by centrifugation. If the cells were unaffected by the device or extract, centrifuging the cells from the mixture will result in little or no hemoglobin in the supernatant fluid. This is a passing result. If hemolysis occurs, manufacturers must determine if the level of hemolysis is significant. This often requires comparison of the device under test to a predicate (already on the market) product with the same claims or usage.

Based on device design and application, additional blood compatibility tests may be required; including coagulation/thrombogenicity, complement activation, implantation, systemic toxicity, cytogenetic tests such as Ames, mouse lymphoma, or chromosomal aberration tests. Devices used in specific areas of the body often need tests designed to simulate the intended use. These would include eye irritation or mucosal irritation tests.

Chemistry

Chemistry tests are usually basic and are designed to determine if the polymeric or other device component received is the one that the FDA was told would be in the device. Chemistry tests are also valuable to characterize new materials to determine the level of extractables or residual manufacturing materials present.

USP Physicochemical series: This series of tests is used to characterize leachable substances. These tests include heavy metals, non-volatile residues, residues on ignition and materials that may change the pH in the body (buffering capacity). These tests are described in the compendia and have defined acceptance criteria. Their intent is to reduce risk when employed in new applications.

Identification tests: Identification tests include Fourier Transform Infrared (FTIR) and differential scanning calorimetry (DSC). FTIR is used to confirm the identity of a polymeric material and DSC characterizes the thermal events that may be significant such as the glass transition point ($T_g$).

Packaging Validation

A manufacturer’s device master plan should consider the environment in which the device will be used. This will help to design the proper packaging. Products that will be used in an emergency vehicle normally require more robust packaging than items dispensed from a shelf pack in a clinic. Products that need to be delivered sterile to a patient in surgery need two packages so that the outer contaminated package can be removed before the inner package is moved to the surgical suite. The seal strengths of the packages should not be too low, which would result in loss of package integrity; or too high, which would cause issues with opening the package at the point of use. Devices with sharp or irregular surfaces often fail shipping and packaging tests due to wear or damage on the package material. Density, number of units per package, device mobility inside a package, and many other factors can delay the project and cause test failures. Preliminary trials, or feasibility studies, should be included in any plan. Careful attention to packaging design can minimize testing failures and prevent extra costs and lost time.

Strength Tests: Strength tests are important to make sure packaging is strong enough to protect the device from the intended environmental conditions.

Burst: The burst test determines packaging strength by pressurizing a package and measuring the pressure inside the package system until the seals or the package bursts.

Seal Peel: This test determines package seal strength by cutting and inserting a segment of the package seal into a physical test apparatus and recording the force needed to pull the seal apart. The test also determines the package’s maximum load.

Integrity, Permeability, and Stability Tests: Accelerated Aging: This test simulates the aging process, and allows a package to be evaluated prior to completion of real-time aging. The duration required for simulated aging depends on the temperature at which the products are stored.

Aerosol Challenge: This test is intended to challenge the entire package to determine the microbial barrier properties of the package. The finished, packaged device is placed in a chamber and exposed to an aerosol of bacterial spores to determine if the microbial spores can penetrate the packaging system.

Dye Migration: The dye migration test involves injecting dye into the package and placing the weight of the solution against each package seal for a specific duration. The package is examined for evidence of seal failure demonstrated by dye migrating through a seal.

Bubble Emission: Bubble emission is a visual test. The whole package is immersed in water and observed for the presence of bubbles. Evidence of bubble emission through the package is considered a failure. This test has the additional advantage of identifying where the failures occur and is often used as a test for failure investigations.

Bacterial Endotoxins

Medical devices and pharmaceutical products can introduce bacterial endotoxins to the human body through the blood, lymph nodes, or cerebral spinal fluid if they are not properly manufactured or cleaned, causing fever and potentially death.

Endotoxin-producing bacteria are dangerous to the human body whether dead or alive. Sterilization does not elim-
Medical Device Testing

Endotoxins. Medical device manufacturers must conduct bacterial endotoxin testing on their medical devices if their product will contact blood or spinal fluid. Some medical devices that do not contact blood or spinal fluid must also be tested. Examples include surgeon’s gloves and some ocular devices. This test is performed on all parts of the device that are designed to come in contact with the blood or spinal fluid. Endotoxin tests are simple, rapid, and use an enzymatic reagent to detect contamination. Endotoxin tests must also be performed on the final product after all manufacturing processes have been completed.

Sterilization

If a medical device must be sterile, manufacturers will need to define and design a sterilization process. It is most efficient to determine the sterilization mode early in the development process. Preliminary tests should be conducted to identify problems that would otherwise require a change in process or a repeat of completed tests. The best sterilization options include dry heat, steam, radiation (gamma or e-beam), ethylene oxide, and vaporized hydrogen peroxide.

Bioburden

Bioburden testing determines the number of microorganisms on devices prior to sterilization. The number of microorganisms on the device indicates the level of microbial control of the manufacturing process and can help determine which sterilization process may be required and the dose of sterilant necessary. Normally, the lower the bioburden, the lower the sterilization costs. For most sterilization processes it is also important to perform organism identification tests to characterize the organisms on a device. Knowing the types of microorganisms on a device is helpful in determining the source of microorganisms and thus how to reduce or control them.

Particulates

The FDA has increasingly been requiring particulate tests for critical blood contact (intravascular) devices. Particulate testing is advisable for all products to determine the potential particulate risk. Some manufacturers have been surprised by high particulate levels, but have been able to control them once they were aware. Regardless, most devices that have direct intravascular blood contact and all devices that have either substantial intravascular blood contact or involve an extracorporeal circuit should be evaluated for particulate counts.

Particulate tests simply quantify the numbers of particles present on the internal or external surface of a device. These tests are performed using product washes that are either counted in an automated liquid particle counting instrument or manually with a microscope.

Summary

Manufacturers should first identify the tests that they think are important to ensure that their device is safe and effective. If the product must be sterile, they should select the mode of sterilization. The proposed tests must be discussed with the FDA division that will review the submission to get feedback on the plan. They should review the test list to determine the order in which the tests must be performed. For example, biocompatibility tests must be performed on any product that has been subjected to the sterilization process. Otherwise, biocompatibility tests will need to be repeated. Often multiple exposures to the sterilization process may be necessary to account for worst-case processing situations. Packaging must be selected and preliminary tests run before bioburden and particulate tests can be performed.

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