



## Heads of Terms

### Innovation doesn't stop at the scientific step

The pharmaceutical industry has always relied on innovation to create new breakthrough medicines. This situation has not changed today, in fact that reliance is becoming greater. Innovation carries risk and management is frequently averse to this, thus threatening its own ability to innovate. However, it is a company's ability to manage risk, not by rejecting it but by smartly nurturing it and turning it into success that defines a company and makes it successful.

Our perception of innovation is often around patents and IP i.e. the ability of scientists to innovate and create new technologies and products. This, of course, is true but that innovation step rapidly becomes a historic event driving the need for new types of innovation. In fact, that first innovation step is highly reliant on the company where it occurs being able to transform it into a commercial success. How it does that depends on both its current skills and competences as well as its ability to manage risk. Managing risk at times itself requires innovative thinking.

Of course, innovation is not restricted to scientists, clinicians and technologists but also to managers who are responsible for strategy and commercialisation. These practices require great inventive minds too. As dealmakers, we at PharmaVentures often see great scientific innovations inside companies but often the innovative skills to develop a clinical or commercialisation strategy are lacking. Failure is not related to the innovation itself but the people who manage it. In the context of deal making, successful negotiation of licensing or sale agreements requires great innovative minds too. Corporate and senior level skills in managing both innovation and its inherent risk are so essential into today's high tech industries.

**Dr Fintan Walton**  
Chief Executive  
PharmaVentures Ltd.

## industry insight

### Is there room to breathe in the Asthma and COPD markets?



**Hanna Schutz**  
Business Development Director, PharmaVentures Limited

Pressure from genericization coupled with increasing demands from payers for even better drugs at lower prices continues to give pharmaceutical companies a headache. Some therapeutic areas however seem to be impacted more than others. In the Asthma and Chronic obstructive pulmonary disease (COPD) markets, this pressure seems to be particularly evident. Although incidences of Asthma and COPD worldwide are steeply rising, the sales in dollars have either been declining or are not reflecting the rising numbers of patients suffering from these diseases.

While the incidence of patients diagnosed with Asthma has reached an all-time high in 2016 (Figure 1), the total market size has dropped over 20% in the last six years, and sales projections also don't look very promising (Figure 2). So, what is happening here? Firstly, underlying sales patterns for the specific drugs here are inhaled steroids, which are very efficacious and very inexpensive. Secondly, almost all drugs to date address only symptoms. There are no disease modifying drugs on the market yet. Furthermore, Asthma drugs also rely on a delivery device (typically inhalation device) and drug device combinations have more complex IP positions. Both the drug and the device are usually patented, as both contribute to the amount of market share achieved.

**Asthma prevalence USA and EU5 (France, Germany, Spain, Italy, United Kingdom)**

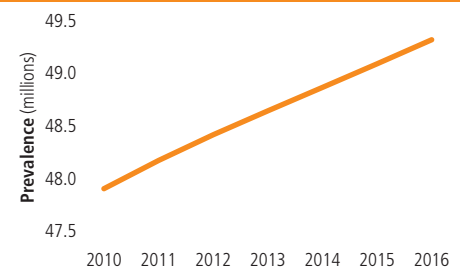


Figure 1 Source: PharmaVentures Analysis, data from Evaluate Pharma

The pharma giant GSK has five drugs in the market, and has currently the greatest market share compared to other big pharma companies. Figure 2 shows the market share of current commercially available Asthma drugs (source: Evaluate Pharma), historic revenues, and forward sales projections to 2022. It is evident that GSK's drug Advair has lost a significant amount of market share due to decreased sales between 2011 and 2016 and is expected to further decline. Advair's decline is a combination of well-known events. First, Advair received some negative publicity in 2012, when death risks were associated with administration of the drug. Based on this, payers in the US dropped the level of reimbursement, which caused financial pressure on

*continued on page 2 . . .*

### Asthma therapeutic worldwide sales

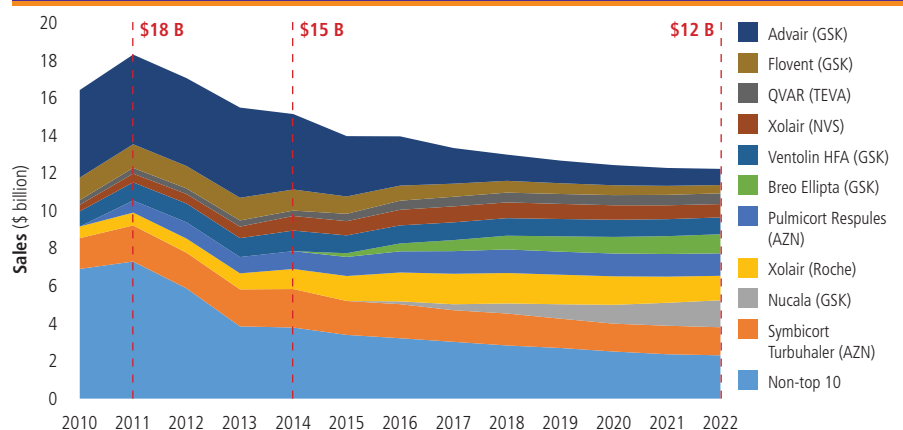


Figure 2 Source: PharmaVentures Analysis, data from Evaluate Pharma

... continued from front page

## Is there room to breathe in the Asthma and COPD markets?

### Global Asthma Sector: Winners and Losers

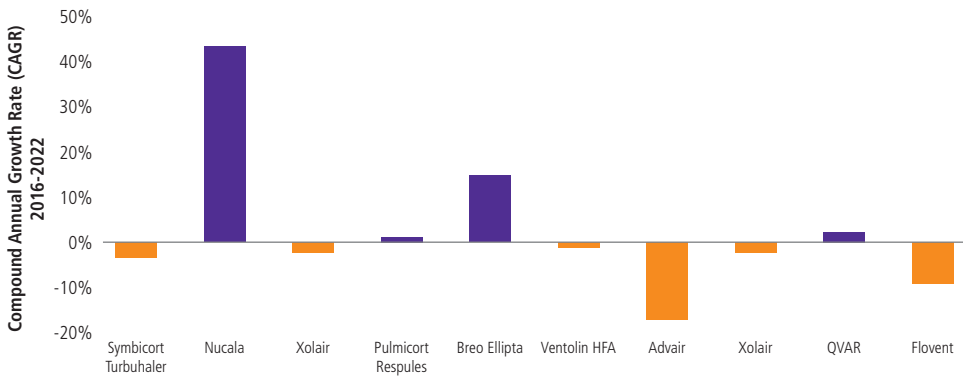


Figure 3 Source: PharmaVentures Analysis, data from Evaluate Pharma

Advair. The drug never fully recovered from the reputational damage, and further decline beyond 2016 is projected due to imminent patent expiry of both drug and device. New market entrants start to erode Advair's share, starting with Breo Ellipta in 2015, as GSK seeks to hold its market share, and no one drug achieves the dominance once held by Advair.

Figure 3 takes a closer look at the Winners and Losers in the space and how effectively GSK is plugging the drop in Advair sales. Nucala and Breo are poised to experience sales growth.

Breo's patent will expire in 2022, which gives it sufficient protection to take some of the market. Nucala's patent also expires in 2022, yet its sales are expected to be 25% higher in the next six years compared to Breo. What is the difference between the two? Breo is a Long-acting beta 2 adrenoreceptor agonist (LABA) & corticosteroid drug, whereas Nucala is a monoclonal antibody, falling into the pharmacological class of biologics. Biologics are expected to be the next generation of asthma drugs and are generally better protected from genericization over and above pure IP due

to difficulty copying the drug and expensive manufacturing costs. Even when generics (biosimilars) do enter the market, price erosion can be as low as 20% (compared to 80-90% for small molecule generics). It is striking to note that a snapshot of the R&D pipeline of selected Asthma and COPD therapeutics (which are currently in late stage development) shows that the majority of drugs that are being developed are biologics.

The importance of patent protection is also reflected in Figures 4 and 5 for COPD drug sales. Whereas Advair has lost its patent protection for both the drug and the device, leading to a steep decline in sales, Boehringer Ingelheim's Spiriva positions itself as a constant major player in the COPD market. Although Boehringer Ingelheim's patent on the Spiriva drug will expire in 2018, the company also holds a patent on the device until 2021, allowing the company to maintain a significant market share over the next years. However, the winners in the COPD market are two other drugs. GSK's Incruse Ellipta and BI's Stiolto Respimat with patent expiry dates in 2029 and 2022, respectively. Once again we see the new entrants picking up market share from Advair post patent expiry and other drugs maintaining market share. In COPD there is generally more patent longevity, so price pressures from genericization do not feature so markedly, and in fact the total market grows by approximately 10%.

### COPD therapeutic worldwide sales

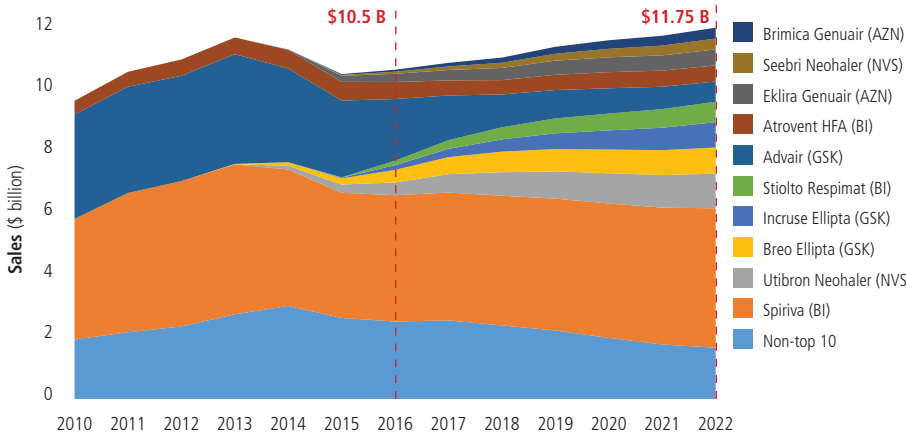


Figure 4 Source: PharmaVentures Analysis, data from Evaluate Pharma

Asthma and COPD tend to be considered somewhat well taken care of probably due to the success of inhaled steroids, but it is the case that these diseases are the third largest cause of death globally after heart disease and stroke. A breakdown analysis of licensing and M&A deals (Figure 6) shows a steady but relatively small number of deals each year.

Significant challenges lay ahead for this sector to develop new efficacious drugs that are disease modifying. There is a greater need than is actually perceived and with a combined (Asthma/COPD) market exceeding \$24 Billion we should expect to see more activity in this area.

For more information: [hanna@pharmaventures.com](mailto:hanna@pharmaventures.com)

### Global COPD Sales: Winners and Losers



Figure 5 Source: PharmaVentures Analysis, data from Evaluate Pharma

### M&A and licensing deals in Asthma and COPD between 2011 and 2016

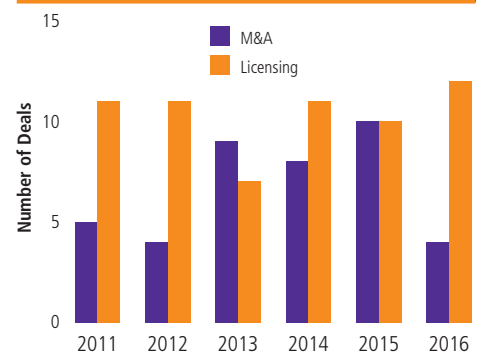


Figure 6 Source: PharmaVentures Analysis, data from Evaluate Pharma

# Antibiotic Resistance

Will diagnostics be the key component in overcoming this problem?



**Adrian Dawkes**

Managing Director, PharmaVentures Ltd.

## Antibiotic Resistance – a global issue

Earlier in September 193 countries signed a landmark declaration at the United Nations General Assembly on antimicrobial resistance. On only the fourth occasion that the UN has held such a high level discussion on a health issue, it was agreed that steps needed to be taken to combat the proliferation of antibiotic resistance. This places antibiotic resistance on the same footing as climate change and recognizes that there is a global requirement for a coordinated effort to do something about this.

## How have we reached this point?

Selman Waksman first used the word antibiotic as a noun in 1941 to describe any small molecule made by a microbe that antagonizes the growth of other microbes, although the first commercially available antibiotic Sulfonamidochrysoidine, (marketed under the brand name Prontosil), was discovered by Gerhard Domagk in 1932. Penicillin was famously discovered by Alexander Fleming and developed in 1945 and thereafter streptomycin, chloramphenicol, and tetracycline, which are produced by soil bacteria, initiating the antibiotic age of medicine and with it what seemed the routine treatment of infectious diseases. Other classes of antibiotic followed in the 1950's and 60's and it was thought that infection as a threat to human health was conquered. Antibiotics became viewed as wonder drugs and were readily prescribed by physicians for a whole range of issues, and in many cases where bacterial infection was not implicated, such as the viral diseases – colds and flu. Such was the perception of the public of the power of antibiotics, that a visit to their general practitioner with an ailment ought to result in the prescription of a course of antibiotics which would cure the problem. What was not realised was that resistant strains of bacteria were emerging right from the first uses of antibiotics which would ultimately render them ineffective. Resistance to penicillin first emerged in the 1940's and similarly for sulfonamides and streptomycin. Resistance rates were running at 10-15% in hospitals in the 1990's but have now reached the alarming level of 60%.

## Why has the pharmaceutical industry not developed new antibiotics?

From a scientific and technical perspective, developing new antibiotics is not without its challenges. Many of the original antibiotics were discovered from natural sources or synthetic chemistry and represented the "low hanging fruit". The vast majority of antimicrobial classes still in use today were isolated in the golden era of antibiotic discovery from a small number of ecological niches and taxonomic groups, mainly from soil Actinomycetes. Modification of existing antimicrobials, use of purely synthetic routes and wider exploration of other ecological domains such as marine environments has yielded little success in the quest for new antibiotics. Furthermore, antibiotics have not been commercially attractive to big pharmaceutical companies. Typically, a course of antibiotics is given once and hopefully the patient is cured. The opportunity to repeatedly treat with a drug is not available as it is in chronic diseases such as rheumatoid arthritis. Add into this the loss of efficacy of the antibiotic due to resistance, alongside the cost of developing new drugs (which is the same for antibiotics as any other drug and currently estimated to be of the order of \$5Billion) it is not hard to see why major pharmaceutical companies exited from this area. Specialist smaller companies now dominate antibiotic discovery and development but with the increasing resistance issues there are signs that the wider industry is waking up to the demands and pressures from governments. Cubist pharmaceuticals was acquired by Merck for \$9.5Billion in 2015 and J&J's acquisition of Alios Biopharma in 2014 for \$1.75 Billion.

## Where do diagnostics come in?

Symptomatology plays an important role in the diagnosis of bacterial infections and many general practitioner prescriptions are written based on this alone. With prescriptions for broad spectrum antibiotics readily given without any knowledge of the specific bacterial infection involved (and in many cases where there may not even be a bacterial infection). Where greater diagnostic information is required, samples are sent to a laboratory for culture and microscopic examination. Bacterial culture can take up to 3 days and whilst this gives a definitive diagnosis of the organism involved and thus which antibiotic is most likely to be effective, patients are not willing to wait, physicians are reluctant to send a patient away without treating and thus take a precautionary empirical approach and use their experience to prescribe the best broad spectrum antibiotic they can. This can be refined once the culture results are back from the lab. In the meantime, resistant strains of bacterial are emerging or are already present in the patient. In acute situations such as sepsis, this has profound implications for patient outcomes. Even in less critical situations such as urinary tract infections physicians want to treat as quickly as possible and patients want their symptoms and infection resolved without waiting. Newer diagnostics technologies are emerging to try and bring results faster. The benefits are twofold in that physicians can give the correct antibiotic sooner and generation of resistant strains are reduced. Furthermore, many of the narrow spectrum antibiotics would still be efficacious and useful if timely diagnostic information could direct their use rather than broad spectrums.

*continued on page 4 . . .*

# PharmaVentures advises the Baylor Scott & White Research Institute

PharmaVentures is pleased to announce that it acted as an adviser to the Baylor Scott & White Research Institute in connection with the creation of Denceptor Therapeutics Limited.

Denceptor Therapeutics will develop immunotherapeutic products to treat cancer and autoimmune diseases using Baylor Scott & White Research Institute's dendritic cell receptor-targeting antibodies. These antibodies will be humanized using Abzena's Composite Human Antibody™ technology to reduce unwanted drug immunogenicity. Denceptor Therapeutics will operate as a virtual business and outsource its development and manufacturing activities. Baylor Scott & White Research Institute and Abzena will be among the outsourced service providers.

Denceptor Therapeutics has an option to exclusively license antibodies from Baylor Scott & White Research Institute with a sub-license to the humanized versions of the antibodies created by Abzena. The antibodies will deliver antigens to specific receptors on dendritic cells to induce or suppress an immune response to treat a variety of cancers and autoimmune diseases.

Nigel Borshell, Vice President, PharmaVentures said; "Collaborations like this are a valuable way of bringing together key technologies and skills so that the whole is greater than sum of the parts. Understanding the value of the contributing parts is key to a successful relationship."

Fintan Walton, Chief Executive, PharmaVentures Capital, Ltd said: "We were delighted to be able to provide Baylor with our extensive commercial sector expertise and help them in the establishment of this exciting new venture with Abzena plc."



... continued from page 3

## Antibiotic Resistance

### New Diagnostic Technologies

Many diagnostic companies have adopted PCR as the technology of choice to assist in the rapid diagnosis of bacterial infections. Two of the leading companies in this area are Alere and Cepheid. The latter recently acquired by Danaher for \$4 Billion and Alere currently using the courts to force through its \$5.8 Billion acquisition by Abbott. Other leading players include Roche (who recently acquired Genewave at a headline price of \$425M), Abbott, Siemens, Grifols, Biomerieux and Becton Dickinson. Cepheids GeneXpert® PCR system can provide results in approximately 30 minutes and Alere's TestTargetTreat™ program does the same. In many cases there is a certain amount of sample processing required in addition to the 30-minute test time, but the time from receipt of sample to delivery of a result is significantly better than traditional culture methodologies. The many PCR based techniques available are very good at identifying the bacteria present in a sample based on the gene sequences present. When it comes to applying the same methodology to identifying antibiotic resistance the method is fine as long as the bacterial gene sequence that confers resistance does not mutate. It is known that mutations can be frequent so keeping testing sequence libraries up to date is challenging and there is a real and growing risk of missing mutated resistant strains or conversely failing to identify the correct antibiotic that will kill the bacteria. Culture based testing is phenotypic and relies on observing bacterial growth or killing to determine resistance and susceptibility. Rapid phenotypic methods may be the ideal solution for resistance/sensitivity testing.

Other bacterial identification methods such as Mass Spectrometry are being widely adopted. The technique is also being applied to antibiotic susceptibility testing. Sample processing is still required and although the tests are inexpensive compared to other methods the instrumentation costs are high and most suited to a central laboratory setting. This requires transport of samples to the central laboratory which introduces time delays between obtaining the sample from the patient and having the test results returned for the physician to act upon. Whilst this scenario is a huge improvement on the 3 day wait for culture it does not bring the testing close enough to the physician and patient, and the door to empiric prescription and resistance generation remains open.

Accelerate Diagnostics are in an approval process with the FDA and are already CE marked in Europe for their bacterial identification and antibiotic susceptibility test and instrumentation. Accelerates instrumentation and assays allow bacterial identification in 90 minutes and antibiotic sensitivity results in 7 hours. The system uses FISH for identification and morphological

analysis for antibiotic sensitivity. In essence it is visually identifying bacterial killing in the presence of antibiotics by observing bacterial cell morphology. The Accelerate technology represents a significant step forward in bacterial identification and antibiotic sensitivity testing providing actionable data on the same day as a patient visit.

Another new company that is developing technologies to address rapid bacterial identification and antibiotic sensitivity testing is a spin out from UCLA called MicrobeDx. MicrobeDx have assembled the best of bacterial gene sequence information, ribosomal RNA (rRNA) as the analyte and phenotypic testing in a single technology. The company has identified key sequences in the rRNA to which they can hybridise solid phase capture probes and reporter probes in a sandwich assay format with any reporter species (fluorescence, luminescence, colorimetric etc.) making it applicable to any suitable instrument platform. The company has exploited the natural amplification of rRNA by the bacteria which provides sufficient analyte for bacterial identification. For antibiotic sensitivity testing the bacteria are allowed to grow for a short period. One of the first events for the bacteria is to synthesise more rRNA. The MicrobeDx assay can differentiate between susceptible bacteria which will not grow (and thus produce less rRNA) and a resistant bacteria, which will grow as normal and thus produce more rRNA. Applying this, MicrobeDx have been able to produce a bacterial identification result in 30 minutes and an antibiotic sensitivity readout in 90 minutes. This, for the first time brings antibiotic stewardship tools into the hands of the physicians who are prescribing the drugs so that they will be able to provide the correct antibiotic right from the outset. MicrobeDx plan to exploit the technology for urinary tract infections in the first instance where currently there are over 70 million community acquired UTIs in the 7 major markets. The 70 million infections represents approximately 20% of the total number of samples tested as the vast majority of samples are negative.

Expanding this and other rapid technologies into other disease areas represents not just a significant commercial opportunity but a chance to significantly benefit human health through good antibiotic stewardship of existing antibiotics. It may also present opportunities that will make the development of new antibiotics more commercially viable through companion diagnostics stratifying patients into appropriate responder groups making payers more willing to reimburse new drugs at higher levels.

New rapid, "near to service" diagnostic testing will be pivotal to tackling the antibiotic resistance issue.

For more information  
[adrian@pharmaventures.com](mailto:adrian@pharmaventures.com)



**Haroon Khan**  
 Analyst

Haroon completed his M.Eng. in Biochemical Engineering from University College London with a focus on process design. He

followed this up with a M.Res. in Biochemical Engineering and Bioprocess Leadership, which laid the groundwork for his Doctorate (Eng.D) in the development of a platform process for novel antibiotic manufacture, both degrees were fully funded by the ESF and EPSRC. During his doctoral education, Haroon completed a number of courses on Innovation and Business development within the Biotech sector, which led to a strong interest in consultancy and strategy.

Prior to joining PharmaVentures, Haroon spent time working as an independent consultant for two SME generic pharmaceutical makers in Pakistan in order to better understand the challenges faced by such companies and the overall business environment in emerging markets.

[haroon@pharmaventures.com](http://haroon@pharmaventures.com)

## conference update

**AusBiotech (International Biofest) 2016**  
 24-26 October, Melbourne

### Bio-Europe

7-9 November, Cologne

If you are interested in learning more about antibiotic resistance, there is a panel being held at Bio-Europe. If you are interested in attending, please visit the event website: <https://ebdgroup.knect365.com/bioeurope>



### Medica

14-17 November, Dusseldorf

### Genesis 2016

1 December, London

### J.P. Morgan 2017

9-13 January, San Francisco

### Biotech & Money London

7-8 February, London

### European Life Science CEO Forum

6-7 March, Zurich

### Bio-Europe Spring

20-22 March, Barcelona

To meet with PharmaVentures' experts at any of these conferences, please contact Rachel Hampstead: [rachel@pharmaventures.com](mailto:rachel@pharmaventures.com)

Or

To arrange an interview with PharmaTelevision, please contact Matt Royan: [matt@pharmaventures.com](mailto:matt@pharmaventures.com)