Part of the problem might reside with the regulatory process itself. The process for clearance of a new drug is complex and as the knowledge base concerning dry eye disease expands, the scientific basis for drug testing changes. According to Michael A. Lemp, MD, clinical professor at Georgetown and George Washington universities, "it was anticipated that the FDA would issue new guidelines for clinical trials in dry eye disease several years ago, but these have not been made public. The delay may rest with senior management within the Agency."

The result is that there is no "one-stop shopping" source where would-be sponsors can learn the guidelines for clinical trial endpoints. Instead, sponsors must go to the FDA and make a proposal as to how they would perform a clinical trial; the FDA reviews the proposal and informs the sponsor if it is acceptable, or which portions are acceptable or unacceptable.

"While the FDA is quite open to these inquires and willing to listen to novel ap proaches, many times companies new to this field feel as if they are guessing what the FDA wants," Dr. Lemp explains. "They wonder if the FDA has changed what is acceptable since the last time they heard. It's like trying to read the tea leaves."

Chugging Along

Despite the regulatory hurdles, some dry eye drugs are making slow but steady progress toward beleaguered physicians and their patients. Most are anti-inflammatories, so their approval would fulfill a wish of Dr. Trattler's. "I use pulses of topical steroids frequently for dry eye patients, and if there were additional anti-inflammatory drugs that could work in this area, that would be very helpful for patients, since dry eye is an inflammatory condition."

• **EGP-437.** The closest drug to the goal is EyeGate's EGP-437. Currently in a phase 3 efficacy study, it's a dexamethasonederived corticosteroid solution delivered to the eye via an iontophoretic drug delivery system that enables the drug to overcome the problem of low bioavailability that limits other topical agents. "You have to try to bypass natural barriers that are in place: the tear film and cornea," Mr. From says. "It's very difficult to get a large quantity of drug into the front of the eye, or any drug to the posterior pole of the eye for retinal diseases." Iontophoresis also allows EGP-437 to bypass the method physicians have had to resort to deliver large quantities of drug into the eye: needles.

The doughnut-shaped applicator holds a sponge saturated with drug; the applicator is placed on the sclera after a topical anesthetic is applied to prevent the patient's blinking. An electrode at the base of the applicator is connected to a small, handheld generator that supplies a charge. A negatively charged drug in the foam portion gets a negative charge to the electrode, thus using the principle of electrorepulsion to push the drug at a high velocity into the eye.

The process, Mr. From says, requires only a couple of minutes. "Depending on how high the current is, or how long we leave this on the eye, will dictate how much drug goes into the eye and how deep it penetrates into the eye."

EGP-437 is a small molecule. In its recently-completed phase 2 study, it was able to treat multiple signs and symptoms of dry eye, rather than just one in each category, Mr. From says, "So we actually had the lucky advantage of being able to choose the best sign and the best symptom for our phase 3 trial." Even better, he says, was its onset of action, which begins within hours. "If you're a Sjögren's patient and you have severe dry eye, you are in a lot of discomfort and pain" and at risk for scarring, Mr. From explains. Such patients would welcome a therapy with rapid onset of action. "No other drug that I'm aware of works as quickly as our drug is working," he says.

Although data from EyeGate's 83-patient phase 2 trial are not yet available, the company did say that staining decreased in both fluorescein and lissamine green dyes, that conjunctival redness was reduced and that tear film breakup time increased.

As for dosage, the drug would be administered in a physician's office, probably on a

enrolling patients for the phase 3 clinical trial of approximately 180 planned. Mr. From anticipates that the trial should be completed during the first quarter of 2011, with top-line data available at the end of that period.

He describes EyeGate's approach as acute therapy for a chronic problem. "We are able to put so much drug in so quickly to the tissues of the eye that we're knocking down the inflammatory cascade very rapidly. The drug doesn't stay in the eye very long, but the pharmacological effect lasts for a long time."

• **CF101.** Can-Fite BioPharma Ltd. recently opened an Investigational New Drug application (IND) with the FDA for a phase 3 study of its lead drug, CF101, for treatment of moderate to severe dry eye disease. Dr. Pnina Fishman, Can-Fite's CEO, says that CF101 exerts an anti-inflammatory effect and also an immunomodulatory one. The study will be initiated in few months.

An earlier phase 2 study, in which CF101 was taken orally as a monotherapy for 12 weeks, showed a statistically significant benefit in the clearing of fluorescein staining in the nasal, temporal, pupillary and inferior cornea, the company reports. CF101 also was found to be safe and well tolerated in the Phase 2. Further, the study showed a decrease in intraocular pressure in patients with dry eye, findings that have prompted Can-Fite to initiate a phase 2 clinical study for the drug's treatment of glaucoma.

The randomized, double-masked phase 3 trial will compare two oral doses of CF101 to placebo. Approximately 240 patients will be enrolled at multiple centers, to be treated for 24 weeks. The clinical endpoints are improvement of corneal fluorescein staining, tear production and dry eye symptom score.

• **Low-dose bromfenac.** Ista Pharmaceuticals' phase 2 trial of low-dose bromfenac (Remura) demonstrated improvement in both a key sign (lissamine green staining) and in symptoms (as measured by the Ocular Surface Disease Index) of dry eye in 38 patients over a six-week period. Further, patients treated with low-dose bromfenac maintained the improvement in signs and symptoms for 10 days after discontinuing treatment. The company is currently in the process of initiating the efficacy portion of the phase 3 program, which will entail two studies with a total of approximately 1,000 patients followed over a six-week period, according to Dr. Chandler. The safety portion of the phase 3 trial is tentatively scheduled to begin later this year and will comprise a six-month and a 12-month trial, with a total of approximately 4,000 patients.

Dr. Chandler notes that low-dose bromfenac could address the impact of inflammation on the ocular surface, a central feature of dry eye. "Controlling inflammation could both quiet the symptoms — that is, irritation, dryness, gritty, sandy feeling, burning in some cases — and improve the signs, such as staining, of ocular surface disease," he explains. The approach yields a dual benefit, Dr. Chandler contends, because of bromfenac's efficacy in dealing with pain as well as its ability to interrupt the inflammatory cycle, thereby allowing the ocular surface to heal. "There are very few medications that truly address the inflammatory cascade that is central to the disease while improving patient comfort," he says.

Although the inflammatory etiology of dry eye remains theoretical, Dr. Chandler says it does explain the results seen in the phase 2 open-label trial. Dr. Chandler contends that low-dose bromfenac has an onset of action that is "much faster" than the approximately eight weeks required for topical cyclosporine. In studies completed to date, he says, the drug produced a response rate that hovers around 70%.

Regarding safety, Dr. Chandler points out that higher-dose bromfenac studied in more than 1,600 patients did not result in any serious corneal adverse events; ocular adverse events observed in these studies resolved with no sequelae. From the perspective of global clinical experience with bromfenac, in about 19 million ophthalmic uses of the currently marketed higher concentration, there have been 22 serious corneal adverse events reported overall. Not all were considered drug related, Dr. Chandler points out, and most were in subjects who had undergone cataract surgery. "Lowering the concentration of bromfenac as we have done could further reduce the likelihood of severe corneal adverse events," he says. As part

of its commitment to patient safety, Ista has incorporated frequent monitoring of the cornea into the protocols for the large safety trials being planned.

• **SAR 1118.** Sarcode Corp. says that the phase 2 results for SAR-118, a topical small-molecule lymphocyte function-associated antigen-1 antagonist, showed clear improvements in signs and symptoms of dry eye at 12 weeks. The trial was a randomized, multisite, doublemasked study involving 230 subjects. Various dose levels (0.1, 1.0 and 5.0%) were compared to placebo, with subjects receiving the drops BID for 12 weeks. The primary objective measure was inferior corneal staining; major secondary measures were OSDI symptom score and tear production by Schirmer test. The company will present full details of the phase 2 study in spring 2011. Sarcode is currently preparing for a phase 3 trial to begin in mid-2011.

• **Mapracorat.** Bausch + Lomb is addressing the issue of tear hyperosmolarity in dry eye disease, which research suggests is a mechanism involved in ocular surface inflammation, with its selective glucocorticoid receptor agonist (mapracorat), currently in phase 2 trials. In vitro studies suggest mapracorat inhibits hyperosmolar-induced cytokine release and mitogenactivated protein kinase pathways in human corneal epithelial cells. Development of the compound continues to progress as a novel product with a new mechanism of action for the treatment of dry eye, according to B+L.

A study in the September 2010 issue of *Molecular Vision* showed it to have comparable activity to dexamethasone in combating inflammation. The investigators evaluated mapracorat's anti-inflammatory effects in an in vitro osmotic stress model that induced hyperosmolar conditions in cultured human corneal cells. The model stimulated the release of pro-inflammatory cytokines interleukin-6, interleukin-8 and monocyte chemotactic protein-1, and also altered the phosphorylation state of p38 and c-Jun N-terminal kinase (JNK), and the transcriptional activity of NFkappaB and AP-1. The researchers found that the incubation of cells with mapracorat inhibited hyperosmolarinduced cytokine release with potency comparable to the dexamethasone control group. Additionally, increased phosphorylation of p38 and JNK caused by hyperosmolarity was inhibited by mapracorat, and the compound caused a significant decrease in the hyperosmolar-induced rise in NFkappaB and AP-1 transcriptional activity.

• **RX-10045.** One of a class of medicines called resolvins, RX-10045 is a small-molecule lipid mediator that Resolvyx Pharmaceuticals says activates the body's own mechanisms for shutting off inflammation. It is administered as a topical eye drop. Resolvyx completed a phase 2 trial last year for chronic dry eye. In the randomized, placebo-controlled, 232-patient trial, RX-10045 produced dose-dependent, statistically significant improvement on the primary endpoints for both the signs and symptoms of dry eye, and was generally shown to be safe and well tolerated, the company says.

The phase 2 study examined three doses of RX-10045 and used a controlled adverse environment (CAE) simulator to measure corneal staining in a stressful drying environment, as well as daily patient diaries using a standard visual analog scale to assess symptom improvement over the course of the 28-day study. The drug produced a significant dosedependent improvement from baseline in symptoms recorded in daily patient diaries. It also reduced staining of the central cornea by 75% ($P<0.00001$) versus placebo, the difference approaching statistical significance ($P=0.11$). Additionally, the drug showed a significant improvement in CAE-induced staining in the inferior cornea and in the composite of central and inferior cornea, which also approached statistical significance over placebo ($P=0.09$).

Resolvyx says the phase 3 trial should begin by the end of the year.

• **AzaSite.** Currently there is no prescription product indicated for blepharitis, a void Inspire Pharmaceuticals would like to fill with AzaSite (azithromycin). The drug is already approved as a treatment for bacterial conjunctivitis, but it did not meet statistically significant endpoints in two phase 2 trials for anterior blepharitis last spring. Though a four-week trial did demonstrate improvement in measured signs and symptoms compared to placebo, statistical significance was not achieved for the primary endpoint of mean lid margin hyperemia.

On the secondary endpoints, however, Inspire president and chief executive officer Adrian Adams reports seeing some statistical significance in the areas of signs and symptoms. In the two-week trial, there were no statistically significant improvements for AzaSite compared to vehicle; this included the primary endpoint of clearing of lid debris.

The company says it will use the data obtained from these studies to continue to develop trial parameters using AzaSite as a treatment for both anterior and posterior blepharitis, and expects to refine the trial design through the end of this year. The refinement will include study populations and "seeking improved mappability for assessing and measuring signs and symptoms," says Mr. Adams. "With that, we are looking to utilize the photographic reading centers to maximize the trial."

Inspire anticipates completing the additional phase 2 AzaSite clinical work in 2011. The initiation of the phase 3 trial should begin sometime later next year.

• **LX-214.** Lux Biosciences' dose-ascending phase 1 trial showed that LX-214, a novel topical formulation of voclosporin, was well tolerated by healthy volunteers. There was no difference in tolerability between the vehicle control and the concentrations of drug tested (0.2% and 0.02%). In five subjects diagnosed with dry eye syndrome, the cohort "showed some improvement in their signs (measured by Schirmer's tear test) and symptoms (measured by the OSDI); most notably, the changes observed occurred in the relatively brief timeframe of the study, two weeks compared to what has been reported previously with cyclosporine emulsion," according to Dr. Anglade.

Voclosporin affects the immune response at the surface of the eye, he explains. "We think by controlling the local inflam matory response, it will allow the tear-producing lacrimal gland and the surface of the eye to heal and improve tear production.

LX-214 belongs to a class of agents known as calcineurin phosphatase inhibitors, developed by the company into a nanomicellar formulation. "This renders LX214, a highly insoluble compound, a solution as opposed to an emulsion," Dr. Anglade explains. He believes the drug's solution formulation will help make it better tolerated than cyclosporine emulsion.

Another advantage, says Dr. Anglade, is voclosporin's higher concentration. "A limitation of other forms of topical cyclosporine is that sufficiently high concentrations may not be achieved locally. The ability to achieve high local concentrations may translate into improved efficacy. We'll be able to assess that concept hopefully in the phase 3 when we do a large dose-ranging study."

Dr. Anglade adds that the company is planning a phase 2 proof-of-concept study for the near future.

• **Restasis X.** Allergan reports that it is currently testing a new variation of cyclosporine, Restasis X, in phase 2 clinical trials. The company is not able to speculate on expected timing for FDA approval.

In related news, in a study published in the August issue of the *British Journal of Ophthalmology*, researchers evaluated the efficacy and safety of two concentrations (0.05% and 0.1%) of cyclosporine A in aqueous solution compared to vehicle in treating the signs and symptoms of moderate-tosevere dry eye patients.[1] At Day 21, the 1% group showed statistically significant improvement ($p<0.05$) in four symptoms and three ocular signs; the 0.05% showed statistically significant improvement in three symptoms and three signs; and the vehicle-only group in two symptoms and two signs. According to the researchers, at Day 42, the 0.1% group performed demonstrated improvement in four symptoms, while the 0.05% group demonstrated improvement in one symptom and one sign.

Hope for The Future

Dr. Lemp's vantage point as a participant in many FDA trials gives him reason to believe that the regulatory situation for dry eye drugs will soon improve. "As we learn more about the pathological processes at work in dry eye disease, new treatment strategies are

For one thing, in a meeting earlier this year, the FDA's Wiley Chambers, MD, expanded the criteria for primary endpoints that the agency will accept, including studies that document a correlation between signs and symptoms. Included in that slide was a list of inflammatory cytokines in the tears and tear osmolarity. "That's new," says Dr. Lemp. "That's potentially big."

Patient-reported outcomes are gaining favor with the FDA as well. The most common vehicle for reporting patient symptoms has been the 100-point scale OSDI. However, showing the required 29-point improvement in symptoms has been onerous. It has required sponsors to find patients who were highly symptomatic — "Who at least start out with 50 to 60 points on the scale," Dr. Lemp says. "And that rules out 90% of the population with dry eye."

New studies re-examining the relationships between subjective patient changes and levels of disease severity, novel ways to assess patient-reported improvement and a better understanding of the relationship between signs and symptoms in dry eye disease all have the potential to open the door to less onerous but scientifically rigorous study designs, Dr. Lemp notes. He believes that this augurs well for demonstration of clinical efficacy and the appearance of an expanded therapeutic portfolio of drugs for the more effective management of dry eye disease.

Perhaps the best reason to believe that the fortunes of prescription dry eye drugs will improve? "Let's put it this way, to my knowledge, there are probably more than 30 drugs in the pipeline," says Dr. Lemp. Many companies are investing in the dry eye market, and not just "the usual suspects" such as Alcon, Allergan and B+L.

The fact that Restasis could generate an approximate half a billion dollars in revenue last year despite its demonstrated effect in only about 15% of the patients studied (according to the package label), indicates significant unmet medical need and a healthy bottom line for those willing to invest.

With industry on board and the FDA willing to update its clinical trial criteria, the conditions for victories seem to be increasingly in place. **OM**

Reference

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Clinical Trial Pearls

Ora, Inc. has been helping drug makers navigate clinical trials for 15 years, says George Ousler, director of the company's dry eye department, so they have a lot of experience in knowing what makes for a successful program. Here are his recommendations:

- **Identify proper inclusion/exclusion criteria.** Because there are many different causes of dry eye, and different medications that could potentially treat it, it is critical that companies take the time to match the medication's mechanism of action to the appropriate patient population.
- **Focus on both signs and symptoms.** Related to proper inclusion criteria, it is necessary to only include patients who show both signs and symptoms of dry eye. "It sounds pretty straightforward, but there's actually a fair amount of lack of correlation between the two," Mr. Ousler says.
- **Design well-controlled studies and standardize.** Certain clinical models enable better control for the endpoints of dry eye. Toward this end, Ora has developed the Controlled Adverse Environment (CAE). By controlling environmental factors such as humidity, temperature, air flow and visual tasking, "you can establish a screening tool to identify the right patient, and an endpoint to demonstrate efficacy. If it's better controlled, there's not so much background noise like traditional environmental studies," Mr. Ousler

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