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Testing

Emphasis On

The Big Three: Tests Manufacturers Need to Know

Product testing is a critical component in the development of a medical device. But how many engineers truly understand the importance of what are arguably the three most crucial tests for a medical device? This article reviews these three tests—cytotoxicity, sensitization, and irritation—and offers some insight that will ideally make them go more smoothly for engineers.



Thor Rollins of Nelson Laboratories

conducts a cytotoxicity test—one of the Big Three tests manufacturers need to be prepared to conduct on their devices.

By Thor Rollins

Of all the tests manufacturers need to be prepared to conduct on their medical devices, none are more important than the Big Three—cytotoxicity, sensitization, and irritation tests. Manufacturers need to understand these three tests because they must be conducted on every device before they can be sub-

mitted to the FDA.

By understanding the Big Three, manufacturers can be better prepared for a submission to the FDA and better prepared to write justifications when the tests indicate a failure.

Cytotoxicity

Cytotoxicity is the only in-vitro test of the three and can begin at any time in the development process. The test costs the least and is also the quickest of the three. The main benefit of the cytotoxicity test is that it can be used on the raw materials of the device and it can be performed before the other two tests to predict their performance. Historically, if a sample is going to fail any of the biocompatibility tests, 90%* of the time it will fail the cytotoxicity test first.

It is a test done at the cellular level and measures any cytotoxic leachables that can be drawn out of the device. The test uses L929 cells (mouse fibroblast cells) to predict toxicity of a

medical device sample. During the test, an extraction of leachables from the device is placed in extraction media. The media is placed on the L929 cells to see how they react to the extract. If there are cytotoxic leachables in the extract, they will interact with the cells.

One of the first items analysts look for are dead cells—an indication of toxicity. To predict the cytotoxicity of the device, analysts look for granules, apoptosis, and a confluent monolayer of cells over the plate. This helps determine cell health and, ultimately, cytotoxicity levels. Some of the sensitive cytotoxins it looks for include metals, colorants, detergents, mold release residues, and adhesives.

Sensitization

Sensitization testing is an in-vivo test that looks for delayed hypersensitivity or Type 4 hypersensitivity. The test determines if a device causes a reaction with repeated exposure. The test looks for a delayed reaction by the immune system (e.g., redness and swelling). The test takes longer to perform and requires careful planning to

*Based on historical test data generated from NLI.

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avoid additional costs and wasted time.

To better understand how sensitization testing works, let's look at poison ivy. The first time someone touches poison ivy, they do not have a reaction. However, the body creates antibodies to protect itself from the poison ivy antigens. The next time someone is exposed to poison ivy, the body reacts to it with redness and swelling.

The sensitization test evaluates Type 4 hypersensitivity by inducing and re-exposing a medical device or device extract to see if it causes redness and swelling with repeated exposure. The redness and swelling is scored between 0-3. Zero is the same as an extraction

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solution with no reaction. The test measures both non-polar (oil-based) and polar (water-based) extractions, which leach off different kinds of toxins.

Sensitization testing is the longest of the tests and should be done only if there is confidence in the cytotoxicity test results. It takes nine weeks to complete and should be conducted on the final product. Having a high level of confidence in the materials and processing before testing limits the potential for failures. The consequences of failing this test can impact both the budget and the timeline to meet FDA regulations.

Irritation

Irritation testing is similar to sensitization testing, but it tests Type 1 sensitivity or an immediate irritation reaction. The test reveals whether the device would create an immediate reaction when it contacts a patient's body.

Soaps and detergents are two examples of substances on a medical device that can cause an immediate reaction. Plasticizers—chemicals used to soften plastics—are toxic if they are leaching off of a medical device. The irritation

test can let engineers know if toxic levels are leaching off of plastic products. The test takes longer and costs more than cytotoxicity, but less than the sensitization test.

It's important to gain a clear understanding of these tests so engineers can look for items that aren't sensitizers, cytotoxic, or irritants from the very beginning of the manufacturing process. With just a little background, engineers can:

- Know the importance of each test and why they have to be performed. It helps to know what each test is designed to detect and the acceptance standard for each.
- Get an idea of the potential dangers in each test and what impact the device may have on the test.
- Know what the reaction to the patient may be based on the results of a failed test. Is it something that can be justified? Do the materials and processes used need to be reevaluated? Can a risk assessment on the toxicity of the device be made or does the toxicity need to be eliminated?

Risk Assessment

Due to the nature of biocompatibility testing, eventually failures will occur. It is important to know what to do when failures arise and how to develop a risk assessment.

If a device fails a test, first realize that it isn't the end of the world. The proper steps are to first make sure the test was conducted properly. Was the right product used? Occasionally, an R&D unit of the device is inadvertently sent to the testing facility—a device that hasn't been cleaned, sterilized, or cured properly.

If the device was properly tested, the toxicity of the device must be confirmed. To accomplish this, additional testing of the failed device is required. Multiple re-tests may be necessary to confirm the device is actually toxic. If multiple failures occur on the re-test, the engineer needs to be prepared to find and fix the problem in the product or justify the failure in order to pass FDA requirements.

In some cases, the benefits of a device outweigh the risks associated with biocompatibility failures, justifying the risk of some toxicity. This should be carefully evaluated and justified as part of the regulatory submission.

Conclusion

The more known about the Big Three, the more prepared engineers will be to work with an FDA reviewer. Keep in mind, FDA reviewers have to look at so many different items, they can't always be experts on a product. They rely on the standards and the expertise of the manufacturer. The biggest mistake manufacturers make is not providing any information about the testing—even ignoring a failure without any investigation. This will get the company nowhere with the FDA.

If, on the other hand, the engineers understand the tests, they will be better prepared to present information to justify the results and build a case for a risk/benefit analysis. If they are well prepared with the details, FDA is more likely to understand and evaluate the justification.

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For additional information on the technologies and products discussed in this article, see *MDT* online at www.mdtmag.com or Nelson Laboratories at www.nelsonlabs.com.



See a video of Dan Floyd, Sterilization Section Leader at Nelson Labs, as he walks the viewer through the validation process for a medical device using EtO sterilization for the first time at MDT's YouTube page:

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