# Trends-in-Medicine

**October 2002**
***By Lynne Peterson***

## SUMMARY

The refractive surgery (LASIK) market is stalled, and the outlook isn't for a quick pickup. Wavefront technology was a hot topic and is likely to catch on, but it won't boost procedure volume any time soon. ? Interest is growing in InterLase's laser for creating LASIK flaps. ? C&C Vision, ThinOptX and Calhoun Vision all have implantable IOLs that look interesting and deserve watching. ? Alcon probably will not be able to use the C-98-03 trial data as a confirmatory study for FDA approval of anecortave, which means it will need positive results from both the pivotal Phase III and the European registration study for FDA approval. ? Six-month data may be enough for FDA approval of Bausch & Lomb's back-of-the-eye steroid implant, Envision, in uveitis but longer term data probably will be required for macular degeneration and diabetic macular edema.



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## AMERICAN ACADEMY OF OPHTHALMOLOGY

## Orlando, Florida

## October 18-21, 2002

*This report is a look at selected topics discussed during the meeting, but it is not intended as a comprehensive overview of the conference.*

### OVERVIEW

Doctors generally agreed that this was not one of the more exciting AAO meetings. It seemed lower key than some previous years, with less new or cutting-edge data. The exhibit floor was busy, though, and some of the companies went all-out to make their presence felt. Alcon, for example, had a huge booth and at least 547 people attending the meeting. The Bausch & Lomb booth also was enormous, and the sales reps were very upbeat, despite the company's recent problems. A B&L official said, "We don't have anywhere to go but up. We still have good products, and people shouldn't write us off."

### GLAUCOMA

According to the NIH's National Eye Institute, 2.2 million Americans age ≥40 have primary open angle glaucoma (POAG), which is 1.9% of the population, and another two million Americans may have the disease and not know it. POAG may be more prevalent in blacks and Hispanics.

The NEI plans to convene a series of meetings to assess new opportunities in the field based very broadly on the current state of science within and outside of vision. An official said, "That includes the retina community, and there are other disciplines interested in the neurobiology of CNS diseases, and they may have contributions in neuroprotection. And we need to assess critically the outcomes of clinical studies and trials based on recent progress in the field."

Data was presented indicating that corneal thickness and disc size affect IOP: Thicker corneas overestimate IOP, and thinner corneas underestimate IOP. Typically, blacks have thinner corneas. One speaker showed data indicating that the average corneal thickness was 558 microns for whites but 31 for blacks. He suggested that the IOP of blacks should be adjusted up by 1.8mmHg.

Not surprisingly, the prostaglandin marketing wars were in full swing at the AAO. Pharmacia (Xalatan, latanoprost), Alcon (Travatan, travopost), and Allergan (Lumigan, bimatoprost) all were trying to convince doctors their product was the

best choice. Among some of the messages doctors got:

- Alcon's FDA-labeled claim that Travatan is especially effective in blacks was challenged. A speaker said, "All the medications may have poorer responsiveness in blacks…The newer medications appear to have equivalent responsiveness."

- Another expert (FDA) said, "All of the prostaglandins are equally effective in blacks. Alcon just did a study to show it…We believe the difference in prostaglandin response is due to iris color. Timolol works better in light irises than dark irises. And I think, though we can't prove it yet, that the prostaglandins work better in dark irises than light irises."

Allergan presented data from a 232-patient head-to-head trial comparing Lumigan (0.005% QD) and Xalatan (0.03% QD), and Lumigan won. The primary endpoints were mean IOP at 8 am and the percentage of patients whose IOP was reduced to <17 mmHg, which showed Lumigan performed better than Xalatan. This data has not yet been published and was presented at the booth and not at a symposium, but the sales reps were touting the findings.

**Lumigan v. Xalatan Results**

| Measurement | Lumigan | Xalatan |
|---|---|---|
| Mean IOP at 8 am | 17.4-17.6 mmHg | 17.9-18.3 mmHg |
| IOP <14 mmHg | 29% | 14% |

## COMPUTERIZED OPTIC NERVE IMAGING

The diagnostic capabilities of scanning laser polarimetry – e.g., Heidelberg's Optical Coherence Tomography and Laser Diagnostic Technologies' GDx Nerve Fiber Analyzer -- is gaining popularity. Has it become standard of care?

- The moderator at one session commented, "The key word is essential. To me, if you declare it essential, then pretty soon it becomes standard of practice, and everyone will be legally required to do it. So, I would say that a computerized optic nerve imaging system is not essential yet, but it is definitely useful."

- A speaker said, "I use computerized optic nerve imaging systems in my clinic…but computerized imaging devices are not yet essential…A $30,000-$60,000 device is not needed to detect moderate or severe damage…At present there is no data to suggest the IOP lowering at a pre-visual field loss stage of damage improves the long-term survival of the remaining axons over adequate IOP-lowering at the onset of HVF loss…The likelihood that (ophthalmologists) will be willing to schedule a patient for two un-reimbursed, confirmatory imaging sessions that each will require data interpretation is low (and this is necessary)…CSLT-detected change events that are not evident in photos may not be clinically important enough to treat. You will not trust them to treat when it is tough…So, they are becoming easier to use and improving in their principal applications. I personally believe they will be important to follow patients at risk for glaucomatous progression, but they are not essential to your practice now.

## RETINA

The Retina Subspecialty Day was a broader and less specific overview of retinal therapies than at the recent Retina Congress meeting (See Trends-in-Medicine article, *2002 Retina Congress*, October 2002), but it was very well attended, and the overall messages appeared the same.

- Bristol-Myers Squibb's Kenalog (triamcinolone acetonide) appears to have value in treating – and is being used off-label for – a variety of ocular disorders, from macular edema to uveitis, retinal vein occlusion (central and branch), and possibly age-related macular degeneration (AMD).

- Retinal specialists have been disappointed with Novartis/QLT's Visudyne (verteporfrin) in the treatment of AMD, and they are anxious for newer, easier-to-administer treatments.

- New treatments are on the horizon and generating significant interest.

### NOVARTIS/QLT'S Visudyne

A retrospective analysis of the TAP and VIP data done by doctors at the Massachusetts Eye & Ear Infirmary found that lesion size was the only baseline characteristic of AMD patients that predicted outcome with Visudyne. The researcher said, "In predominantly classic AMD, PDT showed benefit at all lesion sizes, but in minimally classic AMD, the benefit ceased at 6 DA (disc area). In occult AMD, there was a loss of benefit at >6 DA…Smaller lesions treated with PDT lose less vision than larger lesions."

### BRISTOL-MYERS SQUIBB'S Kenalog

(triamcinolone acetonide)

A speaker discussed several triamcinolone studies and concluded: "Triamcinolone deserves evaluation, but the optimal dose and injection schedule is not known, and the costs of cataract surgery and glaucoma treatment need to be evaluated. Numerous anecdotal reports of 'sterile' endophthalmitis as well as culture-proven endophthalmitis need to be explored…Sustained-release implants may have some advantages, and we also want to explore the combination of triamcinolone with PDT or other anti-angiogenic agents."

- A small (30-patient) randomized, controlled trial in wet AMD that found 87.5% of patients getting triamcinolone had stable or improved vision at three months, compared to 50% of placebo patients (p=.05). A topical glaucoma medication for elevated IOP was necessary for 25% of patients.
- A recently published paper on the use of triamcinolone in 14 failed laser treatment patients that found no cataract progression. A topical glaucoma medication for elevated IOP was necessary for 21% of patients.
- An unpublished, randomized study from Australia of 143 patients with predominantly classic AMD which compared triamcinolone to sham and found no difference vision loss of >30 letters at one year. No cataracts were reported, but a moderate rise in IOP was common.

## ALCON's anecortave

At the Retina Congress in late September 2002, the doctor presenting the data on anecortave did not mention the approximately 40% dropout rate in the C-98-03 trial for AMD, but this time he obliquely referred to it, commenting that "about 60% of patients completed the trial."

Doctors at the meeting who were questioned about their opinion of the anecortave data separated into two groups:

- Doctors not participating in the trial were encouraged by the results but concerned about the validity of the trial given the high drop out rate. One even expressed dismay that Alcon had been less than forthright in its presentation and warned that this could taint the company's reputation if it continued.
- Doctors participating in the pivotal Phase III trial were more enthusiastic about the findings and the outlook for the drug.

The Phase III head-to-head trial comparing anecortave and Visudyne is supposed to be blinded, but doctors participating in the trial had differing opinions on how well this is working. Some insisted that the trial is blinded, and they can't figure out which patients are in which arm, but others said they are able to tell the sham PDT from actual PDT, so the trial is not truly blinded.

## EYETECH's Macugen

(pegaptanib sodium)

This anti-angiogenesis aptamer currently is in a Phase II trial in DME, but there was no new data at this meeting. There have been two deaths in the EyeTech trials so far, but doctors did not appear concerned with this. One researcher said, "There have been 4,221 injections of Macugen so far, and no significant safety findings. Currently, two randomized clinical trials have completed enrollment, with a total of 1,196 patients. In a Macugen only trial, 80% of patients had stable vision, and 27% had a =3 line gain in vision. In a Macugen+PDT trial, 60% of patients showed vision improvement and 90% had stabilized or improved vision.

## GENENTECH'S RHUFAB-V2

Researchers repeated the data presented at the Retina Congress meeting a couple of weeks earlier. They reiterated that the data on rhuFAB looks good, with 26% of patients showing a 3-line gain in vision by 90 days. The average was 8.8 lines gained at day 98 with the 300 µg dose, a 9.1 line gain with the 500 µg dose, and a 4.9 line loss with standard of care. However, sources also emphasized that there are three problems with the rhuFAB trials: no randomized controls, no long-term follow-up, and small sample size.

## IMPLANTS

Several drug-releasing implants are in development, and two of these – a reservoir system and a biodegradable system -- were discussed at the Retina Subspecialty Day meeting.

- **BAUSCH & LOMB/CONTROLLED DELIVERY SYSTEMS' Envision.** There was no new information at the AAO meeting on this back-of-the eye steroid (fluocinolone) implant.
- **OCULEX'S Posurdex.** This biodegradable implant releases dexamethasone (350 µg or 700 µg) from a PLGA polymer over a four to six week period. A Phase I/II trial in persistent macular edema completed enrollment in September 2002. The device currently is surgically placed, but the company is planning to inject it via a 22 gauge in-office system in the next trials.

**Comparison of Implant Technology**

| | Reservoir System (e.g., Bausch & Lomb's Envision) | Biodegradable System (e.g., Oculex's Posurdex) |
|---|---|---|
| Advantage | • Achieve high local drug concentrations<br>• Steady state pharmacokinetics<br>• Relatively long duration<br>• Insignificant systemic dose | • Dissolves in the eye, so no need to replace<br>• Potentially injectable in doctor's office<br>• Less potential for ocular toxicity because of less drug exposure<br>• Can easily modify polymer chemistry to change release |
| Disadvantages | • Needs surgical placement, removal and replacement<br>• Chronic drug delivery may result in ocular toxicity | • Shorter duration than reservoir<br>• Less steady state pharmacokinetics |

## OTHER

Several new experimental therapies are being investigated to treat central retinal vein occlusions (CRVOs) and branch retinal vein conclusions (BRVOs) including:

- **Thrombolytics**, particularly intravitreal injections of tPA (tissue plasminogen activator). However, speakers appeared dubious about the value of this treatment.
- **Corticosteroid injections**, especially Kenalog (triamcinolone). A speaker said, "Two patients developed an endophthalmitis type-picture with triamcinolone, but they retained their pre-injection vision…This looks very promising, but there have been some reports of inflammatory and possibly infectious reactions, and needs more investigation." A Stanford doctor said, "We've had chance to study this in a large number of patients. This may be the best first-line therapy, pending a more controlled trial. We see visual acuity increases and OCT (Optical Coherence Tomography) decreases within two days of injection, so it can't be chance. I think this is a very promising therapy that needs more detailed study…It may be addressing the primary problem instead of the secondary problem." Another expert commented, "We are using triamcinolone for CRVO, uveitis and persistent macular edema, with good results…The effects appear to last about six months." A fourth doctor said, "I tried triamcinolone for macular edema, and it worked well. I am intrigued abut using it as a primary therapy."
- **Laser anastomosis**. A panel of experts reported a very low success rate with this. One said, "I've done a handful, and my success rate is relatively low." Another said, "My recent experience using an Argon 6 watt laser without a Yag had a low 10%-20% success rate, so I've largely abandoned this." The panel moderator concluded, "This is an innovative technique with some success but has technical issues."
- **Arteriovenous sheathotomy**.
- **Bioflavinoids**, such as troxerutin.
- **Isovolemic hemodilution**.
- **Laminal puncture**.
- **Radial optic neurotomy**. One expert said, "For us, this is more drainage procedure." Another said, "Our experience shows a high degree success of decompression, and this may be a more efficient way of creating a shunt than with a laser." A third commented, "I hope it works, but I wish someone could show me one convincing case that it does work. I'm still waiting for that."

## REFRACTIVE SURGERY

**IOLS:** IOLs (intraocular lenses) may be the most exciting area right now in the refractive surgery space. Several private companies have interesting products in development, and most of these are expected to do an IPO when the stock market environment improves.

- **C&C VISION** has completed a one-year, Phase III trial in 300 patients of its CrystaLens, an accommodative IOL for cataracts. The primary endpoint was the percent of patients who see ≥20/40. CrystaLens has been approved in Europe for cataract patients (though use is not restricted to that) for more than two years, and the company plans to file a PMA in the US by the end of this year.

The real excitement about this product is its potential to treat presbyopia. C&C officials said they have no plans for trials in presbyopia but are hopeful doctors will use it off-label for presbyopia. That actually may happen. Refractive surgeons questioned about this lens said they are eager to give it a try, and they indicated that off-label status will not be a barrier to acceptance – if the lens performs. An ophthalmologist said, "I'm excited about this, and I would use it off-label, but the concern will be patients with big pupils or pupils that dilate a lot because it is a small optic, and you could get glare at night in the wrong patients or younger patients."

- **CALHOUN VISION** is working on a light-adjustable IOL that an expert described as "very intriguing."
- **THINOPTX**'s Rollable IOL is an extremely thin IOL that can be rolled up and inserted through a very small (~1.5 mm) incision. A source said the company recently received a CE Mark for this product.
- **STAAR SURGICAL**'s Implantable Contact Lens (ICL), a corrective implantable, posterior contact lens. Starr hopes to gain FDA approval to market this by the end of 2003. An expert said the big issue with this lens will be safety:
  - Risk of induced cataract formation form the surgical procedure. So far, it is reported to be <1%.
  - Endothelial cell count loss.
  - Infections. A surgeon worried that, post-approval, any serious infections that caused significant loss of vision or blindness would result in lawsuits that could threaten the technology.

Medical Device Daily predicted that, initially, Staar's ICL and other refractive IOLs are likely to be implanted mostly in high myopes. Only about 1% of all myopes are high myopes, but high myopes account for 10%-15% of the potential refractive market. Phakic IOLs also may appeal to patients with thin corneas, dry eye and large pupils.

**LASIK:** The refractive surgery (LASIK) market is stalled, and the outlook isn't for any quick pickup. Procedure volume did not meet expectations for 2001, and some (perhaps much) of this was due to reaction to the World Trade Center attack. However, volume did not pick up in the first half of 2002, due mostly to the economy, and the predicted economic recovery

did not occur later in the year. Thus, David Harmon of MarketScope and Irving Arons of Spectrum Consulting are both predicting that total procedures for 2002 will be lower than in 2001, and the outlook is only for a 13%-14% increase in 2003, which still puts 2003 below what had been expected for 2002.

Visx is predicting 2005 procedure volume will be 1.9 million, which would be about 16% per year for each of the next three years. A Visx official said, "The market loosely tracks the consumer confidence index pretty well."

MarketScope estimates that 150 lasers will be sold in 2003, with Visx 46% (69), Bausch & Lomb 12% (18), Alcon's Autonomous 42% (63), and Nidek 0%.

**Refractive Surgery Procedure Outlook**

| Expert | 2002 | 2003 | 2001 v. 2000 | 2002 v. 2001 | 2003 v. 2002 |
|---|---|---|---|---|---|
| MarketScope | 1,200,000 | 1,350,000 | -7.8% | -12.3% | +13% |
| Spectrum Consulting | 1,250,000 | 1,450,000 | -5% | -7% | +15% |

**WAVEFRONT TECHNOLOGY:** This was another hot topic at the refractive surgery sessions, but an expert not connected with any of the companies said, "Wavefront is mostly smoke and mirrors. There is no improvement in vision, but there is some improved contrast sensitivity. Wavefront is not going to boost sales of lasers or cause major market share shifts." A refractive surgeon who plans to do his own comparison of results with the Visx and Alcon systems in his practice said, "Are we just getting better at refracting patients? Are our techs not that good at refraction? It definitely is a real benefit when you look at the number of patients getting 20/20 or better, but the question remains: Are we just getting a better refraction for a normal patient? We're pushing for better and better results (20/15 and 20/10), but most ophthalmologists don't have eye charts that measure between 20/10 and 20/15 or better than 20/10." The leading wavefront systems are:

**ALCON'S LADARWAVE.** During the meeting, Alcon announced that the FDA approved its customized wavefront-guided laser eye surgery application, making it the first company to receive FDA approval for customized LASIK surgery using a wavefront measurement device (LADARWave) and an excimer laser (LADARVision 4000). A researcher reported, "We have had excellent results to date – excellent visual acuity and more gain/less loss of mesopic contrast sensitivity."

**Bausch & Lomb's Zyoptix** system, using a Zyoptix work-station (comprised of the Orbscan II anterior analysis system and the Zywave wavefront aberrometer), Zylink software, Hansatome keratome, and Technolas 217z excimer laser. Orbscan IIz is used for screening patients for eligibility. B&L submitted a PMA for this system on May 30, 2002, and an official claimed it is the only system to fully integrate wavefront and topography. Clinical data on the system was presented for the first time at the AAO meeting. A surgeon who heard a presentation on this system said he was impressed and will look at it further.

Among the claims B&L indicated it will make when it launches this system are:

- Modular design.
- 2 devices in 1 workstation.
- Single data input.
- Small footprint.
- Proven system. A company official said, "We will have done more than 25,000 procedures outside the U.S. We will be able to tell American doctors that this is a proven system with an established track record."

**Visx WavePrint System**, using ActiveTrak eye tracker, the Star3 laser, and the WaveScan diagnostic instrument. Doctors already are performing wavescan-guided presybopia treatments. An industry expert said, "I think the Visx system actually is the best (wavefront system)."

**Zyoptix Results**

| Measurement | Improved at 6 months |
|---|---|
| Light sensitivity | 36.8% |
| Glare | 20.9% |
| Night driving | 40.3% |
| Patients very satisfied | 91% |
| Patients dissatisfied | 0 |
| UCVA =20/20 | 91.5% |
| UCVA =20/16 | 70.3% |
| BCVA improvement | 60.4% |
| No change in contrast sensitivity | 75% |
| Improvement in contrast sensitivity | <25% |

A Visx official said, "Patient fixation is very important, and the keys to proper patient fixation are:

- non-dilated pupil so there is natural adjustment to varying light conditions.
- well-defined fixation target.
- short (<1 minute) overall procedure time."

**WavePrint Results**

| Measurement | 6 Month Data |
|---|---|
| Very satisfied with night vision | 76% |
| Contrast sensitivity | No change from pre-op |
| UCVA =20/20 | 96% |
| UCVA =20/16 | 74% |
| Dissatisfied patients | 1% |
| **Halos** | |
| Never had | 86% |
| Often | 0 |
| Sometimes | 11% |

**MICROKERATOMES:** Bausch & Lomb is the 400-pound gorilla in the LASIK keratome space, but it is facing serious competition from IntraLase, despite its significantly higher cost. An expert predicted that the IntraLase FS laser alternative to a microkeratome will take 20% market share from B&L's Hansatome, a mechanical blade keratome by the end of 2003.

Refractive surgeons refer to the IntraLase technology as all-laser LASIK, or, more officially, IntraLASIK. They use an IntraLase Pulsion FS (105 nm femtosecond) laser to create a LASIK flap, and then the standard excimer laser to perform the vision correction. The Pulsion laser delivers energy directly to the stromal layer of the cornea through a disposable glass lens, creating a flap under very low vacuum. With Pulsion, surgeons said they can minimize errors and increase the accuracy and predictability of flap thickness.

IntraLase reportedly is giving its laser away for free but charging $100-$200 per eye (price depends upon volume). Most surgeons are tacking the added cost onto their procedure fee, though a few are absorbing it. An expert said, "There are absolutely no complications with this keratome! It's all-laser LASIK. Patients are driving use. Where it is advertised, patients are asking for it, and they are willing to pay $300-$400 more per eye for it."

## REGULATORY PERSPECTIVE

An FDA official discussed ophthalmic drug approvals, including generics. He explained that generic drugs in ophthalmology are regulated somewhat differently from drugs used in other specialties.

Pre-1938 products are not regulated by FDA, so three commonly used ophthalmic products do not have FDA approval -- pilocarpine, atropine, and tetracaine. In approving the first ophthalmic generic in 1962, the FDA decided that only the generic manufacturer only had to show:

(1) The active ingredient was the same,

(2) The indications were the same,

(3) Any inactive ingredient didn't affect the safety of the proposed drug product, and

(4) The blood level of the active ingredient had to be 80%-125% of innovator (brand) product.

Since 1992, the FDA has required that ophthalmic generics:

- Contain the same active and inactive ingredients as the brand product.
- Be within 5% of the brand for bioequivalence or demonstrate bio-equivalence in a head-to-head study. To date, all generics have met the 5% threshold, and none have had to do head-to-head trials. An FDA official explained, "In a three month study…a 95% confidence interval must be shown, and all IOP must be within 1 mmHg."
- Contain the active brand ingredient in the same concentration – with the exception of the preservative, buffer, any substance used to adjust tonicity, thickening agents, provided these do not affect safety.
- Must show clinical equivalence for ophthalmic suspensions, ointments, and gels.
- Must be compared to brand product, not another generic, to avoid the problem of "bio-creep." For example, an FDA official explained "Any product containing timolol must be compared to timolol alone, b.i.d."

In theory, it should not be more difficult to get combination products through the FDA regulatory process than non-combination drugs, but in practice, it has proven more difficult. At least in ophthalmology, the combination must show a contribution from each of the two products being combined, compared to either alone. That is, combination products are required to be tested in three-arm trials -- combination, drug 1 and drug 2 – and must demonstrate that the combination is superior by a statistically significant degree from either drug alone. The sponsor does not have to prove synergy, just an additive effect.

The problem has been that the sponsors have not been able to show a superior benefit to the combination product, even though in clinical practice doctors see an added benefit from introducing a second agent. For example, Pharmacia has been unable so far to convince the FDA to approve its combination glaucoma therapy, Xalcom (latanoprost+timolol). An FDA source commented: "There could be an interaction of the two substances, or they may need some slight spacing in administration, but a 1-2 mmHg change in IOP is within the error of the measuring machine, so it is not sufficient to make us believe there is a benefit to the combination." An ophthalmologist said, "Several brand products have been presented to the FDA, and they keep shooting them down. In

some cases, it almost appears the FDA is looking for 1+1=3. The combination has to be more effective than the drugs given separately. The hurdles seem to shift."

Among the combination products seeking FDA approval are:

- Allergan's Combigan (Alphagan+timolol) for glaucoma.
- Allergan's Restasis (cyclosporine A eyedrops) for dry eye.
- A steroid plus an anti-infective.
- Pharmacia's Xalcom (Xalatan+timolol) for glaucoma.

An FDA official offered some guidance on how the agency reviews clinical trial data, particularly in ophthalmology.

**1. Trial size.** Small clinical trials – of five, six, ten or 15 patients – seem to be common in ophthalmology, particularly in retina. An FDA official said, "We tell people they can do off-label studies of five patients because we think no one will believe that data. We used to allow 10-patient trials, but that got published so we reduced it to five patients. These studies are a signal that there may be some effect and provide a basis for a clinical trial."

**2. Disease State.** The FDA looks at ophthalmic drug data based on disease.

- Drugs to lower IOP need three month data.
- AMD drugs require two year data, but the sponsor can submit on one year data. The FDA won't hold up the application for the two year data, but in practice it usually is ready within a couple of months of approval.
- Diabetic eye diseases require three year data. An official said, "What we see early is not what we see later, so we want three-year data for diabetic eye diseases so we don't get fooled."
- In uveitis, only six-week efficacy data is needed but six to 12 month safety data is required. The official said, "Usually, we know in the first six weeks if the drug is working. There are very few surprises after that."

The FDA requires two analyses of the same trial and a comparison of those two analyses. An FDA official said, "The sponsor must compare these two trials, and if there is a difference in the efficacy in the two analyses, there has to be an explanation for that or we won't believe the data." The two analyses are:

1. Intent to treat (ITT) with last observation carried forward (LOCF).
2. Per protocol, with observed cases only (drop-outs excluded).

Reportedly, lack of agreement between these two analyses has been a problem for Novartis and QLT with Visudyne in occult AMD. Alcon's anecortave trial (C-98-03) also may have trouble meeting this test, and C-98-03 may not be acceptable to the FDA even as a confirmatory study. Alcon has started a European trial of anecortave for European registration, and that trial potentially could be used as the confirmatory study for FDA approval.

**3. Safety data**. The FDA official said, "On safety, we are looking for different events. For example, we know cataracts occur with steroids – we expect that -- so we don't have to wait to see that occur." (NOTE: This would suggest that B&L may be able to get approval of Envision based on six-month data – if the FDA accepts the efficacy data.)

An industry expert explained that there are three hurdles that generics, depending on class, have to clear:

**a. Formulary equivalence standards**, where the active ingredient is the same as the brand and is present in a certain percentage.

**b. Bioavailability**. This often can't be done in ophthalmology because blood level issues are not relevant to drops or ointments. A source explained, "It is what gets into the eye that matters, and we can't measure the level in the eye, so bioequivalency is not measured, and the systemic level is not relevant.

**c. Therapeutic equivalency**, where the generic is tested against the parent compound.

Thus, systemic drugs have to meet all three standards, but ophthalmic generics generally focus on formulary equivalency. This means it has the same active ingredient (within a small range), but the excipients are excluded. An expert said, "None of the ophthalmic generics are tested against the parent compound that they are being released against. The clinical efficacy of generics is where the question mark is now. Someone can make the argument that if you just change the buffer or vehicle, what difference does it make? Well, it can make a difference. For example, pH can affect penetration, and excipients can affect bioavail-ability…Obviously, the generic manufacturers have no incentive or desire to do head-to-head studies, and the brand manufacturers are reluctant to throw money at a drug where a generic has been released because of a shrinking market."

B&L and Alcon hope to introduce a generic version of Allergan's Alphagan (brimonidine), but Allergan, not unexpectedly, opposes this. Dr. Louis Cantor, Professor and Director of Glaucoma Service at Indiana University School of Medicine, said, "Generics have one advantage – cost…With Alphagan there is an issue because the generic will be a generic for a product no longer on the market. Regular Alphagan has been discontinued, and Alphagan P is substantially different in concentration, preservative and safety profile (less allergy, etc)…For ophthalmologists the question will be whether the potential benefit of a generic is worth the risk of giving a drug with a higher concentration, higher allergy, more fatigue versus using the available brand name, Alphagan P."