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WEBINAR – PART I

The Big Three: Cytotoxicity, Sensitization & Irritation Testing

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Past Approach

The concept here is about the type of contact and how you will evaluate what testing is needed for your device. You must understand how it contacts the body and specifically, where it contacts the body, and for how long it's going to contact the body. That includes repeat exposure. If it contacts the body for an hour a day, but then it's being used every single day for the rest of that patient's life, you add up those hours, then that determines the contact time. Go down, look at the columns, decide which column it is. Decide on the contact duration and just do those tests.

The problem with this approach is that you don't have to understand the materials that your device is being constructed with. All you have to do is pass these tests. You didn't have to know anything about the color it is, you didn't have to know anything about the adhesive that you're using, or the process residual, as long as it passed an animal test, you felt good about it. And these engineers don't have to understand the testing at all; they just paid for it and sent samples in and got results and then dropped those reports onto the desk. That was the best approach, and because of this, we changed it with the new standards, mostly because we realized that these old animal tests are not as protective as we thought they would be.

Biocompatibility Evaluation Endpoints

We still have the big three, Cytotoxicity, Sensitization, and Irritation, but we'll talk about that here in a moment. There is a second part of the chart where you can see some of the considerations they have in there.

You will need to write a document assessing the materials and chemists, and the residuals of your device before you do the testing. You have to try to understand what the benefit is. So it doesn't tell you to test anymore. It's not a checkbox. You have to evaluate those endpoints. You must evaluate based on your physical or chemical information, and if there's still a risk for Cytotoxicity, or if there's still a risk for senses. Based on that endpoint, you either perform or justify that end point based on the information you gathered.

Risk Management for Biocompatibility Evaluations

You look at the manufacturing processes, what could leave residuals on your device? Could it be detergents, could it be mold releases, any of these things that are in the process that could be residual, and how does sterilization impact my device? Could it change the eligibility profile? These are things to think about with the manufacturing process, and you will still look at the clinical use of that device. So you consider those three things. You consider that, and the risks, then you identify those risks, and then you come up with a

plan. You develop a plan for biocompatibility, and that plan says that you're going to do the test based on your risk assessments for evaluations that addresses that risk. And that's what you justify. So this same approach from 10993 is spelled out in the FDA's guidance doc. Really this is the approach you should take when you're evaluating even these big three tests that historically have always been checked.

Material Characterization

Material characterization plays a big part in the new big three so I want to talk a little bit about material characterization. A lot of people just get some materials from their suppliers, and they say, they're checked, I've done material characterization. That's not really what we're looking for. You really want to first look to see if you want to be proactive when deciding on your materials, which means you will want to look at any testing that your supplier has done. You want to look to see if there's a history of this material being used in this product. You want to understand this and then look at those materials from a functionality standpoint, and from a biocompatibility standpoint. So those include toxicological speaking, chemically speaking, physically, electrical, morphological, all these different endpoints that you have to kind of understand when you're looking at your material characterization.

Biological Evaluation Plan – Material Characterization

Where we get this from is the supplier, so we want to have better relationships with those suppliers. Right now, our suppliers are not used to providing this type of guidance or documentation or information to you guys as medical device manufacturers. We need to change that. The first source of this is from your supplier. Have they done any testing? What testing has been done? Does it match what you need to do? What gaps are there in your risks? What kind of processing did they do it under? Did they sterilize that raw material first? Or was it non-sterile? I want to tell you, there's no such thing as medical grade, you will find medical grade components, but there's no guidance on what that means.

It's up to each individual company to kind of say, I did a cytotoxicity test, therefore I can claim this, or it's been used previously in devices and I don't think it's hurting anybody. So by claiming this clinical grade, it's not just saying that it's medical grade. The one that's standardized is a claim for USP Class VI. Now I'm not a big fan of this. It's less traditionally meant for medical devices, but it does have a place if you're looking to get some information from a supplier on a raw material. I just wanted to warn you for those of you that may see USP Class VI certification from materials, this comes from USB section 88.

Cytotoxicity

So now let's jump into the actual big three tests. The first one we're going to talk about is cytotoxicity. Each one has these little dashboards that you can go back and reference after this presentation to help you a little bit. I'm only talking about one version of the cytotoxicity test, which is involves having an elution. There are other ones that we're testing right now for the standard to try to evaluate which ones we're going to go forward with and will recommend this standard for the MEM Elution Method.

And it's a good baseline for the other tests. For example, MTT XT kind of starts similarly to the MEM Elution but just evaluates a little bit differently. We're just going to look at the MEM Elution right now. So, based on the amount of volume that we need for the device, you see the separate requirements there. You also see the turnaround time since it's a very quick test. These are not GLP turnaround times. GLP would probably be a little bit longer, about two weeks. But you're still looking at the very quick test. It also is not the cheapest by a large margin. You're looking at anywhere between 300 to 600 bucks to run this test.

This traditionally makes the MEM or the cytotoxicity test your best friend and worst enemy. Best friend, because it will be the biggest straight screening testing to look for what could be wrong. It's your worst enemy because if you're going to fail a test, this is going to be the one. In fact, Nelson labs, probably 10 years ago, took a couple of years of data and looked at where clients failed their test, and we identified that this is where the failures were 90% of the time. So if you're going to fail a test, it's likely going to be cytotoxicity.

Cytotoxicity – Grade Reactivity Description

How we score the MEM Elution is a speed score from a scale of zero to four. This is out of the USP section 87 standard. A zero is no toxicity whatsoever. 1 is we see some, but it's not more than 20% of the cells. And by the way, I'll get some people who get a 1 and they freak out. They go, "we're going to fail." And I tell them, okay, even if you have two cells that we see have issues, technically we have to call them a 1. Now that's not the case. Usually we see a few cells or something that we don't think is right, but it's a very few number, but one isn't that concerning. But even 2 is still considered passive. So 0, 1 and 2 are passing, and 3 and 4 are failing. If you get a 2, I will still recommend having some kind of risk assessment.

Stay tuned for Part #2 of this blog feature, which will be posted in the coming weeks.

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