Eye Catching Opportunities

The ophthalmology drug segment continues to shine brightly with a number of deals announced in November such as Genentech’s partnering with Novartis to split ex-US rights to Ophthotech’s eye drug, which could be worth more than $1 billion. Allergan, another of the major players in the market, recently acquired rights to Mimetogen’s tavilermide for $50 million upfront and more payments down the line.

Biopharma’s interest in the segment is buoyed by the strong growth in ophthalmology drug sales which are benefiting directly from substantial increases in the number of people suffering from age related ophthalmologic conditions in Western markets and Japan. The developing world is adding to this momentum as increasing affluence drives increased expenditures in all areas of healthcare including vision impairment and eye diseases. The headwinds created by positive demographics for the sector are being exploited by the emergence of new technologies for treating ophthalmic diseases.

The World Health Organisation estimates that there are 285 million visually impaired people globally with approximately 90% of them residing in low and middle income countries.\(^1\)\(^2\) Approximately 95 million people suffer from cataract, and a further 20 million suffer from diabetic retinopathy, glaucoma, macular degeneration, infective causes and childhood related conditions. A further 170 million people are visually impaired due to causes that have not yet been determined or from refractive errors.

From a drug development perspective, biopharma companies are clearly taking note that the proportion of the total visual impairment and blindness from diseases such as age-related macular degeneration (AMD), glaucoma and diabetes retinopathy (DR) is currently greater than that from infective causes such as trachoma and corneal opacities (Figure 1).

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Global Visual Impairment

Global Causes of Visual Impairment

Prevalance in Countries by Income

Figure 1


As the pathogenesis of these diseases are better understood and advances in diagnostic technology have enabled areas of the eye such as the retina to be better examined, biopharma companies have been able to develop new therapies for ophthalmic diseases. New technologies such as monoclonal antibodies and gene therapies are fueling drug development by offering the tantalising prospect for treating hitherto difficult to crack eye diseases. Eylea, a recombinant protein for treating central retinal vein occlusion and wet AMD, is a prominent example of the rise of these new technologies, generating revenues of $2.8 billion in 2014 for Regeneron and Bayer.

As new technologies emerge and markets grow, increased levels of innovation are also driving deal making in the sector. There are currently over 600 ophthalmology drugs addressing approximately 1,000 indications in various stages of research and development, and since 2010, there have been over 176 M&A and licensing transactions involving ophthalmology assets. Transaction activity can be expected to remain robust as biopharma companies seek to fill out their ophthalmology product portfolio and the capital constraints of later-stage drug development drive new start-up companies to seek development and commercialisation partnerships.

The Fast Growing Ophthalmic Drug Market

The global ophthalmic drug market is estimated to grow at a CAGR of 7% from $16.0 billion in 2010 and to reach $35.6 billion by 2022E with retinal disorders being a clear standout and the segment's expected growth of 14.2% fast outpacing the sector. Much of the growth is being driven by retinal disorders which are expected to jump dramatically from $3.0 billion in 2010 to $14.8 billion in 2022E. This growth in retinal disorders is being driven by new innovative drugs that have been developed for the treatment of disorders such as AMD, diabetic macular oedema (DME) and retinal vein occlusion (RVO). The foundations for growth

Global Transaction Activity

Figure 2

Source: Visiongain (2010)
are already established with the successfully marketed drugs Lucentis and Eylea expected to continue growing strongly, and capturing over $9 billion in revenue by 2020E (compared to $7 billion in 2014).³

There has been a lack of innovation in the glaucoma market for a long period of time, with no new drugs approved in the US for almost 20 years.⁴ Despite this, glaucoma is the second largest market segment at $5.2 billion in 2010 and expected to reach $9.0 billion by 2022E. Current pharmaceutical treatments for glaucoma include generic versions of prostaglandin analogues (PGA), beta blockers, alpha-andrenergic agonists and carbonic anhydrase inhibitors, with PGAs being the most widely prescribed drug class for glaucoma, and Lantonoprost being the most prescribed PGA in the US. After the prolonged hiatus in drug development, there are now a number of classes of new drugs in development such as Aerie Pharmaceutical's Rho kinase inhibitors or Inotek Pharmaceutical's adenosine mimetics, which are expected to offer attractive new treatment options for patients.

Increases in the addressable target population and innovative new products are also driving the growth of the dry eye and anti-inflammatory/infective/allergy segments. Examples of important drugs in this category include Shire’s lifitegrast which analysts expect to exceed peak sales of $1 billion.

New Technologies Bolster the Pipeline

The ophthalmology drug development pipeline is looking healthy with over 600 ophthalmology drug R&D products being developed for almost 1,000 ophthalmic indications. Almost 55% of the current drug candidates are either at the research project or pre-clinical stage, and another 40% in the clinic for development. The large amount of drug candidates in earlier stages of the drug development continuum points to healthy innovation, and is indicative of the strong corporate and investor interest in the ophthalmology drug market.

Ophthalmology R&D Pipeline

By Clinical Development

Figure 3 Source: EvaluatePharma and PharmaVentures Analysis as of October 2015

⁴ Inotek Pharma IPO Prospectus (2015).
Most of the currently approved drugs for ophthalmological indications are comprised of small molecules or use conventional technologies, and have been focused on glaucoma, anti-inflammation, anti-infectives and allergies. However, a greater proportion of R&D dollars is now focused on gene therapies, monoclonal antibodies, DNA & RNA therapeutics, cell therapies and recombinant products targeting retinal disorders and orphan indications. The commercial imperative of increasing genericisation may also be driving the adoption of more complex technologies that may be harder to copy (Figure 4).

The rise of the retina is made clear in the charts above, and is increasingly becoming an important part of the ophthalmology picture, with retinal disorders accounting for approximately 38% of all R&D projects (369 indications). The retina is susceptible to a variety of diseases and novel therapeutic approaches are being researched to treat these retinal disorders. For example, Ocata Therapeutics is developing stem cells therapy to treat both AMD and Stargardt’s macular degeneration. Another agent catching the eye of analysts includes Molecular Partners and Allergan’s use of Designed Ankyrin Repeat Proteins (multi-DARPins) that can simultaneously address two critical pathways (anti-PDGF and anti-VEGF) in a single molecule.

Given the growth in the ophthalmology market, the R&D effort is being carried out by large global ophthalmology players as well as many new start-up companies, and should provide a healthy environment for collaborations and partnerships. Data from EvaluatePharma indicates that there are currently 340 drug candidates which are unpartnered, with the majority of them in the earlier phases of clinical development (Figure 5).
Ophthalmic Deal Making is Accelerating

Deal making in ophthalmology seems to be accelerating from a low of just 21 deals in 2012 to 35 deals already in the first three quarters in 2015. There were 176 licensing and M&A transactions associated with ophthalmology drugs for the period between 2010 – Q3 2015. Of the 72 M&A transactions, close to 60% were for pure ophthalmology targets, while the remainder involved target companies which were focused on multiple therapeutic areas including ophthalmology. M&A transaction activity has been especially robust in 2013 and 2014. Deal sizes have varied but there have been a number of large notable transactions that have commanded strong valuations, including Actavis’ acquisition of Allergan ($66 billion at 25.4x LTM EBITDA) and Merck’s acquisition of Inspire Pharmaceuticals ($430 million at 3.6x LTM Revenue).
Licensing activity has been just as robust with 104 deals in the last 5 years and 26 deals completed in just the first three quarters of 2015, with the level of licensing deal making in 2015 set to eclipse recent performance.

The majority of the licensing transactions involved assets that were in pre-clinical or at Phase II. The concentration of licensing transactions at the pre-clinical stage follows the classic pattern of entrepreneurial biopharma companies developing drugs themselves until outside capital is required for clinical studies. The other peak in licensing activity is with companies at Phase II and this is likely due to this stage being a large value inflection point, as well as a point at which substantial additional capital is required for further organic development. At Phase II, large corporates are more willing to acquire a de-risked asset and the selling shareholders may see strategic benefit from gaining the large corporate’s technical and regulatory know-how, distribution capability and deeper pocket book to fund more expensive late stage clinical studies.

Unsurprisingly given the focus on retinal R&D, most of the licensing transactions occurred in retinal diseases. The trend towards novel technologies was also evidence by the increasing numbers of deals involving biologics, cell therapy and gene therapy. It is very likely that the industry will be seeing the high activity levels in the new technologies sustained as smaller and nimbler start-ups continue to create exciting novel treatments for diseases.

### Strong M&A activity, robust valuations

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Notes:
1. Late stage development of viral and bacterial conjunctivitis product – no product revenues yet
2. Additional GBP 6.0m in Contingent Value Rights
3. Additional $55m in Contingent Value Rights
4. Late stage development of allergic conjunctivitis product – no product revenues yet

Most Licensing Deals Undertaken at Pre-clinical Stage

![Graph showing licensing deals by stage](source: Thomson Reuters ReCap and PharmaVentures analysis as of October 2015)

Note: Licensing deals in ophthalmic therapeutics (2010 – Q3 2015). 45 transactions did not disclose developmental stage data or involved formulations.

**Figure 7**
The broader patterns historically observed in ophthalmology deal making have been reflected in the first three quarters of 2015, with almost a third of licensing deals that involved therapeutics related to the treatment of retinal disorders. In July 2015, Biogen and AGTC entered a collaboration and license agreement with an upfront of $124 million and milestone payments exceeding $1 billion to develop gene therapies for multiple ophthalmic diseases, in particular orphan retinal diseases in children and adults. In the previous year Ophthotech granted Novartis ex-US commercialisation rights to Fovista, an anti-PDGF agent in Phase III for the treatment of wet AMD, with Ophthotech potentially receiving over $1 billion inclusive of $330 million in upfront payment.

**Conclusion**

It is clear that the ophthalmology drug market has strong fundamentals supporting its growth trajectory, which in part is fueling a spate of R&D investment into new technologies that offer hope to the millions of visually impaired people around the world. The market is expected to become increasingly crowded with many drug companies inevitably having candidates that address the same target disease. As such, it will be important for companies to navigate through the changing R&D landscape and focus on truly novel and differentiated solutions. As always this will be a key driver of their M&A and licensing strategies.

PharmaVentures is able to assist clients in M&A, licensing, independent company valuations, expert reports, fairness opinions and sector advice. Our specialist knowledge allows us to better understand complex products and articulate the value of a therapy to potential acquirors, partners or investors. We have a strong global deal making track record within biopharma and would welcome discussing how our deep rooted knowledge can be leveraged by potential clients.
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Kathryn has a bachelor degree in Natural Sciences at the University of Cambridge and a master degree at University College London. Supported by the fully-funded departmental studentship, she then pursued her interest in cancer research through a doctorate at University of Oxford to understand the biology of skin cancer. Her experience working with a medical technology device company during the Student Consultancy programme at Oxford prompted her interest in healthcare consultancy for the opportunity to tackle human diseases with a more direct approach. Kathryn is fluent in Chinese, and social in Japanese.

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Issac has over 11 years investment banking experience in M&A as well as corporate finance in healthcare and consumer sectors. Since joining PharmaVentures, in 2013 Issac has worked with a broad range of clients and recently advised on the sale of NanoSight Ltd. to Spectris plc.

Prior to PharmaVentures, Issac worked with the M&A and corporate finance teams at Citigroup and JP Morgan in New York and Bank of America and Standard Chartered Bank in London. He has executed advisory and financing projects exceeding $30bn in North America, Europe and Emerging Markets for clients including Sinochem Group, Ossur, AstraZeneca, Alliance Boots, Merck, Almirall, Tata Group and Telecom Italia.

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PharmaVentures is a premier transaction advisory firm; a world leader in partnering, M&A deals and strategic alliances. For the past 23 years, PharmaVentures has acted as advisor on over 700 deal related projects covering licensing, mergers, acquisitions, divestments and joint venture activities for companies world-wide.

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Now entering its 24th year, PharmaVentures is based in Oxford, UK, and employs 20 professionals and has associates in N. America, Latin America and Asia-Pacific.

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