

**Notes from Dr. Curt Scribner's presentation at the CRB1 research symposium March 23, 2013**

Curt Scribner, MD, MBA, Senior Vice President of Medical and Regulatory Affairs, RRD International, California, discussed the regulatory situation.

The FDA is asking researchers to demonstrate clinical significance, not just statistical significance, and for up to 15 years, so natural history studies are important. He talked about Lucentis, and how the ophthalmology community accepted routine intravitreal injections. So, too, may they eventually accept performing gene therapy in which a viral vector introduces a gene.

Dr. Scribner said that the FDA's "major concern is badness," and that they will focus on the 15% of patients that don't respond rather than the majority who do. FDA is concerned with adverse effects that emerge with a larger patient population, consistent manufacture, and how to objectively measure a clinical difference. A parent pointed out that kids navigate familiar rooms because they know where things are.

Clinical significance is the hardest part of any program, Dr. Scribner said. "If the drug is safe, the efficacy boundary can be lower. If there are serious safety issues, the efficacy must be very good, like oncology drugs." He then reviewed the order of events in getting a clinical trial running:

1. Orphan drug designation (<1/10,000 in Europe, <200,000 in the U.S.)
2. Fast track designation and priority review
3. Special protocol assessment
4. Pre-IND meeting

Patient-specific iPS cells for transplant will present regulatory challenges. Malignant transformations are possible if certain factors are used to start the cells. Dr. Scribner said the cells wouldn't be regulated like bone marrow transplant, so it isn't clear whether iPS cells intended as implants are drugs or devices. Their use *in vitro* (to test drug candidates) will likely come first.

Dr. Swaroop then returned the discussion to exome sequencing to reveal modifier genes, in the case of RPE65 (LCA2), which might explain the varying phenotypes among patients.

Next Dr. Scribner discussed patient registries, which FDA will require. He's working on one for Friedrich's ataxia. A patient registry requires informed consent and assent from kids under 7. An IRB (academic or independent) is required for manipulating tissues. What do we want to do with the data?

Dr. Nishina described a patient registry that's worked well for the Alstrom syndrome community. "Every 3-4 years, basic scientists and clinicians have a clinic where they bring in patients and do studies," she said. Dr. Maumenee's been maintaining such registries for years.