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Quick Pulse

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ENDPOINTS FOR OPHTHALMOLOGY TRIALS

The FDA has been holding a series of meetings to discuss appropriate endpoints for clinical trials for cancer drugs, and these will continue. Oncology is not the only division of the FDA that is wrestling with issues relating to endpoints. The issues may be more complex in oncology, but there are concerns in other fields, including ophthalmology.

The Ophthalmic Subcommittee of the Dermatologic and Ophthalmologic Advisory Committee met on September 25, 2003, to discuss the design of trials of drugs intended to delay or prevent the development of myopia. "The only endpoint in flux in ophthalmology is in the prevention of myopia," said Dr. Wiley Chambers, Deputy Director of Ophthalmics in the FDA's Division of Anti-inflammatory, Analgesic and Ophthalmologic Drug Products, Office of Drug Evaluation V, Center for Drug Evaluation and Research (CDER). "The problem there is that it hits a very large and vulnerable population, and myopia is a very slow process. It affects kids and potentially half the U.S…That meeting was just a starting point."

From 20% to 50% of the U.S. population has been estimated to have myopia. Experts have predicted that parents will "demand" myopic prevention treatment for their children if a treatment is approved by the FDA. This could result in unprecedented pediatric exposure to a chronically-administered drug by otherwise healthy children. As a result, the FDA is cautiously approaching drugs for myopia prevention.

Among the ophthalmic issues with which the agency is wrestling are:

- Genetic factors.
- Environmental factors.
- Long-term natural history of the disease. Non lens-related refractive changes occur from birth through age 30.
- Testing of children.
- Light exposure.
- Refractive correction.
- Behavioral patterns, such as the frequency and duration of close work (reading).
- The long horizon from enrollment in a trial to clinically relevant events and a relatively low absolute event rate for anything other than a simple refractive error.
- Surrogate markers. Since no long-term studies have been conducted to assess the natural history of myopia, no surrogate marker has been validated as predictive of clinically relevant ocular disease.

No other endpoint meetings are currently planned for ophthalmology. Dr. Chambers said, "There are no other endpoint issues that we've identified. We

have been pretty good at giving people specific endpoints for specific indications."

In some medical specialty areas, missing a pre-defined primary endpoint means almost certain death for a new drug application (NDA). However, that is not always true in ophthalmology. Dr. Chambers explained, "It depends on whether the primary endpoint is something we agreed to in advance or not. We have a lot of people who propose endpoints. We don't approve trials; we only permit them if we think we will learn something and if it is not unsafe. That is no assurance that we will accept those results for proof of an NDA. We frequently have had the case, for example in IOP (intraocular pressure), where sponsors are doing trials world-wide. The Europeans want a single endpoint that is no value to us because it doesn't tell us all we need to know. We care about the endpoints we think are important, whether they are primary or not. But if you pick something important for your endpoint, and you don't meet it, that is a big deal. It is not uncommon for people to pick an endpoint we don't think is legitimate, but we could approve on a secondary endpoint if we think that is important."

The length required for a trial in ophthalmology depends on the indication. Dr. Chambers said, "The timeframe is geared to the science…It is extremely indication-specific." He described timeframes for some common indications:

Anti-infectives: "Bacterial conjunctivitis is self-limiting and goes away in 14 days, so there is no reason to do longer trials."

Dry eye: "If you can show an effect in a single day, we will take that as efficacy because dry eye waxes and wanes; it is not a consistent thing. On safety, we would want longer term data, generally a year for safety, but we will accept an application before that; we just want the sponsor to continue the trial until ultimately they have that time."

Diabetic eye conditions: The longest ophthalmology endpoint is for diabetic conditions. "The DCCT (Diabetic Control and Complications trial showed that results on endpoints during the first year and a half are not reliable. If you had believed any of them -- in most people's opinion -- you would have been wrong. That trial compared IV insulin vs. standard insulin given a couple of times a day, and the group that did the best was the one getting insulin a couple of times a day, not the intensive, better controlled IV insulin. Worse control is better in the first 1.5 years. No one knows why good control is worse. And the two endpoints came together at three years…So, we said we want three-year trials because we don't want the answer wrong. We've said let's get through the period of time where you will be fooled. Anything longer than three years we will believe."

IOP. "With IOP, we've never seen a result at three months or longer that changed. We've seen shorter results that didn't bear out, so efficacy for IOP lowering is three months."

Macular degeneration: Two year data is needed. "There is some evidence things continue to change for at least two years, so we want all macular degeneration trials going on for at least two years. A sponsor can submit sooner…This is an older population (usually at least 60) and the lifespan of 65-70-year-olds is eight to nine years, so we've said a year in their life is an important change. Even if vision is maintained for a year, that is significant, so we are willing to take shorter results -- recognizing that we may say it only worked for a year."

Schirmer and corneal staining are not considered surrogate markers. They are signs, and a sign alone is not sufficient in a dry eye trial; symptom relief also is required. The most common signs in dry eye trials are: Schirmer, corneal staining, tear breakup and osmolality. Dr. Chambers explained, "Dry eye is commonly measured by objective and subjective measures. Our difficulty in dry eye is we don't know how much change in Schirmer is clinically significant or how much tear breakup time is clinically significant. We know they are important, but we don't know how much change is significant…We need to find that out, and we know patients also have symptoms. So, if a trial shows a positive change (in Schirmer, or tear breakup time, etc.) by a statistically significant amount **and** the symptom gets better, then that is significant enough to affect symptoms…If a sponsor does both a sign and a symptom, and it is clinically significant, then it can be on the market."

Using signs alone is problematic. Dr. Chambers explained, "We potentially could use a sign, but we are worried about something. Anesthetics make the eye numb. They are a bad thing because they completely inhibit the ability to feel. They break down cells and patients do poorly, so we are not willing to take symptoms alone…But if you have both sign and symptom, then you have an explanation for the sign."

Using a shotgun approach to finding a sign/symptom that will work raises issues relating to interpretation of the data. Dr. Chambers said, "If you don't know which (sign or symptom) your product will work for, and you do four, five or 20 different signs/symptoms, one is bound to come out…If you do multiple signs, then you have to divide your p-value by an appropriate correction, so you are not just doing a lot of tests to find one."

Of course, a sponsor must show its drug works in two trials. Dr. Chambers said, "The standard rule applies, and we expect the sponsor to show the same signs in both trials."

What does it mean for approval if the sponsor of a dry eye drug, for example, proves a primary endpoint "sign" in two trials but does not show symptom benefit? Dr. Chambers said, "Unless the change in the sign is known to be clinically

significant, we would not approve the product for a dry eye indication with a sign only. The only single sign we consider clinically significant is clearing of corneal staining. Otherwise, a clinically significant change in dry eye is by definition a change that correlates with a change in symptoms.

What if the sponsor proves a primary endpoint "sign" in one trial but not symptom relief, and then in a second trial meets the primary endpoint for symptom relief but does not show a statistically significant improvement in a sign in that same trial? Dr. Chambers said, "The clinical trials need to show the same sign and symptom in each trial."

Sponsors cannot mix and match endpoints -- show the sign in one trial and the symptom relief in another trial. Dr. Chambers said, "The clinical trials should demonstrate replication of the same results."

Whether measurements need to be significant before and after a certain time point in order to be meaningful depends on the indication:

IOPs: "It is equally important that you show – or at least that we know—whether IOP is lowered when you first start using the product or whether it takes X weeks to start working. It is equally important to know peak and trough of the product. So, we measure multiple time points which all are important pieces of the picture. Typically, you measure Week 1 and then Week 12.

Anti-infectives: "You can't look at Week 9 or 10. Everyone gets better by then, so you look at Day 3 or 4, and see if a percentage of people are getting better faster."

Macular degeneration and dry eye: "Just one time point is required unless the sponsor is claiming that the effect lasts for a particular timeframe. If you are making an additional claim for a time point, then you need to prove it.

There is no single "best endpoint" for a dry eye trial. Dr. Chambers said, "It depends on what you are trying to accomplish…Dry eye is not a single disease. It can be from (a) a lack of producing enough water component, (b) the individual constituents, or (c) too quick evaporation. You may have a product that affects one of these – by producing more water or keeping it there longer. Tear breakup affects lipids and osmolality. Schirmer measures tear production. You can hedge the direction depending on what you think the pathologic action of the product is. Sometimes, people do a shotgun when they don't know…but to the extent you know what is happening, you can choose the appropriate endpoint."

The criteria for priority review in ophthalmology is the same as in other disease areas. A drug does not have to be first-in-class to qualify for priority review. Dr. Chambers explained, "Priority review by definition has to be better than currently existing therapy. A different indication is the easiest (way to gain priority review) because there is nothing to compare to. A broader indication is a different indication. The decision to make grant priority review is made prior to the review of the application. Sometimes we don't ultimately know if a drug is better before the review, so we may initially review something under priority review, but it may turn out not to be priority."

How does the FDA decide on whether or not to have an advisory panel for ophthalmology drugs in general and for dry eye drugs in particular? Dr. Chambers said, "In ophthalmology at the moment, there is a combined advisory panel with dermatology. That means there are only four ophthalmologists on the panel. That is not a whole lot, especially with 12 different subspecialties in ophthalmology. So, it is very easy to get into areas where we have no expertise (on the advisory committee). For example, Trusopt (Merck, dorzolamide hydrochloride ophthalmic solution) was the first topical carbonic anhydrase inhibitor. At the time it came up, there were only two ophthalmologist members on the combined committee, which then was ophthalmology combined with anti-infectives. Both those doctors were involved in the trials…There were no members to use to start as a base for an advisory committee meeting, so we didn't have one. Otherwise, we would have had an advisory committee meeting…Generally, there is an advisory committee meeting when a new, different, or potentially controversial agent is considered, but we are much more constrained (than in other areas of the FDA)."

The FDA also is starting a pilot program to test rolling submissions for some drugs and biologics. Commissioner Mark McClellan is trying to reduce the time and cost it takes to bring new medicines to market. With rolling submissions – which already are used by CDRH for devices -- companies can send the FDA parts of their drug applications as each part is completed. The goal is to allow FDA reviewers to identify deficiencies early, so companies will know if they are on the right track. At first, the program will apply to "priority" applications that show promise for treating serious conditions with no current therapy.

The areas where FDA officials would like to see more drug development in ophthalmology include:

- A cure for macular degeneration.
- Something allows people not to lose accommodation.
- Cures for any of the diabetic eye diseases, including diabetic retinopathy.
- A cure for glaucoma.
- Ways to keep corneal transplants from being rejected.
- Ways to reverse dry eye.
- More antifungals.
- Antivirals for the epidemic keratoconjunctivitis.

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