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Quick Pulse

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AMD Drugs: The Regulatory Path

Numerous new treatments to treat the wet form of age related macular degeneration (ARMD or AMD) are on the horizon (*See chart on Page 3*). To better understand the regulatory issues and path that all these agents face, 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), was interviewed. Other FDA officials also offered their expertise. None of these officials discussed specific drugs, but ***Trends-in-Medicine*** has added specific examples of how FDA regulations may apply to particular drugs

Preclinical Studies

Cell line studies

The importance of cell line studies depends on the drug. Asked if certain assays (e.g., SHE or Ames) are considered better than others, Dr. Chambers said, "A number of the screening tests are probably more useful because they are more often negative in ophthalmology products, but there are ophthalmology products that are chemotherapy agents, too, that are going to be positive…So, any kind of screening test is just that, a screening test…If you stay within the limitations of the test, it is useful…The Ames and SHE cell assays both have strengths and weaknesses…If you stay in the limitations, they are useful. If you don't, then they aren't…For instance there are some anti-infectives that can kill the cell line, and then you won't learn anything."

Carcinogenicity

Generally, ophthalmic drugs may not need animal carcinogenicity studies unless there is cause for concern or there is significant exposure. Josie Yang PhD, Supervisory Pharmacologist, FDA's Division of Anti-inflammatory, Analgesic, and Ophthalmologic Drug Products, CDER, said, "There are particular questions we try to get answered, and we use whatever model – human or animal – that best answers that question."

Lack of systemic levels cannot be assumed even if no drug is detected systemically – because the problem may be lack of sufficiently sophisticated measuring equipment. Dr. Yang explained, "Non-detectable depends on the detection level…It is hard to say something is non-systemic…Beta blockers initially didn't show in the blood, but now they are detectable…We do make attempts to measure systemic absorption, so we will have an idea what that is compared to oral drugs."

Some ophthalmic products are exempt from carcinogenicity studies (qualify for a waiver). The ICH guidance document [(S1A – The Need for Carcinogenicity Studies for Pharmaceuticals), (**www.fda.gov/cder/guidance/index.htm**)] that says that you may not need carcinogenicity studies if you have a topically-applied product showing limited systemic exposure or if you have a systemic product indicated for short-term or infrequent use (generally less than three months). Under these criteria, most ophthalmic drugs would get excepted from doing animal carcinogenicity studies unless there is cause for concern. Dr. Yang said, "If you want a waiver, you explain why you meet the factors in the guidance document, and many products do meet that. Is the product carcinogenic? We never know for sure – not even with animal studies – unless there is a study in humans, but we make reasonable guesses. If something is very mutagenic, then you are more likely to want to test that in a longer term study than something that sits there and basically doesn't do anything…To get a waiver, there are multiple criteria."

- **If no waiver is granted, animal carcinogenicity studies are needed.**
- **Whether testing could be done post-marketing depends on the risk level.** Dr. Yang said, "If we think the risk is very high and we need the answer because it will affect the benefit:risk ratio, then we want the data before approval. If we think the chances of a positive result are lower, then we are likely to say okay to doing it in Phase IV (post-approval)."

EYETECH revealed in corporate documents earlier this year that carcinogenicity questions have been raised about Macugen (pegaptanib sodium), and the company is hoping for a waiver – or at least that it will be allowed to do any studies post-marketing. A decision on the waiver could come any time since the submission is now complete.

- The corporate documents read: "…in a test of Macugen and its metabolites in the Syrian Hamster Embryo Assay, which we performed at the request of the FDA, the results were negative for carcinogenic potential. However, one of the animal tests that we performed suggests that two of the metabolites of Macugen are compounds as to which there may be carcinogenicity risk. As a result, we may be required to conduct additional carcinogenicity testing of Macugen. Based on our discussions with the FDA to date, if we are required to conduct further carcinogenicity testing of Macugen in connection with its use in the treatment of wet AMD, we believe that the FDA will allow us to conduct any such testing as a post-NDA approval study…"
- The Eyetech official said that none of the animal studies with Macugen – including hamsters and rabbits – have shown any carcinogenicity issues. However, one of five strains of bacteria, E. coli, showed a small increase in revertants in the Ames test. Then, FDA requested a SHE assay, which reportedly was negative.

CLINICAL TRIALS

Companies are utilizing a variety of clinical trial designs and sizes. Dr. Chambers said, "I don't know of any trial designs that are optimal. It is almost unheard of to have any single trial answer all the questions we want. The best of design has: multiple doses, a product, vehicle, and active control all in parallel. It would be good to have data on the drug alone and in combination with other products. And it is best to have evaluations every three or four months for several years. It is easy to say that, but it is not easy to do it."

Dose response curve

Dr. Jonca Bull, Director of the FDA's Office of Drug Evaluation V, CDER, said, "The FDA encourages sponsors to find the smallest dose with a useful effect or the maximum dose beyond which no further beneficial effect is seen."

However, some of the AMD drugs in development have not shown a dose response curve.

- **EYETECH'S Macugen** did not show a dose response curve. The company chose the 0.3 mg/kg dose to submit to the FDA for approval. The lack of a dose response was not concerning to investigators, who said it simply shows that 0.3 mg is enough. One commented, "This shows all the doses work."
- **ALCON'S Retaane** (anecortave) did not show a dose-response curve in the first Phase III trial. Only the middle dose (15 mg) showed a statistically significant response over placebo, not the lower (3 mg) or higher (30 mg) doses. A researcher explained, "We reached a peak dose effect at 15 mg."

Length

Two-year data is needed for AMD trials, but agents can be approved on shorter, one-year data, provided ultimately the FDA sees two-year results. In 2003, Dr. Chambers said, "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. But a sponsor can submit sooner…This is an older population (usually at least 60) and the lifespan of 65- to 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 – but ultimately we need to know the two-year results."

Number of trials

Data from two trials with similar results are required. Dr. Chambers said: "We routinely ask for two analyses. One is

an intent-to-treat analysis (ITT) with last observation carried forward (LOCF), and one is per-protocol, with only the observed cases – no information carried forward or extrapolated, and in patients who meet the strict definition. These are relative extremes of the typical datasets. One is the largest, and the other is the smallest, and we look to see if those are the same. If they are the same, then we figure the analyses in between are the same. So that eliminates having to look at a lot of other things…These are two extremes, and if they are not the same, then we ask for an explanation of why the sponsor thinks that happened – which one is more representative and what the biases that potentially might influence the two not being the same…For example, did the investigator die, so the data was not available. We are concerned if bias influenced one vs. the other…I think it (the two-trial concurrence) is a reasonable approach, or we wouldn't ask for it."

This is an issue for several agents, including:

- **EYETECH'S Macugen.** Eyetech claims it has two Phase III Macugen trials (VISION) that met the primary endpoint, but the company has only released the results of a pooled analysis of these trials, not the results of the individual trials. Investigators have said that even they have not seen the full results of the individual trials. However, Eyetech officials have said both trials are statistically significant on their own at the 3 mg dose. They also claimed the pooled presentation is similar to the way QLT Therapeutics presented its pivotal TAP trial data on Visudyne (verteporfrin).

- **ALCON'S Retaane (anecortave).** The first Phase III trial had about a 40% drop-out rate, so questions have been raised about whether this can be used as a confirmatory study to support the ongoing pivotal Phase III head-to-head trial vs. Visudyne. If not, Alcon may have to wait

Agents under Investigation to Treat AMD

Company	Brand name	Generic name	Type of agent	Method	Status
Alcon	Retaane	anecortave	VEGF inhibitor	Juxtascleral injection	Phase III
Allergan	---	triamcinolone	Corticosteroid	Intravitreal injection	N/A
Bausch & Lomb	Retisert	fluocinolone	Steroid	Back-of-the-eye implant	Phase III
Eyetech	Macugen	pegaptanib (EYE001)	VEGF inhibitor	Intravitreal injection	Submitted to FDA; Advisory panel 8/27/2004
Genaera	---	Squalamine (MSI-1256F)	VEGF inhibitor	Intravenous infusion or subcutaneous injection	Phase II (Phase III to start in 2005)
Genentech	Lucentis	rhuFabV2	VEGF inhibitor	Intravitreal injection	Phase III
GenVec	---	AdPEDF	Gene therapy	Intravitreal injection	Phase I
Iridex	---	TTT	Laser photocoagulation	810 nm laser	Phase III
Merck	Zocor	Simvastatin	Statin	Oral	Phase I
Miravant	PhotoPoint	SnET2	PDT	Infusion	Submitted to FDA June 1, 2004; fast-track status
N/A	---	indocyanine green-enhanced photodiode therapy	I-PDT	Infusion	Investigator experiments
Pfizer	---	A-4321001	Long-acting depot VEGF inhibitor	Extrascleral injection	Preclinical
QLT Therapeutics	Visudyne	Verteporfrin	PDT	Infusion	Approved but additional indications being studied
Roche	Accutane	isotretinoin	Retinoid	Oral	Phase I (?)
Theragenics	TheraSight	N/A	Low-energy (22KuV) radiation	Implanted extrascleral disc	Request for IDE submitted to FDA in July 2004
TLC Vision	---	Rheophoresis	Blood filtration	Blood filtration	Phase III; approved in Canada
Tulane University	---	NV-5-40	Combrestatin analog	N/A	Preclinical
Tulane University	---	JF-10-81	Camptothecin-somatostatin analog conjugate	Intravitreal injection	Preclinical
Wyeth	Rapamune	Rapamycin	Immunosuppressant	Oral	Preclinical

for the results of an ongoing European trial, which are not expected to be available until 2005. The question is whether the FDA will accept Alcon's explanation that the drop-outs were due to Visudyne's approval during the trial since the patients were not followed to confirm this. Alternatively, a source suggested that Alcon may try to split the pivotal trial into two groups, constituting two trials, "They have a sample size where they can take the number of patients and allocate them to Group A and Group B, and make it into two trials."

- **MIRAVANT'S SnET2.** In 2002, SnET2 failed to meet the primary endpoint in its two-year (103-week) , 920-patient, pivotal trials (98-EA001 and 98-EA004), which resulted in Pharmacia pulling out of its marketing agreement. However, Miravant, after consulting with the FDA, reanalyzed the trial data, and in March 2004 submitted SnET2, based on a per-protocol analysis of the lower of the two doses in the pivotal trials (0.5 mg/kg). In the re-analysis, on an intent-to-treat basis, the visual acuity results were borderline, but in a per-protocol analysis, the visual acuity results were statistically significant.

Time points

Only one time point is required for AMD trials, unless the sponsor is claiming the effect lasts for a particular timeframe or the sponsor wants to make an additional claim relating to time points.

Endpoints

The Ophthalmic Subcommittee of the Dermatologic and Ophthalmologic Advisory Committee met in September 2003 to discuss the design of trials of drugs intended to delay or prevent the development of myopia, but there have been no specific meetings about endpoints in AMD.

Missing a pre-defined primary endpoint does not necessarily doom a product. Dr. Chambers said, "It depends on whether the primary endpoint is something we agreed to in advance or not. We have a lot of people who propose a lot of endpoints. We don't approve trials; we only permit them to go on if we think we will learn something and if it is not unsafe…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."

Subgroups

Asked about the importance of subgroups, Dr. Chambers said, "Subgroups are clearly an important part of our analysis – to say if a product is more important in one part of a study population than another...Visudyne demonstrated greater efficacy in some populations, so that was important information…If multiple therapies are available, then subgroups are important to say which works in which patients or to tell patients what to expect."

Among the subgroup issues Dr. Chambers discussed were:

- **Which subgroups.** Study groups such as age, visual acuity, lesion size, lesion characteristics, etc., all get looked at…For us, race and ethnicity are rarely a factor, but iris color is."

- **P-values:** Some experts have argued that the FDA wants harder criteria in the two registration trials than a $p<.05$ value. However, Dr. Chambers insisted subgroup analyses do not hinge on p-values. He said, "This is not a p-value issue…Studies aren't powered to look for subgroups…Subgroups are not expected to generate p-values…If we look at a trend in one trial, and it goes one way, and then it goes another way in another trial, we have little confidence in that. If there is a strong trend in both trials the same way, and they are twice the magnitude of the effect, most people will believe it…The results with Visudyne were fairly dramatic, and that is why it generated a lot of discussion."

In the case of Eyetech's Macugen, an investigator said the results are statistically significant for each subtype in the individual studies, though the numbers are small. He commented, "In all three subtypes, there was a statistically significant benefit, but the numbers are small." At the end of April 2004, this subgroup analysis was still ongoing.

Steroids

Interest in off-label use of triamcinolone acetate (Bristol-Myers Squibb's Kenalog) remains strong. Many retinal surgeons are using it successfully in combination with PDT. However, Kenalog contains a preservative, benzyl alcohol (BA), that causes transient toxicity. Thus, experts have been recommending that doctors remove the BA before using Kenalog by decanting it, pharmacologic washing, and/or filtering.

ALLERGAN is working on getting FDA approval of triamcinolone for intraocular applications. The company plan is to offer it in a pre-filled syringe, probably without BA, and is supplying its ophthalmic formulation of triamcinolone for two macular edema clinical trials sponsored by the National Eye Institute (NEI).

On steroid use (e.g., Kenalog) in AMD trials, Dr. Chambers said, "We strongly encourage clinical trials of most off-label products, including steroids. We'd like to see clinical trials done with them…Intravitreal injections of steroids certainly represent a significant increased risk vs. the labeled use. So, if they are done in a study, they should be done under an IND …And ultimately, we can't approve something unless it is submitted."

PRIORITY REVIEW

Priority review (fast-track status) can be granted even if a drug is not first-in-class. The criteria for priority review are the same center-wide at the FDA. In 2003, Dr. Chambers said, "Priority review by definition has to be better than currently existing therapy. At least in theory, it is supposed to be better than what is on the market. 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 grant priority review is made prior to the review of the application. It is in the acknowledgement letter. 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."

ROLLING SUBMISSIONS

The FDA has a pilot Fast Track program underway to reduce the time and cost it takes to bring new medicines to market using an "early submission" process or what are informally referred to rolling reviews or rolling submissions. (See FDA guidance for Fast Track Drug Development Program – Designation, Development, and Application Review.)

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 is being applied to "priority" applications that show promise for treating serious conditions with no current therapies. Rolling submissions are reviewed on a resource-available basis. Eyetech's Macugen was a rolling submission.

A newer program, implemented in the fall of 2003, is CMA Pilot 1. This is described in the FDA guidance "Continuous Marketing Applications: Pilot 1 - Reviewable Units for Fast Track Products Under PDUFA." Susan Johnson PhD, Science Policy Analyst, FDA's Office of New Drugs, CDER, explained, "The pre-submitted portions of an NDA or BLA are called 'reviewable units' in this pilot program and are given a six-month review clock."
(See **www.fda.gov/cder/guidance/5739-fnl.pdf**).

As to the outcomes of the pilot, Dr. Johnson said, "Per the CMA Pilot 1 guidance, we are in the process of engaging an external expert contractor to conduct an evaluation of the program (and other programs mandated by PDUFA 3 agreements). There is no data yet available from the contractor evaluation. We have not shared information about the enrollment of NDAs or BLAs into individual review divisions for Pilot 1. The firms may choose to make their acceptance into the program public, but we leave it to their own discretion. We have shared that there are several products enrolled and interest in additional enrollments. The guidance document provides timelines for reports from the contractor/evaluator."

Asked how the rolling submissions have been working in ophthalmology, Dr. Chambers said, "It is a pilot program, and the evaluations have not yet been completed."

ADVISORY COMMITTEES

The next advisory committee on an AMD drug is Eyetech's Macugen on August 27, 2004. Advisory panels are generally used when a new, different, or potentially controversial agent is considered. Dr. Chambers said, "Generally, there is an advisory panel for things that are new – new in class or new in the delivery system – or if we have questions we want to have a wider discussion about or to get additional expertise."

Several of the AMD agents under investigation utilize novel modes of administration, including juxtascleral injections (e.g., Alcon's Retaane) and back-of-the-eye implants (e.g., Bausch & Lomb's Retisert). ♦