

HUGE THERAPEUTIC ADVANCES: BIGGER DRUG DELIVERY OPPORTUNITIES

By Paul Ashton, PhD

The landscape for ophthalmic pharmaceuticals has been undergoing a seismic shift as drug development has turned its focus to treatment diseases of the retina. The two biggest products in the field, with more than US\$5 billion (£3.3 billion) in annual sales between them, both treat retinal disease and were approved in the US only within the last eight years. Diseases of the retina, a thin layer of photosensitive tissue at the back of the eye responsible for generating

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electrical impulses, are the major causes of irreversible vision loss and blindness in the developed world, affecting hundreds of thousands of people each year.

For decades, ophthalmologists (and their patients) realised that diseases of the retina represented a huge, unsolved problem, but little research went into developing anything that wasn't an eye drop. Twenty years ago, eye drops for glaucoma were the best-selling ophthalmic products. While eye drops can be a very effective way to get drugs into the front of the eye (the target for all approved glaucoma drugs), it has thus far been impossible to achieve therapeutic concentrations of drug in the back of the eye, where the retina is located, with topically applied drops in humans (although there are many reports in the literature of eye drops being used to treat retinal disease models effectively).

The only ways to deliver adequate concentrations of drugs to the retina have historically been by administration of systemic doses or by injections directly into the eye. Unfortunately, both can be problematic. Since ocular clearance rates are fast, the half-life of small molecules is typically less than 12-24 hours, while biologics such as antibodies have half-lives of up to 4-6 days. In addition, systemic delivery requires large doses to overcome the blood-eye barrier with attendant side effects. Complications of injections include intraocular infection, perforated sclera, vitreous haemorrhage and cataract formation. As a result, seeking to develop effective treatments for retinal disease has brought significant challenges of effective drug delivery.

Delivery of drug to the retina began to change with the AIDS epidemic and the development of Vitrasert®, the first ophthalmic sustained release product. Patients in the late stage of AIDS often developed cytomegalovirus (CMV) retinitis, a member of the herpes family that led to blindness. There were drugs available to control CMV retinitis, most importantly ganciclovir, but it needed to be administered as an IV infusion every day. Not only did the regular infusions have a risk of infection (particularly in immune-compromised patients) but the high systemic doses (necessary to overcome the blood-eye barrier) caused life-threatening neutropenia. Small doses of ganciclovir could also be delivered as intraocular injections every three days. Long term, both of these options were untenable.

The unmet need led to the very rapid development of Vitrasert, a small core of ganciclovir coated in a series of polymers surgically implanted into the back of the eye. Vitrasert provides sustained release for more than six months. Systemic exposure is minimal, and intraocular drug levels are higher than those achievable by



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systemic administration. When Vitrasert was approved by the US FDA in 1996, six years after the initial animal studies were performed, it was the first drug approved to treat retinal disease.

The next advance in ophthalmic sustained delivery was Retisert®, which extended the duration of sustained delivery to 30 months. Marketed by Bausch + Lomb, it delivers fluocinolone acetonide to treat posterior uveitis, a serious retinal disease that can lead to gradual or sudden vision loss. Also a drug core coated with polymers, Retisert is smaller than Vitrasert. However, it still needs to be surgically implanted. This product was approved in the US in 2005.

Next came Allergan's Ozurdex® (0.7 mg dexamethasone PLGA matrix), which provided the advances of being both bio-erodible and injectable. It was first approved in 2009 for vein occlusion, then in 2010 for uveitis, and in 2014 for diabetic macular edema. This implant is small enough to be injected into the eye. Being a matrix drug, release is relatively rapid. Over 90% of the drug is generally released in the first month) but in uveitis, the pharmacodynamic effect can last three to six months. However, as the device is bio-erodible, it can be administered frequently without the build-up of depleted devices in the eye, but still has the risks associated with frequent intraocular injections.

The most recent advance in sustained drug delivery for the eye is Iluvien®, also injectable but with extended duration of 36 months. It was approved in 2014 for the treatment of diabetic macular edema. It is composed of 0.19 mg fluocinolone acetonide in a polyimide tube the ends of which are capped to control release.

Currently this is where things stand. Sustained delivery systems have been approved for two steroids and an anti-viral. However, none of these systems deliver biologics. The three most-used drugs for retinal disease right now are biologics: the antibody Avastin® (approved for oncology but used off-label), the antibody fragment Lucentis® (a fragment of Avastin) and the trap molecule Eylea®, all of which target vascular endothelial growth factor (VEGF). These drugs have revolutionised the treatment of wet age-related macular degeneration (AMD), the leading cause of vision loss in people over 65 years old, and other retinal diseases. Unfortunately, these biologics must be injected directly into the eye typically eight times per year to control the disease. This

is tolerable, but perhaps only because the alternative is rapid deterioration of vision and blindness.

Another very common disease is dry AMD, which is approximately eight times more prevalent than the wet form and is

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characterised by a slow atrophy of the retina. There is currently no approved treatment for dry AMD, and most observers believe that frequent intraocular injections will not be a viable treatment option for this disease.

COMMON EYE DISEASES: SUMMARY

Glaucoma affects 1.5-2% of the population. It is normally characterised by high intraocular pressure (IOP), which leads to progressive damage to the optic nerve and blindness. Drugs that reduce pressure can slow down or halt this process. Two strategies are either to reduce the production of aqueous humour (drugs such as Timolol®) or speed up its drainage from the eye (drugs like Xalatan® (latanoprost). Since the process that governs both aqueous production and outflow are located in the anterior chamber, topically applied eye drops are a convenient way to achieve therapeutic concentrations of drug and assuming good patient compliance, glaucoma is generally a well-managed disease.

Posterior uveitis is inflammation of the back of the eye, and is estimated to affect 175,000 people in the US. It is responsible for about 30,000 cases of blindness in the US. While it can be associated with other autoimmune diseases such as lupus, multiple sclerosis and rheumatoid arthritis, approximately 50% of the time, posterior uveitis is idiopathic. In some relatively rare instances, it can be genetic. The mixed aetiology and chronic nature of the disease can make it difficult to manage effectively. Posterior uveitis can also be associated with other ophthalmic conditions such as cataract, glaucoma (thought to be due to particulate matter blocking the normal outflow channels) and paradoxically hypotony (too-low eye pressure), due to reduced ability of the eye to make aqueous

humour. Approved treatments include oral and injected corticosteroids and immunosuppressants and Retisert.

Retinal vein occlusion is the second most common vascular disease of the eye, estimated to affect over one million people in

the US. Occlusion of the retinal veins causes elevated pressure in the vessels of the eye and impairs oxygen supply to the retina. The immediate result is swelling of the macula (macular edema) and a slow death of the affected region of the macular. Left untreated, the retina will usually re-perfuse and the swelling resolve. However, any death of the retina is irreversible. Approved treatments include regular intraocular injections of anti-VEGFs (Lucentis and Eylea) and intraocular injections of sustained release steroids (Ozurdex).

Diabetic macular edema (DME) is the most common cause of vision loss in people under 65 years of age and the most common vascular disease of the eye. Approximately 10% of people with diabetes will develop DME. It is caused by progressive failure of the micro blood vessels feeding the retina, in much the same way as blood vessel failure causes other conditions associated with diabetes such as ulcers leading to limb amputations and other vascular perfusion problems. As the blood supply to the retina becomes insufficient, stressed tissues exude cytokines (including vascular permeability factor or VEGF), which makes the vessels more leaky and leads to swelling of the macula (edema). DME can be treated by burning the macula and retina by laser. More recently the treatment of DME has been revolutionised by intra-vitreous injection of the anti-VEGF drugs, Lucentis and Eylea. When injected into the eye on a regular basis (typically every 4-8 weeks), these can be very effective in resolving edema with significant increases in visual acuity. However, the DME of the majority of patients is not optimally managed with VEGF drugs and long-term (over five-years) results are less impressive, since these treatments merely mask the effects of diabetes. Finally, in 2014, both Ozurdex and Iluvien were approved in the US for DME.

Age-related macular degeneration is characterised by a progressive breakdown of the retinal pigmented epithium (RPE), a layer of cells under the retina and resulting atrophy of the retina. Although this process can be very slow, it leads to irreversible loss of vision. There are no FDA-approved treatments for dry-AMD, the most prevalent incidence of AMD. In approximately 15% of cases, new blood vessels grow under and through the RPE, which are leaky and fragile, causing bleeding and edema. This can result in a rapid loss of vision. Fortunately, the two anti-VEGFs, Lucentis and Eylea, have been recently approved and found to be remarkably effective at least in the short to mid-term in treating wet AMD. The major downside for these agents is that they must be injected into the eye approximately every four to eight weeks.

CONCLUSION

The size of the market for effective treatments of serious retinal eye diseases should drive a flow of potential drug candidates to treat them. The challenge and opportunity facing the ophthalmic pharmaceutical world

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is to take the next steps to develop effective long-term (months or years) delivery systems for the current and expected increasing number of drugs, particularly biologics, designed to prevent or treat retinal disease.

Many companies and academic groups are working on this problem. In the not too distant future, we will hopefully look back and wonder that patients had to resort to monthly injections into their eyes to preserve their vision. The challenge for drug delivery scientists is to make this happen soon; the prize is enormous, helping the millions of people who suffer from blinding eye diseases.

ABOUT THE AUTHOR:

Paul Ashton, PhD, has been President & Chief Executive officer of pSivida since January 2009, having previously served as Managing Director of the Company from January 2007 to January 2009 and Executive Director of Strategy from December 2005 to January 2007. Dr Ashton was the President & Chief Executive Officer of Control Delivery Systems (CDS) from 1996 until its acquisition by pSivida in December 2005. CDS was a drug delivery company that Dr Ashton co-founded in 1991. Prior to co-founding CDS, Dr Ashton was a Joint Faculty Member in the Departments of Ophthalmology and Surgery at the University of Kentucky, served on the faculty of Tufts University, and worked as a Pharmaceutical Scientist at Hoffman-La Roche. Dr Ashton received a BSc in Chemistry from Durham University (UK), and a PhD in Pharmaceutical Science from the University of Wales.

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Publication Month	Issue Topic	Materials Deadline
February	Prefilled Syringes	Closed
March	Transdermal Patches, Microneedles & Needle-Free Injection	February 3rd
April	Pulmonary & Nasal Drug Delivery	March 2nd
May	Injectable Drug Delivery: Devices Focus	April 13th
June	Novel Oral Delivery Systems	May 4th
July	Wearable Bolus Injectors	June 1st
October	Prefilled Syringes	September 7th
November	Pulmonary & Nasal Drug Delivery	October 5th
December	Delivering Biotherapeutics	November 9th
January 2016	Ophthalmic Drug Delivery	Dec 14th



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