



WEBINAR – PART II

The Big Three: Cytotoxicity, Sensitization & Irritation Testing

Thor Rollins' Presentation



Irritation Testing

The next test we're going to talk about really quickly is irritation. Irritation is just a quick kind of immediate allergic response from some kind of reaction. So it could be a chemical. It could be detergent, or anything that's an immediate response. Also, different parts of the body have different sensitivities to these different irritation actions. So, the one most of us run historically for most devices is Intracutaneous. This is extracted just like we do for the cytotoxic tests, but this one's extracted both in a polar and non-polar extraction. So Ocular and oral, like I mentioned before, injected intracutaneously, so just under the skin looking for irritation.

Sensitization

Sensitization is going to look a lot like irritation. Actually, it looks exactly like irritation. You see the same redness and swelling, but the difference is how your body gets there. For irritation, it's an immediate response based on whatever the contact is with the chemical touch. For sensitization, it's called delayed hypersensitivity or type 4 hypersensitivity. It's a cellular based reaction.

So the next time you touch it, you break out the greatest example here that everybody uses, poison Ivy. The first time you contact poison Ivy, nothing happens. You don't remember. You don't even realize you touch the plant, but then next time, or the third time you touch it, you break out. So that's what we're looking for.

There are historically a couple of test methods that we can run to look for this. It's Guinea pig sensitization, there's a Local Lymph Node Assay (LLNA) and the Buehler method. Most everybody today runs the Guinea Pig Maximization.

What If I Fail a Test?

I don't want you guys to think of these tests as checkboxes. Now, I know it's easier to even do your risk assessment and just say, we're going to do those three tests. That's fine. But I want you to understand the standard does want you to evaluate risks. If you're using a piece of stainless steel or titanium, and you're having a cleaning validation to show that you're cleaning every process out there, it's possible.

They are trying hard to get rid of animal tests, but it's a lot of work to try to reduce or eliminate these animal tests. And one of main points here is to understand the risks effectively and not automatically jump to an animal test, but if you are going to do the testing, there's a chance you could fail specifically, like I said, with cytotoxicity.

The first step is just to confirm the procedure, the next is to confirm the results. And this is a little bit easier with cytotoxicity testing because it's cheaper. But you also don't want to do just one retest because

if you have one pass or one fail that doesn't really give you anything to go on. So, I always like to do at least three retests. The other thing I'd like to do is break down this device into its components and not just as components, because I want to keep the extraction volume of the finished device, consistent with its components. If the device is made up of four different components, and one of them has 90% of the surface area. I want to make sure that my volume is consistent. So I will put that 90% in the same extraction volume as the finished device and the 5%, 2%, whatever the other three are.

You can also do chemistry. This has been very useful, and this helps with metals. So like I said, metals are a popular source of cytotoxicity, and it's possible to run an ICPMS or OES looking for metals coming off your device and be able to identify no cytotoxic metals at high levels.

Conclusion

I want to just say one last thing, we talked about these tests, what you have to do, and remember they're not the biological end points you have to assess, right? Don't think of these as tests and think you have to run there. You have to worry about sensitization, you have to worry about irritation, and you have to worry about cytotoxicity or any of the other biological endpoints you may have based on your device's use. So, yeah, there's one way to assess, that is to test them for those endpoints, but you really need to understand the risk of each of these biological endpoints and see if your device has gaps in that risk assessment. And then how are you going to mitigate them? That's really the approach here. And so, that's the way the new standards are written and that's the way the new FDA guidance documents are written. And I know it's easier to step back on the testing, but we really want to encourage people to start with a risk-based approach.

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