EXPERT OVERVIEW: DEVELOPMENT OF SUSTAINED-RELEASE OCULAR DELIVERY TECHNOLOGIES

The global cost of vision loss is nearly US$3 billion (£2.1 billion) for the 733 million people living with low vision and blindness worldwide in 2010.[1] The global pharmaceutical market was estimated at $18.1 billion at year-end 2013, estimated to grow to approximately $23 billion by year-end 2018. Within this time period, retinal indications are demonstrating the greatest growth from $6.9 to $9.9 billion or 7.5% compounded annual growth rate (CAGR). Glaucoma is the second largest segment, forecast at $5 billion by the end of 2018, which is 3.1% CAGR followed by dry-eye at $3.1 billion, or 4.3% CAGR.[2]

There have been major advances in recent years in developing and launching new sustained-release ocular drug delivery systems to treat vision loss better. However, only a small number have achieved both global regulatory approval and commercial success. Only four posterior segment products to date have overcome the challenges of development and achieved broad regulatory approval with a degree of commercial success since 1995. These include:

- Vitrasert® (ganciclovir 4.5mg) – approved 1995
- Retisert® (fluocinolone 0.59 mg) – approved 2005
- Ozurdex® (dexamethasone 0.7 mg) – approved 2009
- Iluvien® (fluocinolone acetonide 0.19mg) – approved 2011.

Yet despite the challenges there remains a significant market opportunity to enhance current delivery technologies or develop new technologies offering improved treatment options for patients suffering from the major blinding eye diseases.

THERAPEUTIC FOCUS

The major blinding diseases, wet age-related macular degeneration (w-AMD), diabetic retinopathy (DR), diabetic macular edema (DME) and glaucoma, due to their whole or partial impact on the posterior and anterior segments of the eye, and their growing market sizes, may offer the most promising opportunities for future ocular drug delivery technologies. They affect large numbers of people and pose significant risk of vision loss and blindness for those affected.

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Current therapeutic options for these diseases may at best manage the condition, slowing or halting further deterioration or disease progression. New breakthrough treatments would benefit from robust sustained delivery of the drug to the target tissues in the posterior segment and, importantly, enhance compliance of patients with long-term treatment regimens for these chronic diseases, for example avoiding or reducing the need for frequent injections.

In addition, from a product "market need" perspective, there are arguably at least five "Holy Grails" that would offer not only significant clinical and medical progress but would also offer multi billion dollar market opportunities and provide major competitive advantages over today's therapeutics; some or all could include sustained-release therapy:

1. Sustained release glaucoma therapy
2. Sustained-release large molecules including proteins, peptides, and aptamers

Michael O'Rourke
President and Founder
T: +1 813 323 1438
E: scotiavc@gmail.com

Scotia Vision Consultants
1027 South Dakota Ave
Tampa
FL 33606
United States

www.scotiavisionllc.com

Michael O'Rourke is a specialised ophthalmic pharma consultant with expertise in pharmaceutical, drug delivery and medical device strategies.

3. Sustained anterior delivery to posterior segment
4. Dry AMD Rx therapy
5. Neuroprotection.

Drug-delivery developments to the posterior and anterior segments of the eye, for both small and large molecules may therefore provide a pathway to new market advances for the launch of new therapies based on enhanced current technologies or through innovation with new innovative approaches.

MEETING THE CHALLENGES OF SUSTAINED DRUG DELIVERY

Several factors contribute to the challenge of developing new sustained-release drug delivery systems including:

1. The primary need to match the drug with the delivery technology. This requires the demonstration of sustained delivery pharmacokinetics and using the appropriate animal models for testing the drug's safety and efficacy.
2. Tolerability of drug with the technology.
3. The right clinical trial design and understanding that platform compatibility differs with compound solubility and molecule size.
4. The identification and ultimate granting of intellectual property rights.
5. In addition, sourcing the appropriate funding or partnerships to move the technology through its IND and clinical stages is a critical success factor.

Despite these barriers, multiple technologies and approaches, both posterior and anterior, are in either pre - or clinical development. Based on recent analysis conducted by Scotia Vision for new or enhanced technologies in development, there are at least 11 in retina, 20 in glaucoma and six anterior delivery technologies.[3]

The current gold-standard to treat posterior segment conditions, such as w-AMD and diabetic related retinal disease, remains intravitreal injection (IVT) with anti VEGf agents. In 2005, approximately 22 million IVTs were administered globally.[4] However, this multi-billion dollar IVT injection market has demonstrated that a proven sustained-release implantable technology itself is not a prerequisite for commercial success, but that a sustained clinical and targeted effect of the drug may be critical. The onerous need for monthly or bi-monthly injections may not be ideal from a patient adherence or comfort perspective and, potentially, for safety reasons.

The future for sustained-release ocular drug delivery will include reducing the treatment burden of IVTs through innovations in delivery technology for both small and large molecules and in all cases combining effective therapeutics with the appropriate drug delivery system. Established big pharma companies will need to consider product lifecycle extension strategies to include new drug delivery technologies, although it is most likely that the innovation for the technology will come from the start-up environment.

All technologies approved today incorporate existing generic drugs, so the choice of drug comes first, then is matched with a delivery technology, although the process itself is not an exact science. It may be ideal to have a broad drug delivery platform technology, customised to new drugs, or a class of drugs, remembering each drug compound will require a different release profile and formulation.

Due to the large numbers of products in the pipeline, the selected product development strategy must offer a disruptive technology; that is, disrupting the market compared with what already exists or is in the development pipeline. It should offer true innovation both to patients and doctors, meet a significant market need, and offer both clinical feasibility and potential reimbursement.

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Some examples of such technologies in development include:

Posterior Segment Delivery

- Refillable drug reservoirs
- Encapsulated cell technology
- Cell-based programs, including stem cells for neovascular AMD
- Iontophoresis
- Novel adeno-associated viral (AAV) variant technology for long-term protein delivery to the eye in DME, neovascular AMD, glaucoma and other conditions
- Prostaglandin analogue delivery systems
- Hydrogel technology
- Supra choroidal implants or injectable suspensions
- Injectable protein delivery systems
- Microparticle and nanoparticle systems.

Anterior Segment delivery

- Topical systems for example semi-fluorinated alkane delivery, enhancing drug solubility
- Contact lens delivery systems
- Mucosal delivery
- Topical peptides for neovascular AMD and corneal injuries.

CONCLUSION

Novel technologies required to deliver agents specifically and effectively to the eye are rapidly evolving. These will have the potential to radically alter the way many ocular conditions are treated, especially retinal blinding diseases and glaucoma. The next decade promises great strides in therapy achieved through sustained-release drug delivery for many currently poorly-treated or untreatable ocular diseases.

REFERENCES

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