



THE STATE OF THE UK HEALTHCARE & LIFE SCIENCES SECTORS

MYTHS, REALITIES AND CHALLENGES

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ABOUT THE AUTHOR



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A LETTER FROM BIOTECH AND MONEY

The genesis of this report can be found in the discussions and debate that occur in Biotech and Money's CEO and Investor Forum - a Chatham House Rule exclusive gathering of some of the industry's leading CEOs and stakeholders that meet to discuss their common challenges and strategies to help grow the industry.

It became apparent very quickly that there is a huge disconnect between the realities of the sector and the understanding investors have of the opportunities and risks involved. Too often, myths and misconceptions about the challenges, benefits and potential of returns on investment in the UK healthcare sectors have deterred the financial community from supporting the sector. It was with this in mind that the idea was born of pulling together a report that would demystify the sector, expose and debunk myths, showcase success stories, and provide the fundamental truths that investors need to know about investing in healthcare.

Over thirty of the sector's leading CEOs have joined forces with stalwarts such as the Minister for Life Sciences, the BIA, EY, LSE, Imperial Innovations, and Neil Woodford to endorse and contribute to this bold initiative. Biotech and Money is extremely proud to act as the vehicle for this endeavour.

So what can you expect?

- hard facts, data and in-depth case studies demonstrating how and where investors have

made money from the sector

- deep analysis of the myths, misconceptions and realities of investment in the sector
- analysis of access to capital in the UK, including VC investment trends
- comprehensive current market overview and assessment
- investor insight from Neil Woodford
- perspectives on the future of life science investment in the UK
- analysis and conclusions on the attractiveness of UK healthcare opportunities

We would like to acknowledge and thank each contributor for their effort and our analyst author Elizabeth Klein for her tireless efforts. I would like to also thank our company endorsers and members of the CEO forum, as well as Melanie Toyne-Sewell of Instinctif Partners without whose support this report would not be possible. We are particularly indebted to Darrin Disley, CEO of Horizon Discovery Group and Peter George, CEO of Clinigen Group for their vociferous support and enduring commitment to the project.

Terence O'Dwyer, Neil Darkes,

Co-Founders - Biotech and Money

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THE LIFE SCIENCES IN THE UK:

A LETTER FROM GEORGE FREEMAN, MINISTER FOR LIFE SCIENCES

I am delighted to contribute to this report, and to do so as the UK's first Minister for Life Sciences.

There is a huge amount to be proud of in UK life sciences. We have one of the strongest and most dynamic life science industries in the world. The sector generates an annual turnover of £56bn and ranks top in Europe in attracting foreign direct investment. Our life science companies, at all levels, compete confidently in global markets. In 2014, the total value of health and life science goods exports was approximately £27bn – 10% of all UK manufactured product exports. And the very latest trade data shows a 23% growth in exports of pharmaceutical goods in the first three quarters of 2015.

Underpinning this success is strong and consistent investment in R&D. The UK pharmaceutical sector alone accounts for 20% of all UK business R&D, more than any other sector. Standing behind this industry investment is the UK's world class science base and an increasingly strong and informed relationship between our universities and the wider life sciences community. It is fantastic that life science companies comprise by far the highest proportion of spin outs from UK universities – 42% over the past ten years, and 48% since 2012.

The Government is clear that life sciences is a priority sector for the UK economy. Since the Prime Minister launched the Strategy for Life Sciences in 2011, we have built a long term partnership between Industry and Government and provided direct and enabling support to unlock new growth and innovation. This has included:

- £2bn in public investment in health life science research via the Research Councils and National Institute for Health Research Programme;
- Over £250m awarded to 318 early stage companies and university ventures under the Biomedical Catalyst, attracting £120m of further industry investment and over £1bn in post-project financing through licensing deals and acquisitions;
- Over £200m dedicated to sequence 100,000 whole genomes, with a commitment to further funding made in the recent Spending Review;
- £55m to develop the Cell Therapy Manufacturing Centre;
- The Patent Box incentive that gives an effective 10% corporation rate tax incentive for qualifying profits on products derived from UK or EU patents. This has been particularly welcomed by the pharmaceutical industry (in the words of the GSK [GlaxoSmithKline] Chair Sir Andrew Witty, "The introduction of the Patent Box has transformed the way in which we view the UK as a place for new investments").

More broadly, the Government's recent Spending Review has strengthened the research foundations on which the life sciences sector is built. The Science Budget has been ring-fenced in real terms, we will invest £6.9bn in science capital between 2015-2021, and spending on the UK's Catapult network will increase during this Parliament.

So what does the future hold? How can we ensure that UK life science continues to compete successfully in a global healthcare market forecast to grow up to 10%

per annum over the next ten years? Continued investment in R&D, innovation, productivity and skills are clearly all vital. As well as this, there are a number of specific areas where the Life Sciences Industry and Government are working closely together, which offer strong potential to improve patient outcomes and deliver economic growth. I would like to highlight some of these here.

The first is the Accelerated Access Review that I announced in November 2014. The review, which is independently chaired by Sir Hugh Taylor, has seen an unprecedented coming together of patient, NHS, industry and academic voices behind a common goal – to revolutionise the speed at which 21st Century innovations in medicines, medical technologies and digital products get to NHS patients. The AAR's core assumption is that what is good for patients will also be good for growth, by making this country the world leading place to design, develop and deploy medical innovations. I am delighted that UK life science businesses are playing a full part in the review and contributing to solutions to simplify the pathways to regulatory approval so that patients get earlier access to good products. Sir Hugh published the review's interim report in October 2015 and is due to publish his final recommendations to Government by April 2016.

Genomics is another area of huge opportunity. The UK is already ahead of the curve here, and we need to stay there. The global genomics market is expected to grow 12% annually over the next three years, reaching a value of £19bn by 2018. Through the 100,000 Genomes Project, we are building one of the largest datasets in the world linking genomic and medical

data. I am delighted that the UK life sciences industry is contributing so actively to the Project through the Genomics Expert Network for Enterprises (GENE) consortium – a unique partnership between the NHS's Genomics Medicines Centres, industry and academia focusing on unlocking patient benefits from the data.

Finally, it is important that we grasp the health and innovation potential to UK life sciences from Digital Health. Developments in data analytics, mobile technology and personalised medicine offer us major opportunities to improve patient experience and outcomes, driving economic growth and reducing NHS costs. McKinsey have estimated that savings of between £8bn and £14bn could be generated for the NHS by 2020/21 by new digitally enabled services. The Government's Office for Life Sciences is working closely with industry and NHS partners to unlock opportunities in this area, feeding into a cross-Government Digital Transformation Plan to be published shortly.

Whilst these are exciting and challenging times, I am confident about the future of UK life sciences, and the long-term prospects for our investor community. Breakthroughs in genomics, new digital innovation and big data all bring disruptive challenges, but also great opportunities for increased productivity and UK leadership in this global industry. The Government will continue to be an active and supportive partner in helping you seize these opportunities, while working to make the UK the best place in the world to develop and bring new medicines and medical technologies to market.

INTRODUCTION

This report is a rallying cry to the wider financial community to support the UK Healthcare and Life Sciences sectors. These sectors have valuable companies that have delivered an attractive financial return to many investors and are likely to do so again. But these sectors need capital and development expertise to allow them to demonstrate their world-class technology and to compete against other key financial markets with a significant bioscience presence, such as the NASDAQ in the US.

We make the case for the UK Healthcare and Life Sciences sectors in four ways.

1. ***We present important facts about the UK Bioscience sector*** and in so doing debunk a number of myths. Our overview shows that UK companies in this sector can become global heavyweights, can raise money and, most critically, can deliver a return on investment.
2. ***We highlight challenges in these sectors***, not least the challenge of raising sufficient funds when they are needed. There is a strong, though relatively small, pool of highly supportive fund managers and VCs in this market, but a number of fund managers believe the sectors are too complicated, the timeframes are too long and investment carries too high a risk. Our evidence suggests that these worries are exaggerated, but tackling this damaging perception is a key task for the industry.
3. ***We demonstrate that the UK Healthcare and Life Sciences sub-sectors are world-class and positioned for strong growth***. We argue that Healthcare and Life Sciences in the UK are mature, well-managed, investable sectors that have global reach and global presence with innovative companies and opportunities available to investors. The sector is well supported by the government, charities and the global investment community, and further support and better access to capital would address many of the challenges identified.
4. ***We discuss access to Capital***, one of the drivers of success. Those investors who have had confidence in the Biosciences sector, and patience, have seen a return on their investment.

We finish the report with a series of ***case studies*** on five very different companies. We will discuss the features of successful businesses and how these characteristics overcome the challenges discussed previously, before reviewing examples of companies in the sector:

- a large, global therapy and devices business – ***BTG***
- a clinical trial and pharmaceutical services business – ***Clinigen Group***
- a high-tech technology and services business – ***Horizon Discovery Group***
- a rapidly emerging specialty pharma and drug delivery business – ***Midatech Pharma***
- a drug technology business – ***Skyepharma***

We will explain how and why these companies have been successful and what lessons can be learned from the challenges they have overcome.

This report is itself an illustration of the supportive and creative environment within which the UK Healthcare and Life Sciences sectors operate. A number of key stakeholders in the sectors have contributed articles for the report.

These include: George Freeman, the first Minister for Life Sciences who discusses the government's support for UK Life Sciences; Steve Bates, the CEO of the UK BioIndustry Association (the association for many in the industry) who gives an overview of the sectors and the BIA's role; Neil Woodford from Woodford Investment Management, one of the most influential investors in these sectors; Nigel Pitchford, CIO of Imperial Innovations, a key supporter of early stage businesses from one of the world's best universities; Andrew Jones of Ernst & Young's Transaction Services who discusses sector financing and Chris Mayo of the London Stock Exchange (LSE) who discusses some of the strategies the LSE has adopted to make London a favourable exchange for bioscience businesses.

Please note that all prices mentioned in the report are at close of business 19 January 2016.

THE UK BIOTECH ECOSYSTEM IS FLOURISHING AND CONTINUES TO LEAD EUROPE:

WRITTEN BY STEVE BATES,
CEO OF THE UK BIOINDUSTRY ASSOCIATION

As initial figures start to emerge on 2015 it is expected that UK bioscience will have seen another bumper year for biotech investment and this positive trend looks set to continue. The BIA and EY report on the State of the Nation at the end of last year showed that the UK biotech ecosystem is flourishing and continues to lead Europe in terms of capital raised and the pipeline of products.

Despite the tough economic choices that the Chancellor faced in the Spending Review it was great news to see that the £4.7 billion annual science budget has been protected in real terms, rising by a further £500 million by 2020. This is testament to the collaborative effort from the science community last year in advocating the importance of science investment.

The UK is home to two of the world's top three universities for life sciences, as well as 4,398 life sciences companies and their sites developing, manufacturing and marketing products and services to the UK and global markets. The BIA has been at the forefront of creating an environment that makes the UK stand out from international competitors and there are a number of key areas that attract investors to the UK bioscience industry.

The UK has a strong and supportive fiscal environment: The BIA continues to lobby on behalf of the industry to create an environment that attracts the private sector investment that the industry needs to grow and succeed. Undoubtedly the fiscal environment for

emerging life science in the UK is globally competitive and this is a crucial factor influencing companies' decisions to invest here. We will continue to promote the valuable role of the Patent Box, R&D tax credits and tax-advantaged investment schemes for encouraging and supporting investment in our sector, and we welcome the Government's ongoing positive focus on this area.

The UK produces investable science and has a great deal of translation capability: Investors and globally mobile life science multinationals will seek out investable science from wherever it comes; public funding support such as that provided via the Biomedical Catalyst enables UK science to be developed to a similar technology- and investor- readiness level as state funding does for science in the USA. The UK's strategy for life sciences is clearly working as over the last four years, the UK has attracted more than £3.5 billion of industry and private sector investment.

Following the Government's Spending Review at the end of last year, the key challenge in 2016 will be addressing the issue of to what extent existing Innovate UK grants will be replaced with loans or other non-grant products. What is essential now is to track this development and ensure fit-for-purpose initiatives are developed for high risk, high innovation sectors such as bioscience and that Innovate UK can continue to effectively bridge the so called 'valley of death' for early stage research in life sciences.

The UK is a society that's supportive of life science innovations to further human health: In February last year, the UK became the first country to pass laws approving mitochondrial transfer, by a majority vote of 254. At the time, government minister Earl Howe commented: "Families can see that the technology is there to help them and are keen to take it up, they have noted the conclusions of the expert panel."

It's important that we celebrate investor confidence in UK bioscience as we take another step on the way to the BIA vision of building the third global cluster in the UK. To allow the sector to build on this success, the BIA will continue to work with the Government to maintain its support that is crucial to attracting investment into the sector.

SECTION 1. THE TRUTH ABOUT THE UK'S HEALTHCARE AND LIFE SCIENCES SECTORS

Too few people recognise that Britain is a global player in Life Sciences. This is typical of a nation that often celebrates failure more than success. We're useless at football (winning the Men's World Cup only once in twenty championships). We are hopeless at the Eurovision Song Contest (winning only five times in 60 years¹). We're not much good at rugby, as demonstrated by the pitiful performance in the most recent World Cup. But we are world beaters in Life Sciences and Health².

There are certainly a few fables about UK Life Sciences,

which we discuss below. But three of the world's largest healthcare companies (GlaxoSmithKline, AstraZeneca and Smith & Nephew) began in the UK and are still based here. Numerous other companies are conducting research in the UK. There is a robust pipeline of new therapies, a health system that is the envy of many, a highly innovative Small and Mid-Cap sector, a supportive government, a strong charitable sector, generous philanthropy and some of the best universities in the world. We summarise the fables and truths below, and discuss the UK's attributes in more detail in Section 2.

FIGURE 1: MYTHS & FACTS

Myth	Fact	Verdict
All Life Sciences companies are similar	Life Sciences companies are represented in two FTSE sectors in the UK: Pharmaceuticals & Biotechnology, and Health Care Equipment & Services ³ . Even the AIM companies could be broadly split along the same lines. However, these two sectors do not do justice to the huge variations of size, strategy, focus and therapy. For instance, the largest is the pharmaceutical giant GlaxoSmithKline with a market capitalisation of £67.9bn while one of the smallest is Akers Bioscience, a point of care diagnostics business with a market cap of under £5m. In between lies everything from manufacturers of respiratory equipment (Consort Medical market cap £495m), to gene editing technologies (Horizon Discovery Group market cap £126.8m).	Untrue
The UK can innovate but can't commercialise	This enduring myth is based on a few famous cases, such as penicillin, which was discovered in 1928 by Alexander Fleming at London's St. Mary's Hospital and commercialised in the US. But there are many more examples where the UK has successfully commercialised technology or generated income from commercialising it. For instance, the CAT scan, invented in 1972 by British engineer Godfrey Hounsfield ⁴ was successfully commercialised from the UK. So too was Campath/Lemtrada ⁵ , a drug now used to treat Multiple Sclerosis: it was originally synthesised by Herman Waldmann in Cambridge, and licensed by BTG. It is now in the hands of Genzyme (Sanofi).	Was partly true but managing IP in the UK is now more refined

Myth	Fact	Verdict
All British biotechs are British Biotech ⁶	Investors often cite the rise and demise of British Biotech as a reason to shy away from investing. British Biotech was founded in 1986 in order to investigate two therapies: marimastat (for the treatment of metastatic pancreatic cancer) and lexipafant (for pancreatitis). It floated in 1992 at a price of 42p, and at its peak was worth c£1.9bn ⁷ . But there were problems both around management of the business and the clinical trials, and the company later came under investigation ⁸ . While this is one of the most notorious biotech disasters, it is not the only one ⁹ and many of the others were outside the UK. But focusing on this one calamity obscures ¹⁰ the multiple successes. These include: Cambridge Antibody Technology which was acquired by AstraZeneca in 2006 for £702m having been founded in 1986 ¹¹ , and which discovered Humira (for the treatment of rheumatoid arthritis), one of the world's bestselling drugs; Circassia Pharmaceuticals which was floated out of Imperial Innovations and is focused on the allergy and respiratory sector; and Vectura another key respiratory development business in the UK with multiple deals with major Pharmaceutical businesses.	Untrue
It is all about Big Pharma	While the three largest UK listed Life Sciences companies, GlaxoSmithKline, Abbott Laboratories and AstraZeneca accounted for 72% of the Main Market and AIM Life Sciences total market capitalisation ¹² , the vast majority of companies (113 in total ¹³) and deals for funds in the UK Life Sciences sectors were in the Small and mid-cap area. The same is true for the development of new drugs: 70% of over 3400 clinical stage projects currently in development have been advanced by small companies ¹⁴ .	Untrue
The Life Science sector is the only risky sector in the UK	Yes, there are risks around the development of new therapies, not least the long time to approval, the high costs ^{15/16} and the relatively high failure rate – around 8-13 projects are needed in the pre-clinical stage to result in one successful launch ^{17/18} . But this is by no means the only risky sector: high failure rates are a feature of the IT sector, for instance, as well as the oil and gas sectors ¹⁹ .	Untrue
The UK is fixated on healthcare that saves money	There is a belief that because we have the cash-strapped NHS in the UK, the Life Sciences and Healthcare sectors are solely focused on saving money. While there are indeed companies that offer services to the NHS to better manage its limited resources, this is only a small proportion of the UK industry. Most companies are involved in high-tech, innovative science. In any case, the NHS constraints can be a source of positive pressure, incentivising companies to become more innovative and not reliant on an expensive healthcare system. See page 30 section for a more detailed discussion.	Untrue
It is difficult to raise money in the sector	The UK had one of its best years in 2014, and raised further significant funds during 2015. True, much of this money came from a small group of supportive shareholders. But many companies came back to the market for further funds. For instance, of the 845 companies on AIM in 2015, 79% of monies raised were for further funding ²⁰ .	Only partly true

Myth	Fact	Verdict
Biotech and Healthcare are too complicated for generalists	Many of the UK's science based businesses are founded by scientists and are based on highly innovative concepts. Unfortunately, many generalist investors have no scientific background and are, understandably, wary of investing in things they don't understand. However, a strong communication strategy can help overcome this hurdle and the science can be made accessible.	Partly True
The golden age of biology in the UK has passed	While we are no longer in the era of Watson & Crick and their ground-breaking research into DNA, the UK has some of the best universities in the world and has made many key technology leaps over the last fifty years. In the UK we are still living in a golden age of biology with immuno-oncology, genetic engineering, and antibody development companies based here.	Untrue

1 Source <http://www.eurovision.tv/page/history/facts-figures>. Downloaded 6/10/2015

2 A Report by the All-Party Parliamentary Group on Global Health. Hasan, N. et al "The UK's Contribution to Health Globally: Benefiting the country and the world" Published 29th June 2015.

3 Note that not all Bioscience businesses are in these sectors.

4 From <http://www.imaginis.com/ct-scan/brief-history-of-ct>. Downloaded 6/10/2015

5 See <http://www.whatisbiotechnology.org/exhibitions/campath/introduction> for an interested history of the drug. Downloaded 1/10/15.

7 Murray-West, R. "British Biotech reborn as Vernalis" The Telegraph 4 July 2003.

8 <http://www.publications.parliament.uk/pa/cm199798/cmselect/cmsctech/888/88804.htm>. Downloaded 13/10/15

9 Booth, B. "This time may be different" in Volume 34 Number 1 January 2016 Nature Biotechnology

10 Hodgson, J. "Ten years of biotech gaffes" in Nature Biotechnology 24, 270 - 273 (2006)

11 <http://www.astrazeneca.com/Media/Press-releases/Article/20060822--AstraZeneca-UK-Limited-Completes-Acquisition-of-Cambr>. Downloaded 13/10/15

12 See <http://www.londonstockexchange.com/statistics/companies-and-issuers/companies-and-issuers.htm> for 31st Dec 2015 analysis.

13 See <http://www.londonstockexchange.com/statistics/companies-and-issuers/companies-and-issuers.htm> for 31st Dec 2015 analysis

14 Booth, B. "This time may be different" in Volume 34 Number 1 January 2016 Nature Biotechnology

15 http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study. Downloaded 1/10/15

16 <https://www.london.gov.uk/sites/default/files/Drug%20Development%20Funding%20Report%20250615%20For%20Publication%20%28Fin%20al%29.pdf> 14/10/15

17 DiMasi, J. et al Briefing: Cost of Developing a New Drug November 18, 2014 TUFTS

18 Bains, W. "Failure rates in drug discovery and development: will we ever get any better?" in Drug Discovery. Fall 2004

19 Gotham, R. "The Story Behind the High Failure Rates in the IT Sector" Callear Consulting Ltd <http://callear.com/WTPF/wp-content/uploads/articles/Whatmakes.pdf>. Downloaded 13/10/15.

20 See <http://www.londonstockexchange.com/statistics/historic/aim/aim-statistics-archive-2015/dec-15.pdf>

SECTION 2: CHALLENGES

There is much evidence that the Biosciences sectors are crucial to the strength of the UK economy, and crucial to investors' success. Investors may be concerned by the long timescales and risks involved in drug development, the impact of ongoing austerity policies in the UK, the funding gap for earlier stage businesses, the upcoming US election this year, uncertainty around the global macro-economy, the heightened volatility in financial markets and the "global capacity glut"²¹. But the Government certainly believes in and supports the sector, and it has ring-fenced the science budget in real terms, as discussed in the contribution by the Minister for Life Sciences, George Freeman (see page 4). However, while short-term economic challenges exist and must not be downplayed, the long term challenges are more critical to the ongoing evolution of the UK health sectors.

From our investigation of the market and the case studies, we believe there are certain challenges which must be addressed:

- **To enlarge the pool of investors.** The culture in the UK is more cautious than in the US where "VCs bet big or they go home"²², and it can be difficult to fully fund development and to raise financing for later stage projects²³. Whilst there is unlikely to be any dramatic shift in the ethos in the short term, the companies and players in the sectors can help UK investors by:
- **Making the science accessible.** Even specialists in the sector, with backgrounds in medicine or biology, can be baffled when some founders and senior executives attempt to explain their ideas. Our case studies highlight businesses that have succeeded by clearly communicating science and strategy to investors.
- Being **upfront about the risks**, the costs and the long time frames. For instance:
 - Not all drugs will work – but a portfolio approach can help spread the risk. On average

8-13 projects are needed in the pre-clinical stage to result in one successful launch of a new drug^{24/25}.

- The most recent estimates from the TUFTS Center for the Study of Drug Development suggest that developing a new drug can take a decade and cost around US\$2.6bn (encompassing out-of-pocket cost of US\$1.4bn and time costs of US\$1.2bn)²⁶.
- These risks are understood by the more supportive shareholders, who take numerous positions in many businesses. These investors can enjoy the rewards later, possibly with multi-billion-dollar blockbuster drugs or technology, and a significant return on their investment.
- Understandably, **generalist investors can struggle with the high-risk, long-term nature of the sector.** Often those that remain uncomfortable have looked to invest in those companies with lower risk profiles – e.g. companies that are generating revenue with products already on the market. Interestingly, executives who are upfront about the risks often receive a better response from investors.
- **Managing the public relations controversies about drug pricing**²⁷. Recent price hikes for drugs are straining healthcare systems. While some of these price rises seem unwarranted²⁸ and counterproductive²⁹, the UK Life Sciences market needs to convey the reasonable message that pharma companies have to make an economic return from the risks of drug development³⁰.
- **Applaud successes and ensure monies are reinvested in the sector.** In classic British fashion, the UK Bioscience sector tends to downplay its successes. The investment community, along with management, academics, and the government, need to acknowledge what the UK is good at and

remind investors that they can make an attractive financial return. This report will start to do that. And, those who have made a profit in the sector should be encouraged to reinvest, supporting new and innovative businesses.

- ***To retain and build a pool of exceptional management.*** Good management make the right decisions for their companies at the right time and can communicate these decisions clearly and effectively. The UK has a limited number of brilliant, experienced managers – and some of these managers are being enticed away by the IP commercialisation businesses and by experienced venture capitalists. Of course, this will benefit many of the companies that will become stalwarts of the sector. But somehow the sector has to enlarge its cohort of managers who possess the appropriate communication skills and experience. The shortage of quality management is a challenge acknowledged by key players in the sector. And although this report does not offer solutions to this problem, some commentators, for instance the CEO of F-star (a developer of novel bispecific antibodies), believe that the barriers to recruitment from overseas into the UK are too high.

21 <https://woodfordfunds.com/insight/a-letter-from-america/>. Downloaded 8/10/15

22 Cadwallader, C. "Is the dotcom bubble about to burst (again)?" in The Observer 4/10/15

23 <https://www.london.gov.uk/sites/default/files/Drug%20Development%20Funding%20Report%20250615%20For%20Publication%20%28Fin%20al%29.pdf> - Downloaded 14/10/15

24 DiMasi, J. et al Briefing: Cost of Developing a New Drug November 18, 2014 TUFTS

25 Bains, W. "Failure rates in drug discovery and development: will we ever get any better?" in Drug Discovery. Fall 2004

26 Estimates from http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study

27 Booth, B. "This time may be different" in Volume 34 Number 1 January 2016 Nature Biotechnology

28 See https://www.chathamhouse.org/expert/comment/medicines-pricing-there-better-way?utm_source=Chatham%20House%20Newsletter&utm_medium=email&utm_campaign=6254470_Newsletter%20-%202009.10.2015&dm_i=1TYB,3Q1ZA,KGWX7A,DEFI5,1. For Chatham House's interesting take on this issue.

29 Koons, C. "This Drugmaker Suffered the Consequences of Price Increases" Bloomberg 12/10/15

30 Neumann, P. J. & Cohen, J. T. "Measuring the Value of Prescription Drugs" in the NEJM November 18, 2015

SECTION 3. THE UK LIFE SCIENCES AND HEALTH SECTORS ARE WELL-POSITIONED

This section tackles many of the concerns raised by investors, delivering detailed evidence to remind investors of the strength and opportunities available in the UK Life Sciences and Health sectors. Despite the challenges highlighted in the previous section, the weight of evidence supports our contention that the UK has world-beating Life Sciences prospects. Certainly a number of commentators believe that the sector is still able to deliver a positive return following the strong performance of the global sector over the last 15 years, despite the choppy start to 2016. Reasons cited include: favourable demographics, increased innovation, an increase in the number of new therapy approvals, improved productivity and significant M&A opportunities. All of which we discuss in more detail below.

31 For instance: Booth, B. "This time may be different" in Volume 34 Number 1 January 2016 Nature Biotechnology; the author of this paper etc.

FUTURE GROWTH IN THE GLOBAL PHARMA/MEDTECH MARKET

The market opportunity for companies in the Biosciences sectors is large and growing. Between 2014-17, global healthcare spending is projected to rise by 5.2% p.a.³². Meanwhile, forecasts³³ suggest that:

- Worldwide **MedTech** sales will reach US\$477.5-514.0bn by 2020, even though MedTech is growing marginally slower than the pharma market at a CAGR of 4.1% between 2014 and 2020 vs 4.9% for pharma³⁴. MedTech R&D spending was US\$22.9bn in 2013, and is projected to grow by 4.2% pa to reach \$30.5bn in 2020.
- Global Pharma sales were c.US\$749bn in 2014 and are projected to grow by 5.1% pa to reach US\$1tn by 2020. The early part of this decade saw a contraction in revenues, but because of the acquisitive nature of these businesses we expect pipelines to be maintained. In 2013 there were 545 Pharma companies in the UK, 47 of which had a turnover greater than £100m. Together they employed 70,000 people. Total combined turnover was £32.4bn.

- In 2014 there were over a thousand Biotech companies in the UK, generating a turnover of £4.8bn and employing 23,000 people. This sector has the fourth-largest pipeline of drugs in the world and the largest in Europe (460 drugs). Biotech is expected to become one of the main sources of treatments with revenues in 2013 of US\$165bn projected to reach US\$291bn in 2020. In addition, Biotech companies are expected to originate more than half of the top 100 pharmaceutical products.

DEMOGRAPHICS

The global market opportunity in healthcare is growing substantially. In part this is through centralised healthcare systems, in particular the US Affordable Care Act (aka Obamacare). But the main driver is demographic. The average life expectancy at birth now stands at 71 years³⁵ and the developed world in particular will have to face up to the challenges and costs of dealing with a growing number of elderly people.³⁶

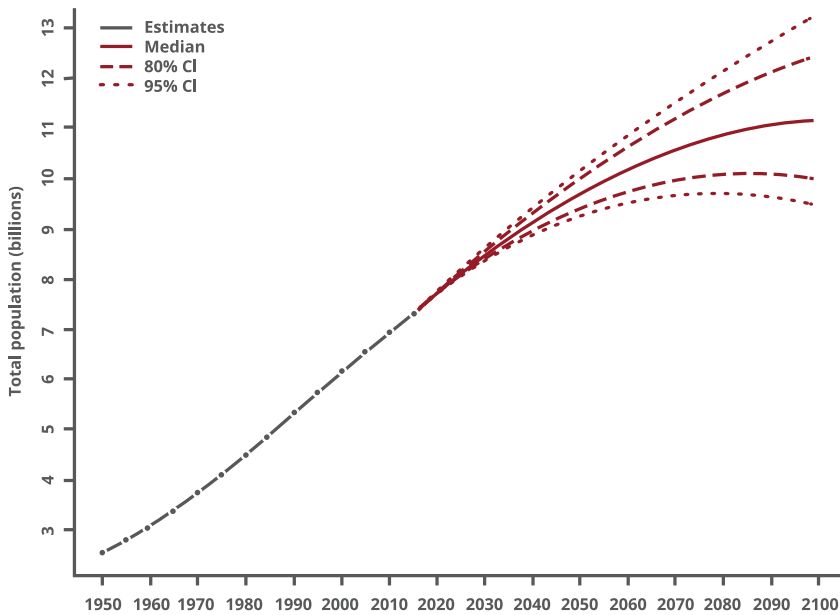
FIGURE 2: ESTIMATES OF POPULATION AND ITS PERCENTAGE DISTRIBUTION, BY AGE AND SEX AND SEX RATIO FOR ALL AGES FOR THE WORLD, MAJOR AREAS AND REGIONS: 2013

Major areas and regions	Population (millions)												Sex ratio
	Both sexes				Male				Female				
	All ages	0-14	15-64	65+	All ages	0-14	15-64	65+	All ages	0-14	15-64	65+	
WORLD TOTAL													
Number	7,162	1,878	4,713	570	3,610	971	2,385	254	3,552	907	2,328	317	
Percent %	100	26.2	65.8	8	100	26.9	66.1	7	100	25.5	65.5	8.9	101.7
AFRICA													
Number	1,111	454	618	39	555	230	308	17	555	224	310	21	
Percent %	100	40.9	55.6	3.5	100	41.4	55.5	3.1	100	40.4	55.8	3.8	100
LATIN AMERICA AND CARIBBEAN													
Number	617	166	406	45	303	85	199	20	313	81	207	25	
Percent %	100	26.9	65.9	7.2	100	27.9	65.6	6.5	100	25.9	66.1	8.0	96.8
NORTHERN AMERICA													
Number	355	68	237	50	175	35	118	22	180	33	119	28	
Percent %	100	19.2	66.7	14.1	100	20	67.5	12.6	100	18.5	65.9	15.6	97
ASIA													
Number	4,299	1,065	2,926	308	2,200	558	1,500	143	2,099	507	1,426	165	
Percent %	100	24.8	68.1	7.2	100	25.4	68.2	6.5	100	24.2	68	7.9	104.8
EUROPE													
Number	742	116	502	125	358	59	248	50	385	56	254	75	
Percent %	100	15.6	67.6	16.9	100	16.6	69.3	14.1	100	14.6	65.9	19.4	92.9
OCEANIA													
Number	38.30	9.13	24.81	4.36	19.16	4.7	12.45	2.01	19.15	4.43	12.36	2.35	
Percent %	100	23.8	64.8	11.4	100	24.5	65	10.5	100	23.1	64.6	12.3	100.1

Source: United Nations Statistics Division Year Book 2013.

The global population is expected to expand from 7 billion today to 8.5 billion by 2030, and life expectancy is expected to reach 83 years by 2100³⁷. With the aging population comes more chronic disease.

FIGURE 3: POPULATION OF THE WORLD: ESTIMATES, 1950-2015, MEDIUM-VARIANT PROJECTION AND 80 AND 95 PER CENT CONFIDENCE INTERVALS, 2015-2100



Source: United Nations, Department of Economic and Social Affairs, Population Division (2015). World Population Prospects: The 2015 Revision. New York: United Nations.

HIGHER BURDEN OF DISEASE

Diseases that hit the elderly have become the main cause of death, a development that is likely to become more pronounced. This will aggravate the already high cost of disease. For example:

- According to the Five Year Forward Plan³⁸ for the NHS: "...one in five adults still smoke. A third of people drink too much alcohol. A third of men and half of women don't get enough exercise. Almost two-thirds of adults are overweight or obese. Even more shocking, the number of obese children doubles while children are at primary school. Fewer than one in ten children are obese when they enter reception class: by the time they're in year six the figure is one in five. These patterns are influenced by, and in turn reinforce, deep health inequalities which can cascade down the generations."
- The same plan estimates that a third of over-65s in the UK will develop dementia before they die. Dementia affects c.47.5m worldwide at a

cost of US\$600bn³⁹. The burden of this disease is expected to triple globally by 2050. In the UK this will need to be shouldered by the NHS, local government and family carers. So, in March 2015 the UK announced a US\$100m Dementia Discovery Fund – creative financing for dementia research. Alzheimer's UK has also launched a £100m campaign over five years aimed at testing promising new treatments. Meanwhile, the Medical Research Council, in conjunction with six companies (including GSK and AZN), has announced the world's biggest study into dementia, involving two million people.

APPROVALS ARE INCREASING

The pharma companies are responding to the worsening disease outlook with new therapies. In the pharma market, approval rates have increased dramatically since 1996. In 2014, 44 new drugs were approved, spanning ten therapeutic areas – a

record high, which was only surpassed in 2015 with 45 new approvals towards the end of December⁴⁰. Large pharma companies continue to dominate with J&J (Johnson & Johnson), GSK, Roche and AZN getting 44% of approvals⁴¹.

In the MedTech market the regulatory environment is favourable too. The number of first-time PMAs (Pre-Market Approvals) and HDEs (Humanitarian Device Exemptions) was up 43% in 2014 to 33. So-called 510(k) clearances (where a product is approved because it is similar to another, already approved product) increased 5% in the same year to 3,244. In the first eight months of 2015, the FDA approved 30 new PMAs⁴². At the same time, worldwide MedTech R&D expenditure is forecast to increase 3.5% pa to US\$29.5bn by 2020 – impressive, but slightly lower than sales growth.

Over the last three decades the global biotech market has spawned 260 new biotechnology products for 230 diseases and these have generated global sales exceeding US\$175bn⁴³ in 2013 - from more than 4600 biotech companies worldwide.

M&A

With increasing numbers of new drugs, thin late-stage Big Pharma pipelines and a higher burden of disease, comes more aggressive competition. Large companies are looking for new technologies to retain their competitive edge and to maintain their pipelines. Smaller businesses can be nimbler and more creative: new therapies, such as the CAR-T, often originate from smaller companies and from universities. M&A

has therefore become an attractive exit strategy for companies in the Small and Mid-Cap space, and 2016 is expected to see a substantial amount of M&A activity⁴⁴, and fewer IPOs⁴⁵.

Over the years, many UK companies have been acquired by US peers. The US market remains buoyant, driven in the past decade by a number of megamergers, and more are expected in 2016⁴⁶.

FIGURE 4: THE 20 LARGEST M&A DEALS IN LIFE SCIENCES FROM 1995-2015

Date	Target Name	Acquirer Name	Seller Name	Value (US\$m.)	Payment Type	Total Value/EBIT DA
23/11/2015	Allergan	Pfizer Inc		160,000	Stock	11.10
04/11/1999	Warner-Lambert Co	Pfizer Inc		87,319	Stock	31.11
26/01/2004	Sanofi-Aventis SA	Sanofi		73,477	Cash and Stock	11.30
17/01/2000	SmithKline Beecham Ltd	GlaxoSmithKline PLC		72,445	Stock	19.05
17/11/2015	Allergan Inc/United States	Allergan PLC		65,024	Cash and Stock	31.23
15/07/2002	Pharmacia Corp	Pfizer Inc		64,264	Stock	
26/01/2009	Wyeth LLC	Pfizer Inc		64,234	Cash and Stock	8.08
17/04/2015	Mylan NV	Teva Pharmaceutical Industries Ltd.		49,912	Cash and Stock	27.63
09/03/2009	Schering-Plough Corp/Pre-merger with Merck & Co	Merck & Co Inc		47,147	Cash and Stock	15.62
15/06/2014	Covidien PLC	Medtronic PLC		46,236	Cash and Stock	17.05
21/07/2008	Genentech Inc	Roche Holding AG		44,047	Cash	15.72
08/04/2015	Perrigo Co PLC	Mylan NV		34,870	Cash and Stock	28.56
09/12/1998	Astra AB	AstraZeneca PLC		30,408	Stock	15.06
07/03/1996	Ciba-Geigy AG	Sandoz AG		28,977	Stock	8.63
12/11/2014	Zoetis Inc	Potential Buyer		28,000	Undisclosed	24.73

Date	Target Name	Acquirer Name	Seller Name	Value (US\$m.)	Payment Type	Total Value/EBIT DA
07/04/2008	Alcon Inc	Novartis AG	Nestle SA	25,851	Cash	22.99
05/12/2005	Guidant LLC	Boston Scientific		25,228	Cash and Stock	25.31
19/12/1999	Pharmacia & Upjohn Inc	Pharmacia Corp		25,196	Stock	
18/02/2014	Forest Laboratories Inc	Allergan plc		20,781	Cash and Stock	60.36
04/03/2015	Pharmacyclics Inc	AbbVie Inc		19,777	Cash and Stock	155.98

Source: Bloomberg

With fewer, but larger, companies remaining in the sector, competition is expected to become yet more fierce. Despite the substantial amount of M&A over the last ten years, the two top companies in the major markets of US, Japan and UK have remained the same: the behemoths are still the critical players.

FIGURE 5: TOP 3 LARGEST LIFE SCIENCES BUSINESSES BY MARKET CAP

2015	1	2	3	Total Market Cap (m)
Japan	Takeda Pharmaceutical Co Ltd	Astellas Pharma Inc	Chugai Pharmaceutical Co Ltd	¥ 10,676,859.07
UK	GlaxoSmithKline Plc	AstraZeneca Plc	Shire Plc	£145,612.05
US	Johnson & Johnson	Pfizer Inc	Gilead Sciences Inc	\$604,894.79

2005	1	2	3	Total Market Cap (m)
Japan	Takeda Pharmaceutical Co Ltd	Astellas Pharma Inc	Daiichi Sankyo Co Ltd	¥ 9,985,873.96
UK	GlaxoSmithKline Plc	Astra Zeneca Plc	Smith & Nephew Plc	£135,188.51
US	Johnson & Johnson	Pfizer Inc	Amgen Inc	\$448,032.72

Source: Bloomberg. Data as of 02/09/2015

2015 M&A

A recent report by Mergermarket showed that 2015 was a very active year. The first three quarters saw the highest value M&A since 2001 with 954 transactions worth US\$367.6bn (including Perrigo/Mylan). Of these, 268 deals worth US\$231.5bn were Pharma, Biotech accounted for US\$12.6bn, and the rest were MedTech. The majority of the deals were in the US (US\$271bn), while the European deals were worth US\$62.1bn⁴⁷.

This impressive figure for 2015 actually masked a small decline in the number of deals, the headline sum being skewed by the inclusion of Medtronic's US\$49.9bn acquisition of Covidien (Irish Listed) in January 2015⁴⁸. In H2, meanwhile, the merger of Pfizer and Allergan was announced – the largest pharma deal ever, worth c.US\$160bn⁴⁹. This is expected to complete in H2 2016. One of the main attractions for Pfizer was the chance to move to Ireland's more attractive tax regime – its tax rate will drop from 25% in 2014 to an expected

pro forma adjusted effective tax rate of 17%-18% by the first full year after closing⁵⁰. However, the move has been controversial in the US with some politicians complaining about the loss of taxes. Some tax loopholes may be closed – and this could discourage some mooted megamergers.

Meanwhile, the Mergermarket report estimates that there are 360 potential target companies in the US and 178 in Europe.

MegaMergers aren't the only option

Where megamergers are not realistic, large companies have been active in buying IP or smaller businesses or using other methods to get access to assets and IP of interest. Sometimes there are small deals. To give one example, UK-listed ophthalmology business, Optos, was acquired by Nikon in May 2015 for US\$397m, filling a gap for Nikon, at an attractive price, while allowing Optos to get its products to market more quickly and cheaply. Some are not complete acquisitions, only certain assets may be acquired: for instance, on 18th Dec 2015, GlaxoSmithKline-controlled ViiV bought the Bristol-Myers Squibb pipeline of HIV drugs for up to US\$3bn (US\$317m upfront).

M&A is not the only option

A number of the larger pharma companies have been engaging in asset swaps: Novartis and GlaxoSmithKline started a trend with a sale-and-asset-swap announced in 2014; more recently in Q4 2015, Sanofi and

Boehringer Ingelheim traded the former's animal health business for the latter's consumer healthcare division. It wasn't a straight swap: Boehringer paid an additional €4.7bn.

At the same time, more innovative company structures are having a positive impact on the deal climate. For example, private F-star (which is developing a series of oncology therapies) set up two asset-centric vehicles into which it has moved certain key oncology assets. The aim is to accelerate development and find partners. The first of these vehicles, created in October 2013, subsequently entered into an exclusive option with Bristol-Myers Squibb for up to US\$475m (including a US\$50m option fee, milestones and royalties)⁵¹.

Finally, some companies are raising money in a completely non-traditional manner. For instance, Axol Biosciences (a partner of Horizon Discovery Group) – see below – which was co-founded by Jonathan Milner (of Abcam fame) is going down the crowdfunding route.

It is not uncommon in the pharmaceutical sector for companies to be taken over multiple times. For instance, in 2013 Otsuka acquired Cambridge-based oncology specialist Astex Pharmaceuticals for US\$886m, the seventh largest deal that year⁵². While private, Astex had previously been acquired by SuperGen in 2011 for c.US\$55m, and the name of the combined entity changed to Astex.⁵³ During this time, it acquired more partners and continued its drug development programmes.

32 A Report by the All-Party Parliamentary Group on Global Health. Hasan, N. et al "The UK's Contribution to Health Globally: Benefiting the country and the world" Published 29th June 2015

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50 www.pfizer.com Presentation on merger with Allergan

51 See www.f-star.com

52 HBM Pharma/Biotech M&A Report, 2013

53 See www.astx.com

THE UK LIFE SCIENCE SECTOR IS A GLOBAL PLAYER.

A recent review by the All-Party Parliamentary Group on Global Health confirms that the UK excels in many aspects of the sector. For instance:

- The UK has a strong commercial sector, generating exports of £749m in 2014/15 alone (with total export opportunities worth nearly £12bn), up 34% yoy. There are more than 4800 Life Sciences businesses in the UK in total, which employ 180,000 people and generate £55bn pa in revenues⁵⁴.
- They include 3,200 MedTech companies, generating a turnover of £18.1bn and employing 88,000 people. Of these, 97% are SMEs. From 2009-2014, the whole MedTech subsector saw revenue growth of c.5.8% pa and employment grew at 9.1% pa.
- The UK has Europe's leading biotech sector⁵⁵.
- The UK has a strong network of relationships with numerous hospitals and agencies around the world, through both government and NGO sectors⁵⁶.
- The UK spends considerable sums on health research. In 2009, the UK spent the fourth highest amount on health research at US\$12bn, after the USA (US\$119bn), Japan (US\$18bn) and Germany (US\$13bn). As a proportion of GDP, the UK is sixth, after Switzerland, Iceland, Denmark, the USA and Sweden⁵⁷.
- The UK is well known for its research and scientific creativity, though there remain some challenges. See Figure 8.

FIGURE 6: THE PHARMACEUTICAL INDUSTRY IN THE UK

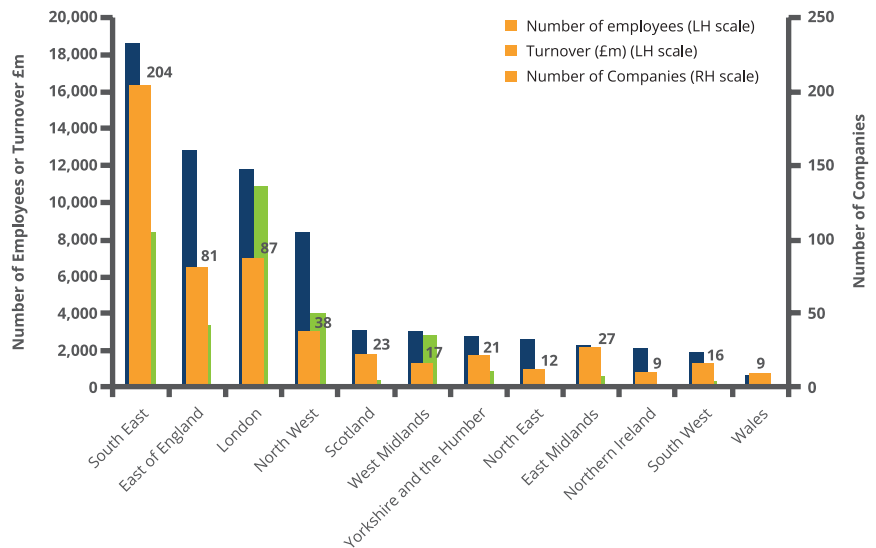
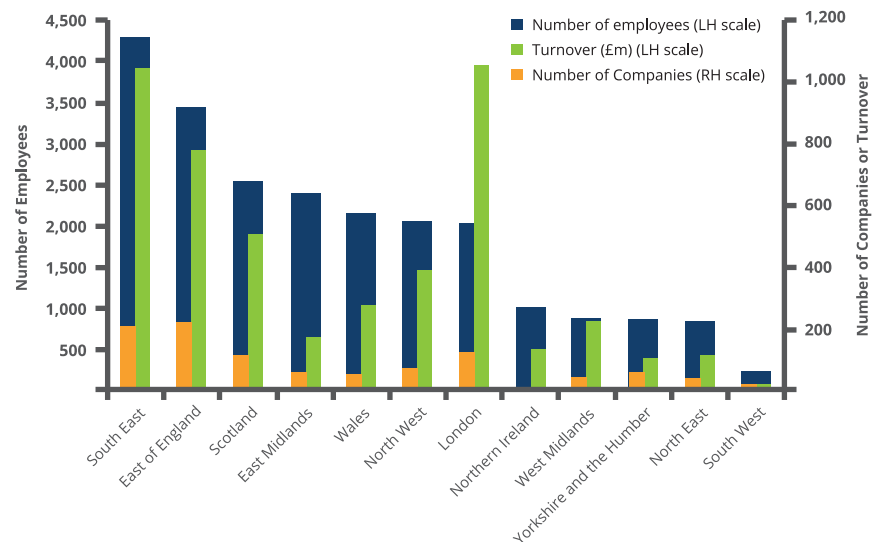


FIGURE 7: THE BIOTECHNOLOGY INDUSTRY IN THE UK



Source: London as a test bed for innovative models of finance – maximising the economic impact of life sciences research and development June 2015 Mayor of London Office.

FIGURE 8: ALL-PARTY PARLIAMENTARY GROUP ON GLOBAL HEALTH – REVIEW OF THE UK’S STRENGTHS AND CHALLENGES

Strengths	Challenges and risks
Partnerships, collaboration, networks	Changing world power
Education, research and development	Human resources and commercial funding
The NHS, health systems and influence globally	Uncertainties surrounding, and alternative models, for the NHS
Commitment to international development	Focus on only a few countries with large regional gaps
Culture, creativity, standards and probity	Competition

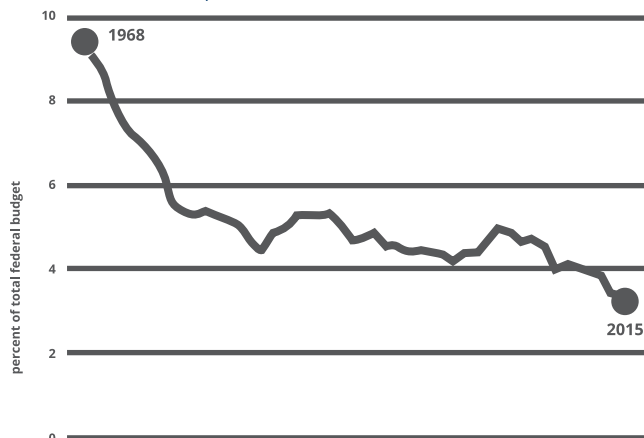
Source: A Report by the All-Party Parliamentary Group on Global Health. Hasan, N. et al "The UK's Contribution to Health Globally: Benefiting the country and the world" Published 29th June 2015.

WHERE IS THE COMPETITION?

Much has been made of the US as the main competitor for the UK Life Sciences and Healthcare sectors, and it remains an important market. But according to a report by the Massachusetts Institute of Technology, the US is declining in importance⁵⁸. From 1999-2009 US R&D expenditure fell from 38% to 31%⁵⁹, and the NIH budget has remained broadly static at c.US\$31bn⁶⁰. Funding is constrained: for instance, the National Institute of Aging in the US only has enough money to support 6% of the research ideas it receives⁶¹.

At the same time, other regions have seen a substantial increase in spending. The European Commission has increased spending significantly over the last 15-20 years and the figures are expected to rise further. A few years ago, the European Commission

FIGURE 9: FEDERAL R&D | OUTLAYS AS SHARE OF TOTAL FEDERAL BUDGET, 1968–2015



Source: American Association for the Advancement of Science

recommended the Horizon 2020 project, under which member states’ R&D budgets should be increased to €80bn, spread over the period 2014–2020 (up 40% from the previous seven years)⁶². The largest growth in global R&D spending has come from the southeast Asian markets: they saw their share of worldwide R&D expenditure increase from 24% in 1999 to 32% in 2009. Chinese R&D spend is expected to hit US\$113bn in 2020⁶³ and the spending gap between China and the US on biomedical research could close by 2022⁶⁴.

Therefore, we believe that companies in our Biosciences sectors should not be overly focused on the US, but should look to compete worldwide. This international strategy is paying off for the likes of Abcam and Clinigen.

UK VS US LISTING

Over the last two years, there has been a favourable climate for IPOs. In 2014 there were 40 MedTech IPOs, up from 23 the year before⁶⁵. 2015 started well across both markets: there were 46 Biotech IPOs in the US, the second highest number in 29 years⁶⁶. But new issues tailed off in Q4 across both markets as economic concerns dampened confidence⁶⁷.

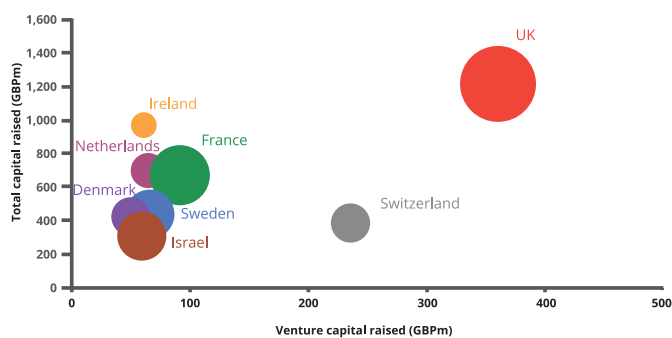
A bigger structural worry is the number of UK companies moving into the US from UK listings, or IPOing in the US despite the technology originating in the UK. In recent years a number of UK companies have either been bought by US businesses or floated in the US such as GW Pharma, Lombard Medical and Oxford Immunotec. In fact, 40 UK companies listed in the US in 2014, raising c.US\$3bn in funding⁶⁸. As discussed, there is the sense among a number of UK executives that UK investors are not as supportive as they could be of longer-standing businesses which may need further funds. In that respect, the US can appear a more attractive option⁶⁹ with a larger pool of investors willing to take more substantial bets. These investors are often more knowledgeable and wealthier. Importantly, they do not tend to subsistence fund, instead giving companies sufficient cash and enough of a war-chest to develop products.

However, other large companies, such as BTG, have maintained their listing in the UK despite having most of their revenues originating in the US. For these companies, the difficulties of maintaining a UK base and a US list – the onerous regulations, the tax regime, the expense – is unattractive.

UK looking increasingly attractive

Meanwhile, the UK's investment community has begun to view the sector more favourably. Data from the BIA suggests that funding of the UK Life Sciences industry reached a record high in 2014 with IPOs raising c.£408m, around 40% of total IPO financing over the last decade. VC funding in the same year increased by 71% to US\$430m⁷⁰.

FIGURE 10: CAPITAL RAISED BY LEADING EUROPEAN COUNTRIES, 2014



Source: EY, Capital IQ, BioCentury and VentureSource
 Size of bubbles shows number of financings per country. Capital raised is illustrated by the centre of the bubble.
 Average annual exchange rates used for 2014 of £0.607/\$1 and £0.806/€1

Another key attraction of the UK is AIM, the Alternative Investment Market, which has a different set of rules to the London Stock Exchange and allows businesses to rapidly respond to financing requirements without having to jump over several of the tricky, time-consuming regulatory hurdles. The UK's AIM market attracted 118 new businesses in 2014, 23 of which were international. These companies raised £2.6bn in new money⁷¹.

But the monies raised in the UK are still a fraction of those raised in the US, where interest rates are low and the appetite for risk is high. While the US raised US\$37bn in venture capital in the last decade, the UK only managed US\$2.4bn⁷². In 2014, the UK raised the fourth largest capital in Biotech behind San Francisco, New England and San Diego. But it raised the most capital of any European market⁷³.

54 A Report by the All-Party Parliamentary Group on Global Health. Hasan, N. et al "The UK's Contribution to Health Globally: Benefiting the country and the world" Published 29th June 2015.
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 70 July 9, 2015 UK life sciences funding at 10-year high Andrew Ward, Financial Times.
 71 See <http://www.londonstockexchange.com/statistics/historic/aim/aim-statistics-archive-2015/dec-15.pdf> 72 July 9, 2015 UK life sciences funding at 10-year high Andrew Ward, Financial Times.
 73 BIA and E&Y "Building the third global cluster State of the Nation 2015"

CREATING THE OPTIMAL ENVIRONMENT FOR INVESTORS AND ISSUERS IN LIFE SCIENCES:

WRITTEN BY CHRIS MAYO, PRIMARY MARKETS,
LONDON STOCK EXCHANGE

The London market has seen a resurgence of life science issuance activity in the last two years. Corporate issuers and investors have benefited from the strong performance of the sector through enhanced access to capital and significant outperformance of the sector relative to general indices. We increasingly see issuance activity in small-cap companies on AIM strongly complemented by mid-cap activity on the Main Market, which has combined to make 2014 and 2015 the best years for UK life science capital raising in a decade and we see a broader menu of life science investment options emerging for investors.

A key change in the structure of life science financing in the UK market is the emergence of tech transfer / IP commercialisation listed entities. Companies such as Imperial Innovations, Woodford Patient Capital Trust and IP Group (and now even US-based London-listed companies such as Allied Minds and PureTech Health) have become important players in the provision of private financing for life science companies, many of which originate from Britain's world class universities and research base. These listed IP commercialisation companies use their access to public equity which they can subsequently redeploy for underlying private investments.

The resulting increase in private financing (alongside US and European based venture capital, corporate venture capital and crossover interest in UK companies) has allowed investee companies to advance their programmes further before considering the public markets, whilst investors can simultaneously gain exposure to a diversified portfolio of life science related risk but still acquire knowledge about individual portfolio companies in advance of them going public. We look forward to an increasing number of standalone company floats from this source: Circassia, which was the largest biotech IPO in 2014 by proceeds raised and raised a further £275 million in 2015, marks just one example of what we see as an important future trend and an increasing

maturity of the London life science capital markets.

Investor support for recent issuers has been very strong with approximately 70% of the life science companies which floated in 2014 already having returned to raise further primary capital, in many cases to help finance acquisitions. Investors have in turn been rewarded with strong returns. In addition to the strong performance of the healthcare indices as a whole, in 2014 the best performing Main Market IPO was US-based IP commercialisation company Allied Minds, the best performing IPO across all of our markets was 4DPharma and life science company MotifBio counts among the top 5 performers for 2015.

At London Stock Exchange, we are doing our utmost to buttress this support and increase awareness amongst investors about the opportunities within the sector. One initiative of note is our annual Future of Healthcare Investor Forum where we showcase a mixture of innovative public and private healthcare companies as well as use key industry opinion leaders to highlight significant investment trends which will drive sector performance. It also marks an opportunity for investors to establish or deepen their relationships with exciting companies. The event will take place at London Stock Exchange for the second time in January 2016 with an audience of more than 120 investors and industry stakeholders. The event is fast becoming a fixture in the sector and for investors' calendars.

We also continue to engage with life companies to demonstrate the benefits of being listed in London. That will ensure a high quality pipeline of investment opportunities for investors from the sector. We believe from a corporate issuer perspective, London offers a number of benefits:

- Access to a more diversified, global pool of capital including most US institutional investors who are frequently accessed in London IPOs using existing US securities laws exemptions and have significant shareholdings in UK listed life science companies

- A supportive dedicated small and micro-cap research and broker community
- Typically more flexibility over sale of shares by existing investors as part of an IPO
- A flexible IPO process allows for extensive pre-IPO investor engagement and the production of deal research which enables superior price discovery. In addition, confidential filing of the prospectus for all issuers allows more control over the public aspects of the process
- Generally, more cost effective in terms of underwriting fees and ongoing compliance costs

In short, London offers the optimal environment of innovative, science-driven companies coupled with one of the world's strongest, most diverse institutional shareholder bases. The prospects for life science activity in the London markets have never looked more exciting.

UK IS A SUPPORTIVE AND ATTRACTIVE MARKET

The UK has a supportive and well-established infrastructure for early stage Life Sciences business development, with a strong university sector, IP commercialisation businesses, good grant funding for early stage research, a receptive hospital and physician network and solid governmental support. This all translates into a highly receptive environment to launch new technology – and goes some way to explaining why UK companies are such attractive M&A targets for overseas competitors. We discuss our view of the UK market in more detail below.

THE UK HAS SOME OF THE BEST UNIVERSITIES IN THE WORLD

Robust comparative data on UK and US universities is difficult to come by. However, a myriad of surveys and analysis concur that the UK has some of the best universities in the world⁷⁴. According to one report, the UK has the second-largest number of top 100 universities in both Medicine and Life Sciences⁷⁵.

Oxford, Cambridge and Imperial College are ranked 2nd, 4th and 8th, respectively in the latest Times Higher Education World University Rankings 2015-2016. These three universities are closely linked to two of the longest standing IP commercialisation businesses.

FIGURE 11 TIMES HIGHER EDUCATION WORLD UNIVERSITY RANKINGS: TOP 25 UNIVERSITIES IN THE WORLD

	Institution	Teaching	International Outlook	Research Citations	Industry	Overall	Country	
					Income			
1	California Institute of Technology	95.6	64	97.6	99.8	97.8	95.2	USA
2	University of Oxford	86.5	94.4	98.9	98.8	73.1	94.2	UK
3	Stanford University	92.5	76.3	96.2	99.9	63.3	93.9	USA
4	University of Cambridge	88.2	91.5	96.7	97	55	92.8	UK
5	Massachusetts Institute of Technology	89.4	84	88.6	99.7	95.4	92	USA
6	Harvard University	83.6	77.2	99	99.8	45.2	91.6	USA
7	Princeton University	85.1	78.5	91.9	99.3	52.1	90.1	USA
8	Imperial College London	83.3	96	88.5	96.7	53.7	89.1	UK
9	ETH Zurich	77	97.9	95	91.1	80	88.3	Switzerland
10	University of Chicago	85.7	65	88.9	99.2	36.6	87.9	USA
11	John Hopkins University	77.6	70	90.4	98.2	100	87.6	USA
12	Yale University	86.5	64.3	87.8	97.2	43.3	87.4	USA
13	University of California, Berkeley	80.4	61.9	91.1	99.7	47.9	87.2	USA
14	University College London	78.1	94.4	91	94.2	40.5	87.1	UK
15	Columbia University	85.9	73.5	82.2	98.1	-	86.1	USA
16	University of California, Los Angeles	80.8	56.4	88.6	98.5	47.9	85.2	USA
17	University of Pennsylvania	82	49.5	86.9	98.6	49.9	85.2	USA
18	Cornell University	77.9	63.9	86.1	97.2	33.7	84	USA

Institution	Teaching International Outlook	Research Citations	Industry Overall Income	Country			
19 University of Toronto	75.9	77.8	89.3	90.9	49.1	83.9	Canada
20 Duke University	76	56.5	78	99	100	82.7	USA
21 University of Michigan	76.8	53.7	85.2	94.4	56.3	82.4	USA
22 Carnegie Mellon University	67.4	57.1	88.8	99.1	57.5	82.3	USA
23 London School of Economics and Political Science	69.8	93.6	80.6	94.3	32.2	81.3	UK
24 University of Edinburgh	68.6	89.8	77.2	96.3	36.1	80.3	UK
25 Northwestern University	69.8	53.9	78.4	96.5	81.2	79.5	USA

Source: <https://www.timeshighereducation.com/world-university-rankings/2016/world-ranking#/page/0/length/25>. Downloaded 10/10/15.

Note: The higher the score, the higher the institution in the rankings

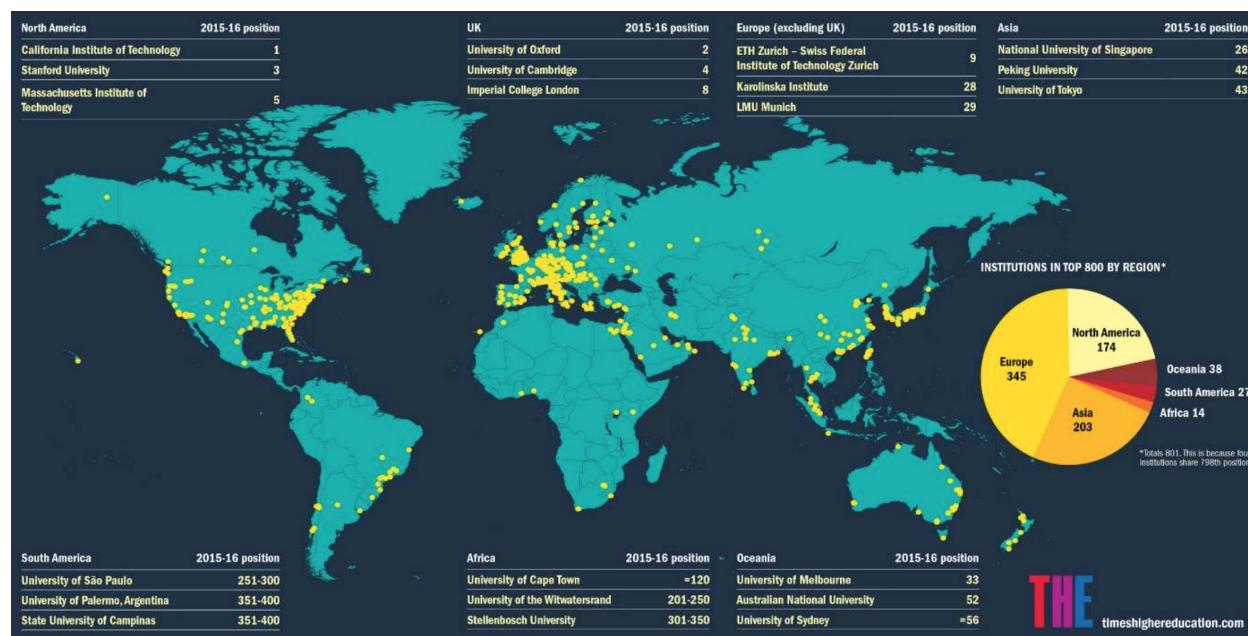
The 2015-2016 QS World University ratings⁷⁶, based on a different set of criteria, place Oxford, Cambridge, Imperial and UCL in the top 10 worldwide: with Cambridge third, after Massachusetts Institute of Technology and Harvard, then Stanford and California Institute of Technology (Caltech), followed by Oxford sixth, University College London seventh and Imperial College eighth.

The December 2014 Research Excellence Framework⁷⁷ (REF) report highlighted that many of the UK's universities have a broad range of "world leading" and "internationally excellent" research, while others, such as Birmingham and Warwick have exceptional research in specific areas. The REF is the system used by UK government for assessing the quality of research

in publicly-funded UK universities and is conducted every 5 years or so. Funding for these institutions for the following five years is partly dependent on the outcome of this assessment: crudely, high rankings allow these institutions to continue to access significant levels of government funding.

In total, the universities of Oxford, Cambridge, Imperial and UCL received c.£1.4bn in grant funding in 2013⁷⁸. From 2008 to 2013, total research income (and income-in-kind) for UK universities was £24.1bn⁷⁹. Sources of funds include: 38% from the UK Research Councils, 19% from UK government bodies, 19% from UK charities (mostly from The Wellcome Trust), 6% from UK industry and 9% from EU government bodies.

FIGURE 12: WORLD'S BEST UNIVERSITIES BY GEOGRAPHY



Source: <https://www.timeshighereducation.com/sites/default/files/wur-2015-2016-top-universities-by-region-large-v2.jpg/> Downloaded 10/10/15

THE UNIQUE ENVIRONMENT AROUND UK'S BEST UNIVERSITIES -THE IMPACT OF THE CLUSTER PHENOMENON

The IP Commercialisation sector (a distinctively UK phenomenon with no equivalent listed sector in the US) has only been possible because of the strength of UK universities, and the support of certain UK investors such as Invesco and Woodford Asset Management.

This sector has become an important contributor to the growth of early stage Life Sciences businesses. The IP commercialisation businesses have experience of finding the right management and accessing the public and private markets to raise money for their portfolio businesses. For instance, IP Group and Imperial Innovations have around 22 publicly-listed businesses in total, the vast majority of which are Biosciences businesses which are listed in the UK. (See Nigel Pitchford's discussion for a more detailed description of this important contributor to the UK Life Sciences' success.)

More universities worldwide are expected to follow the success of these UK university-linked companies, and may eventually list in the UK too. The University of California announced a US\$250m fund in December 2015 to invest in its biotech spin-outs.

At the same time, a number of clusters have built up around the key universities – there are now 100 Science Parks in the UK⁸⁰. Most famous are those in Oxford and Cambridge. In Cambridge, for instance, in the 30 months leading to October 2015, there were nearly US\$80bn worth of deals.

Overall, the UK ranks first for medical research in the G7⁸¹ by citation impact and over 81% of UK clinical research is ranked as world-leading or internationally excellent⁸². Two of the top four medical journals in the world (The Lancet and the British Medical Journal) are based in the UK, as is Nature, the top ranked science journal globally⁸³. It is not hyperbole to state that the UK has some of the best research in the world.

74 See <http://www.theguardian.com/science/occams-corner/2015/oct/06/worlds-best-university-rankings> for an interesting editorial on these surveys. Downloaded 10/10/15

75 A Report by the All-Party Parliamentary Group on Global Health. Hasan, N. et al "The UK's Contribution to Health Globally: Benefiting the country and the world" Published 29th June 2015.

76 See <http://www.topuniversities.com/university-rankings/world-university-rankings/2015#sorting=rank+region+=country+=faculty+=stars=false+search=10/10/15>. Note: The rankings are based on a combination of Academic reputation, employer reputation, faculty/student ratio, citations per faculty, international student ratio and international staff ratio Teaching: the learning environment (worth 30 per cent of the overall ranking score). Research: volume, income and reputation (worth 30 per cent). Citations: research influence (worth 30 per cent). Industry income: innovation (worth 2.5 per cent). International outlook: staff, students and research (worth 7.5 per cent)."

77 From <http://www.ref.ac.uk/media/ref/content/pub/REF%2001%202014%20-%20full%20document.pdf> Downloaded 20/9/15

78 Imperial Innovations presentation.

79 From <http://www.ref.ac.uk/media/ref/content/pub/REF%2001%202014%20-%20full%20document.pdf> Downloaded 20/9/15

80 A Report by the All-Party Parliamentary Group on Global Health. Hasan, N. et al "The UK's Contribution to Health Globally: Benefiting the country and the world" Published 29th June 2015.

81 Canada, France, Germany, Italy, Japan, UK, US, EU

82 A Report by the All-Party Parliamentary Group on Global Health. Hasan, N. et al "The UK's Contribution to Health Globally: Benefiting the country and the world" Published 29th June 2015.

83 A Report by the All-Party Parliamentary Group on Global Health. Hasan, N. et al "The UK's Contribution to Health Globally: Benefiting the country and the world" Published 29th June 2015.

IP COMMERCIALISATION BUSINESSES ARE A UNIQUE RESOURCE FOR THE UK'S HEALTH SECTORS:

NIGEL PITCHFORD CIO, IMPERIAL INNOVATIONS

It will surprise many to learn that a new financial sector has been born in the UK, and one with game-changing ambitions when it comes to commercialising life science IP. This sector should contribute to building a vibrant, highly-innovative, sustainable UK life sciences cluster which can finally rival those established clusters in the US.

The current crop of IP commercialisation companies has a combined market capitalisation of around £4bn, and with a shade under £1bn of capital available to invest, can be seen to be a powerful new force in the market.

Whilst each company has a thematic approach which differentiates it from the others, there are important unifying factors which are fundamental to all. Chief amongst these is a corporate structure which places cash on the balance sheet raised from supportive long-term shareholders. This is permanent capital with no fixed repayment term. Income or capital realisations are recycled back into this cash pot, making capital available for future investments.

The IP commercialisation companies are therefore evergreen vehicles whose structure affords them significant flexibility around how and when they invest, and more importantly, when they seek to realise value from their portfolio companies.

This longer-term horizon is much better aligned to the business of creating valuable and sizeable companies from IP-centric start-ups or university spin-outs, where experience suggests a 10-15 year perspective is preferable to the 5-7 year constraint under which traditional venture funds operate.

The combination of a patient approach to building companies, enabled by deep pockets of permanent capital, is a powerful one, and constitutes the bedrock upon which to build a cluster of well-capitalised, high-growth, life science companies in the UK.

As with most stories concerning the commercialisation of intellectual property, the emergence of this sector has not happened overnight.

Its origins trace back to the ground-breaking deal in 2000 between Oxford University's Chemistry Department and what is now IP Group (LSE: IPO) – the largest of the IP commercialisation companies with the broadest coverage of UK universities. To date, IP Group has raised over £300m of equity capital, and has built a portfolio of 90+ companies.

Imperial Innovations (AIM: IVO) soon followed, initially leveraging its pipeline agreement with Imperial College to build a portfolio of Imperial spin-outs, before extending these company creation activities to nearby hotbeds of scientific innovation in Oxford, UCL and Cambridge. Innovations has raised almost £350m of equity capital since its IPO in 2006, and has invested into a portfolio of 40+ companies.

Over the last three years the pace of creation of IP commercialisation vehicles has increased.

Syncona was formed by the Wellcome Trust in 2013 with £200m of initial capital, and was followed later in the year by Cambridge Innovation Capital who raised £50m. More recently, Oxford Science Innovations raised £300m. Despite currently being private companies, each of these three has long-term supportive founding investors with a shared vision of how to build companies in this space.

In the public markets we have seen Allied Minds (LSE: ALM) raise £400m at IPO in 2014, Mercia Technologies (AIM: MERC) raise £70m the same year, and PureTech (LSE: PRTL) raise almost £120m on its IPO in 2015.

The sector would not exist but for the vision and support of principals at Lansdowne Partners, Invesco Perpetual, and Woodford Investment Management - and their continued support is vital if the ambition of

building meaningful companies is to be achieved. This is even more prescient given the continued reluctance of the wider fund management community to support UK life science companies seeking to raise funds for growth through the UK public markets.

The path to creating really valuable companies takes time, particularly given the early-stage nature of the starting points. However, there is evidence that the approach is starting to pay off.

Circassia (LSE: CIR), received £2.0m in start-up funding from Imperial Innovations back in 2007 to develop allergy technology that had originated at Imperial College. Following an IPO in 2014, the company now has a market cap of £836.7m and resides in the FTSE-250. With a Phase 3 trial in cat allergy expected to read out in 2016, and several Phase 2b studies for other allergens completed, this is a good example of what is possible when reliable capital, experienced management, and novel technology are brought together.

Another example is Oxford Nanopore, which received seed funding from IP Group in 2005, and though still a private company, has subsequently raised in excess of £250m to fund development of its proprietary technology platform for the direct electronic analysis of single molecules.

With the vast majority of the capital flowing into the sector's IP commercialisation vehicles only over the last five years, it will take time to see the fruits of this investment. However, the pace has undoubtedly been increased, and the ambition and confidence raised. New companies are beginning to surface with the potential to grow into world leaders.

In the Innovations portfolio is Mission Therapeutics, which is building a strong platform around deubiquitylating enzymes based on the work of Professor Steve Jackson. It has significant potential to dominate an important biological space.

Meanwhile, the ground-breaking epigenetic tools being developed by Syncona-backed Cambridge Epigenetix could help unlock new areas of basic research, discovery and diagnostics.

Cambridge Epigenetix was founded by Professor Shankar Balasubramanian, and it is worth noting that both he and Professor Jackson are back starting companies up for the second time – following earlier successes with Solexa/Illumina and KuDos Pharmaceuticals respectively. The pool of talent in the UK is deepening, and the ambition to build on earlier successes is growing.

The IP commercialisation companies are leading a drive to change the trajectory and environment for life science start-ups. This group is well-financed, ambitious and determined, and over the coming years will hopefully create the next generation of leading lights which will form the backbone of a rejuvenated life science industry here in the UK.

THE NHS

No report on UK Life Sciences can fairly assess the market without looking at the largest employer in the UK and a unique healthcare system – the National Health Service (NHS). The NHS spends over £124bn across the UK, covers 64m people and employs 1.6m people across 300 different careers⁸⁴. Many criticise it for being bloated and inefficient, while others from outside the UK look enviously at the availability and access to healthcare for the whole population.

Funding issues for the NHS

There are a number of well-known issues with the NHS, not least the uncertainties surrounding recent and proposed changes^{85/86}, and the estimated £30bn mismatch between patient needs and funding in 2020/2021⁸⁷. But, the UK has its first ever Life Sciences Minister and has ring-fenced certain spending.

The latest announcement from the UK Chancellor, George Osborne, delivers extra funds providing “the NHS in England [with] £10bn per annum more in real terms by 2020-21 than in 2014-15, with £6bn a year available by the first year”⁸⁸. But much of this extra money is coming from cuts in other parts of the Department of Health budgets⁸⁹. The Forward review summarises the looming problem in its Executive

Summary:⁹⁰ “The NHS has dramatically improved over the past fifteen years..... Progress has continued even during global recession and austerity thanks to protected funding and the commitment of NHS staff. But quality of care can be variable, preventable illness is widespread, health inequalities deep-rooted.”

Interestingly, the All-Party Parliamentary Group On Global Health⁹¹ acknowledges the overlap between the main players in the UK market – the NHS, the commercial sector, the NGOs etc., recognising that there are no rigid boundaries and that each relies on the other. The NHS has been, and will continue to be, critical to the overall success of the UK Life Science sectors because:

- **All UK physicians train within the NHS.** According to the General Medical Council⁹² there are 274k doctors registered in the UK. 64% of these trained in the UK, with India and Pakistan accounting for another 13%. The number of registered doctors has risen dramatically since a low in 2009, to around 260k in 2013⁹³, but this is not estimated to be enough.
- **All new therapies and technologies have had their economic viability scrutinised by NICE**⁹⁴. The UK is having to respond to both the changing health of the population and rising costs. The reality of

FIGURE 13: COMMONWEALTH FUND COMPARISON OF HEALTH SYSTEMS IN HIGH-INCOME COUNTRIES

	Aus	Can	Fra	Ger	Neth	NZ	Nor	Swe	Swiz	UK	US
Overall ranking (2013)	4	10	9	5	5	7	7	3	2	1	11
Quality care	2	9	8	7	5	4	11	10	3	1	5
Effective Care	4	7	9	6	5	2	11	10	8	1	3
Safe care	3	10	2	6	7	9	11	5	4	1	7
Coordinated care	4	8	9	10	5	2	7	11	3	1	6
Patient-centred care	5	8	10	7	3	6	11	9	2	1	4
Access	8	9	11	2	4	7	6	4	2	1	9
Cost-related problem	9	5	10	4	8	6	3	1	7	1	11
Timeliness of care	6	11	10	4	2	7	8	9	1	3	5
Efficiency	4	10	8	9	7	3	4	2	6	1	11
Equity	5	9	7	4	8	10	6	1	2	2	11
Healthy lives	4	8	1	7	5	9	6	2	3	10	11
Health expenditures/capita (2011)	\$3,800	\$4,522	\$4,118	\$4,495	\$5,099	\$3,182	\$5,669	\$3,925	\$5,643	\$3,405	\$8,508
Top 2					Middle					Bottom 2	

Source: A Report by the All-Party Parliamentary Group on Global Health. Hasan, N. et al “The UK’s Contribution to Health Globally: Benefiting the country and the world” Published 29th June 2015 page 30

the £30bn disparity means that the NHS must assess new therapies, and possibly restrict or reject some, on grounds of expense. NICE (the National Institute for Health and Care Excellence, established 1999), is tasked with assessing all new therapies approved in the UK and deciding which meet its stringent financial tests. From 1 March 2000 to 30 September 2015, NICE published 189 single technology appraisals and 167 multiple technology appraisals; 356 appraisals in total, containing 596 individual recommendations. Overall, 62% of decisions made by NICE were ‘recommended’⁹⁵, but NICE will not approve new therapies if they cost too much. And, because the NHS serves such a large patient population, NICE can be instrumental in getting prices lowered. For instance, NICE put pressure on Roche to lower the cost of a breast cancer therapy⁹⁶. Interestingly, its decisions are taken seriously by other health services elsewhere⁹⁷ and have been used to help pressurise drug companies on prices in those regions too. The economic reality mean that companies must show that there is a positive economic value for the prescriber of the therapy⁹⁸.

- ***Businesses have developed technologies in response to these limited resources.*** The NHS is cash-strapped as ongoing austerity policies bite further into its funding⁹⁹. At the same time, demographic changes mean that an increasingly elderly and obese population is requiring more medical treatment. (Diabetes UK estimates that c.£10bn is being spent on treatment in the UK each year, and the diabetic population is expected to get bigger.) New technologies are dramatically improving outcomes, but are proving costly.
- ***Many UK businesses have had trials conducted by the NHS.*** Many of the case studies in this document have strong links with the NHS. For instance, many of BTG’s original out-licensing programmes came from UK health researchers and the UK continues to invest in this area.

LONG-TERM GOVERNMENT & RESEARCH SUPPORT

The government, meanwhile, has recognised that the UK Life Sciences and Healthcare sectors are critical to economic success and has made significant moves in recent years to improve their support for it. For instance, the first ever Minister for Life Sciences, George Freeman, has been appointed. Prior to becoming an MP, he gained significant Life Sciences

sector experience. See the beginning of the document for his comments on the sector.

Not only is the NHS the largest single employer in the UK, but the research industry currently employs around 180,000 people¹⁰⁰, with all the major pharma companies either having research space, or relationships with researchers in the UK. The UK has a broad funding base including MRC (Medical Research Council), NIHR (National Institute of Health Research), The Wellcome Trust, charities and life sciences companies – which together spend over £7.3bn pa on supporting medical research¹⁰¹. Breaking this down, the charity sector spent £1.3bn, industry £4.1bn, NIHR £1.1bn, and the MRC £0.9bn.

On top of this, the UK has some of the most valuable Life Sciences Clusters in Europe which thrive “where companies, research centres, academic institutes and government agencies cooperate effectively”¹⁰². Government investment is a vital component of research success.

Government investment

An exciting recent development is the building of the Francis Crick Institute in Central London, which will amalgamate six of the UK’s leading scientific and academic organisations, including the Medical Research Council, and become the biggest centre for translational biomedical research in Europe. It will employ 1,500 staff (of whom 1,250 will be scientists) and is part of MedCity¹⁰³.

In addition, the government is currently investing (both directly and indirectly) in the UK Life Sciences market using the following routes:

- Biomedical catalysts, jointly operated by the Medical Research Council and Innovate UK^{104/105}, provide support, through grants, for life sciences opportunities in the UK to help move research to commercialisations. Over £250m public money and over £100m matched private funding has been used to support around 180 business-led projects.
- Innovate UK has set up 9 “Catapults” of which two – Cell Therapy, based at Guy’s Hospital, London and Precision Medicine – are in the health arena. The Catapults are a series of not-for-profit physical centres designed to foster innovation in specific areas¹⁰⁶.

- The Mayor of London's proposed £10bn Megafund¹⁰⁷ will combine debt and equity financing and be focused on bridging the funding gap for emerging Life Sciences businesses. It will work with the already established MedCity vision¹⁰⁸.
- Other government investments include direct Innovate UK grants to interesting new tech. For instance, it recently awarded Congenica (genome-based discovery and diagnostics) £300,000¹⁰⁹.

In addition, there is significant infrastructure spending to boost Life Sciences, and regional governments are keen to spend in this area too. Examples include:

- In September 2015, the Manchester Science Partnerships announced a £45m fund managed by fund managers Catapult Ventures. (Greater Manchester and Cheshire and Warrington Local Enterprise Partnerships secured £20m of Government funding, which has been matched by private sector investors.) It is aimed at the region's small life sciences businesses¹¹⁰.
- The London Mayor's office has a £110 million revolving capital fund¹¹¹ and London has MedCity.
- Cambridge, where an important Cluster has evolved, is expected to see at least £2bn worth of government investment in road capacity before 2021.

Finally, aspects of the UK tax structure are designed to be favourable to R&D businesses:

- UK corporation tax rate as of 1 April 2015 is 20%, the lowest in the G7 and G20. Corporation Tax R&D relief: for every £100 of qualifying R&D expenditure, the reduction in corporation tax is £130 while for SMEs, this reduction is £225.
- The Patent Box scheme, a complementary policy to the R&D tax relief. It involves a reduction in

corporation tax from 20% to 10% on worldwide profits from inventions patented by the UK Intellectual Property Office and the European Patent Office. The scheme is due to close in June 2016, to be replaced by a new, though similar, one.

The European Commission is increasing spending too. This builds on a substantial increase in EU government spending over the last 15-20 years, a period during which there has been a relative decline in equivalent spending in the US. From 1999-2009, US R&D expenditure declined as a proportion of global R&D in the Life Sciences from 38% to 31%¹¹². Meanwhile, the European Commission recommended the Horizon 2020 project: encouraging member states to increase their R&D budgets as already discussed.

THE WELLCOME TRUST AND OTHER CHARITIES

The final piece of the puzzle is the very supportive charitable sector in the UK, which funds many development projects. The UK has over 130 medical research charities funding a third of all publicly funded research¹¹³. The UK public rank top in the G7 (and fourth in the world) for charitable donations¹¹⁴. The largest single non-government, non-business source of funds in the UK is the Wellcome Trust, which was established from a bequest by the co-founder of Wellcome, one of the first pharmaceutical businesses in the UK. Wellcome was later sold to Glaxo (in 1995). In 2014, the net investment base (after bond liabilities) of the Wellcome Trust was a staggering £18bn, and the overall investment return was 15.4%. In 2014 the Trust handed out £674m¹¹⁵.

Cancer Research UK is another importer supporter of research. It had an income of £621m in 2014, and spent £393m on research activities, funding over 4,000 scientists in the UK¹¹⁶.

84 A Report by the All-Party Parliamentary Group on Global Health. Hasan, N. et al "The UK's Contribution to Health Globally: Benefiting the country and the world" Published 29th June 2015

85 FIVE YEAR FORWARD VIEW of the NHS, Published October 2014. Downloaded from <http://www.england.nhs.uk/wp-content/uploads/2014/10/5yfv-web.pdf> 12/10/15

86 See <http://www.kingsfund.org.uk/publications/implementing-nhs-five-year-forward-view> for an interesting model on how to implement the new NHS five year forward plan. Downloaded 11/10/15.

87 FIVE YEAR FORWARD VIEW of the NHS, Published October 2014. Downloaded from <http://www.england.nhs.uk/wp-content/uploads/2014/10/5yfv-web.pdf> 12/10/15

88 HM Treasury, "Policy paper: Spending review and autumn statement 2015" Downloaded from <https://www.gov.uk/government/publications/spending-review-and-autumn-statement-2015-documents/spending-review-and-autumn-statement-2015> 1st December 2015

89 King's Fund, Response to Spending Review November 2015.

90 FIVE YEAR FORWARD VIEW of the NHS, Published October 2014. Downloaded from <http://www.england.nhs.uk/wp-content/uploads/2014/10/5yfv-web.pdf> 12/10/15

91 A Report by the All-Party Parliamentary Group on Global Health. Hasan, N. et al "The UK's Contribution to Health Globally: Benefiting the country and the world" Published 29th June 2015.

92 From http://www.gmc-uk.org/doctors/register/search_stats.asp. Downloaded 12/10/15

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- 93 See GMC UK data on Medical training.
- 94 A Report by the All-Party Parliamentary Group on Global Health. Hasan, N. et al "The UK's Contribution to Health Globally: Benefiting the country and the world" Published 29th June 2015.
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SECTION 4. ACCESS TO CAPITAL IS KEY TO SUCCESS

A crucial concern for many of the companies in these sectors is that they require relatively high levels of funding over a long period. It is not just the up-front development costs: resources are needed to overcome technical problems and navigate regulatory issues.

Money can come from a variety of sources – IP commercialisation businesses (such as Imperial Innovations and IP Group), traditional funds, private individuals, venture capitalists and a number of more recent and novel funds. We have argued that funding is a critical challenge for the UK Biosciences sectors¹¹⁷, though the situation is slowly becoming more favourable.

Below, Ernst & Young assess the current state of the market. They believe that the trend is for more disciplined investing in a more robust set of businesses.

117 Evaluate "UK Biotech a 10 Year Horizon" May 2015. Downloaded from http://info.evaluategroup.com/rs/607-YGS-364/images/EP_BIA_UKBIO_2015.pdf 19/1/2016

THE CURRENT STATE OF THE MARKET:

WRITTEN BY ANDREW JONES, DIRECTOR,
EY TRANSACTIONS ADVISORY

In 2008 the oxygen supply to the biotech sector was all but cut off as the force majeure of the financial crisis took hold. At the same time large pharma portfolio rationalisation and reorganisation in the wake of mergers and anaemic top-line created additional turbulence and uncertainty for biotechs as strategic reviews led to the wholesale exit from certain therapeutic areas and, in turn, the termination of R&D programs and partnerships.

The ensuing new normal for the biotech sector was characterised by an investor flight to “quality” (mature companies with late-stage pipeline or commercialised products), tumbling valuations for pre-commercial biotechs and a tightly closed IPO window. Many companies were left struggling to survive. As funding options dried up swathes of companies restructured and paired back pipelines to extend cash runways and over the ensuing years the distribution of financing became increasingly skewed in favour of mature companies widening the gap between the “haves” and the “have nots”.

Wind the clock forward to June 2015 and the picture couldn't be more different. For the second straight year, biotech companies have delivered strong, and sometimes unprecedented results on almost every metric EY tracks — revenues, profitability, financings, new drug approvals and more.

Looking at the preceding years, the global biotech recovery has been apparent. Biotech indices have climbed steadily reaching new heights in 2015 and the IPO market made its comeback in 2013 with US\$3.2 billion raised – a volume not seen since the genomics-driven market of 2000. Capital raised by IPOs increased a remarkable 83% to US\$5.8 billion in 2014 only to be exceeded in 2015 with US\$6.0 billion – a new industry record. Importantly, historic amounts of innovation capital have been available to the smaller players in the industry evidenced by a dramatic increase in the number of pre-commercialisation companies in the US

with a market cap of more than US\$1 billion.

So what has underpinned the recovery? Quite simply, the widespread optimism that the sector is delivering a resurgence in innovation. R&D spending has been rising steadily across the sector, there has been a sustained recovery in new drug approvals by the FDA (42 NME approvals as at mid-December 2015) and the late-stage pipeline is promising (as many as 10-12 products with blockbuster potential could be approved in 2016).

Critically, over the past few years we have also witnessed the commercialisation of high-profile breakthrough therapies originating in the research labs of biotechs and small pharma. For example, Biogen's disease modifying drug for MS, Tecfidera (dimethyl fumarate), and Gilead's HCV medicines, Sovaldi (sofosbuvir) and Harvoni (ledipasvir and sofosbuvir). These product successes coupled with scientific advances and promising novel therapeutic approaches including immune-oncology, cell-therapies, mRNA, CART and CRISPR gene editing technologies have buoyed investor sentiment in a fundamentally strong innovation base. Against a backdrop of booming stock markets these achievements propelled the biotech industry's market capitalization above the US\$1 trillion threshold, a new high.

A standout couple of years for M&A and alliances have also rewarded biotech investors. With more financing options and large pharma seeking to replenish pipelines, biotechs have benefitted from more negotiating power. This sellers' market has resulted in premium prices paid and greater shareholder returns on exit.

Another key trend that has driven Biotech IPOs has been the emergence of non-VC “cross-over” investors that are willing to provide pre-IPO financing to companies in the run-up to entering public markets.

During the summer of 2014 concerns that we were at the top of the cycle became widespread with market commentators and participants openly debated whether we were in a biotech bubble. The bubble, if not popped, has since been deflated and the momentum taken out of the market as pricing issues in the US ended biotech's bull-run wiping out the stock market gains achieved the first half of 2015 in the third quarter. In the second half of 2015 IPOs slowed to a trickle, and aftermarket performance on new issuers remained muted in spite of discounted IPO pricing. In response to market conditions many companies postponed or withdrew offerings.

Unprecedented pricing remains a key issue for the industry, and companies must continually demonstrate how products deliver value and contribute to the overall sustainability of health care systems. Yet the autumn's events in the US are arguably uncorrelated to the fundamental drivers of the biotech recovery, having more to do with specialty pharma pricing strategies than the pricing of innovative medicines. Regardless, some degree of damage has been done and it looks unlikely we will see a return to the staggering momentum of the past few years in the near-term. With the loss in capital market momentum, marginal non-specialist investors will feature less prominently in 2016 leaving the action to specialist investors more focused on fundamentals and catalysts / milestone driven investing than following rising stock prices. The net result is likely to be less capital and more disciplined investing creating an environment more challenging than the past few years for companies without a strong story or catalyst-driven requirement for capital. The prospect of further interest rate-hikes in the US provides an additional headwind for the sector. Nevertheless, the biotech sector's fundamentals are strong, plenty of attractions remain for investors and the markets are capable of turning again in response to positive corporate catalysts and further breakthroughs.

We might be returning to a more "normal" capital market environment for now, but today's biotech story is seemingly underpinned by a true renaissance in innovation giving the sector a solid footing from which to move forward and, perhaps, with a stronger cohort of companies than we've ever seen before.

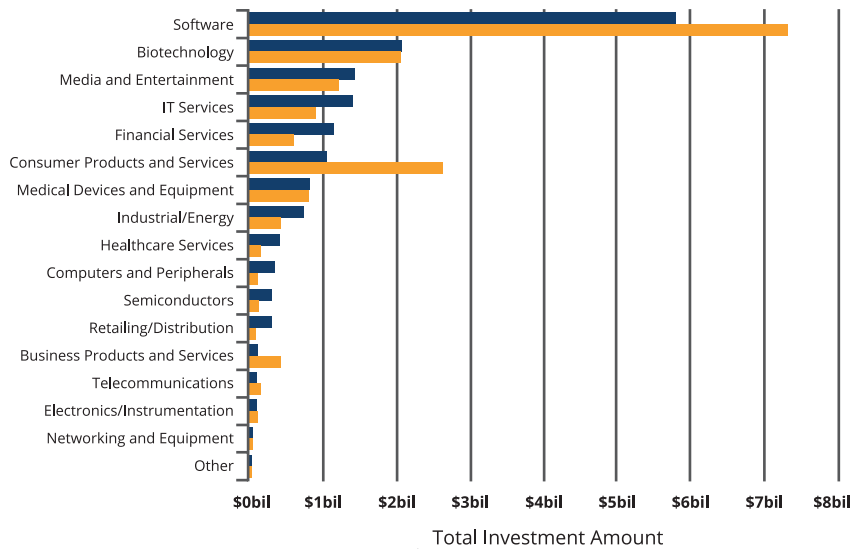
VC INVESTMENT¹¹⁸

One advantage for the UK and Europe is the significant amount of money going into novel funds, as well as into ethical funds, and the increasing number of US investors looking to Europe because of the lower valuations¹¹⁹. For instance, Woodford Investment Management's Patient Capital fund raised £800m in 2015, Epidarex Capital launched a new £47.5m VC fund for early-stage life sciences companies¹²⁰, OrbiMed (a global life sciences VC/Private Equity business with US\$15bn under management) closed a US\$950m fund on 21st December 2015 and aims to invest in c.30 businesses, and Sofinnova Partners (a high tech VC) raised US\$324m¹²¹. Meanwhile, 71.7% of global SRI (Social Responsible Investing) monies are invested in Europe¹²². The amount of money in SRI funds is expected to increase further as a result of favourable legislation, a rise in demand from investors with new funds, and the growing awareness of socially responsible investing¹²³.

Between 2006 and 2011, c.30% of transactions in the North American Healthcare industry (the largest portion) were in the US\$1-5m range¹²⁴. Only 11.6% of transactions were over US\$25m. A plausible explanation is that VCs became more cautious, leading to a drop in valuations. There was also a decrease in the value of deals at each round – post recession in 2009 the value of late stage deals was down nearly 74% from 2006. Interestingly, the number of “round 1” investment deals decreased by nearly 50% between 2008-2011¹²⁵, suggesting that the early stage companies were suffering too.

After the 2008 financial crash, VCs made fewer large deals and a greater number of smaller ones – looking to become more focused with their investments. We believe that, since 2011, the market has opened up a number of times – and the numerous deals are evidence of this. For instance, there was a 71% jump in investment from US\$251m in 2013 to US\$430m in 2014¹²⁶. While in Q3 2015, there were 121 deals in Biotech, valued at US\$2bn, about the same as the previous quarter. Meanwhile, fast-growth businesses in the UK raised £1bn in equity investment in Q3 2015 alone, much of this skewed to certain large companies

FIGURE 14: VENTURE INVESTMENT BY INDUSTRY
(Blue: Q3 2015, Yellow: Q2 2015)



Source: PwC/NVCA MoneyTreeTM Report, Data: Thomson

in the Bioscience sector: Mereo Biopharma, Immunocore and Oxford Nanopore accounted for a third of this sum¹²⁷.

In the MedTech arena, the value of venture financing fell by 14% in H1 2015 and the number of deals decreased 13%. At the same time, after a stellar 2014, Global MedTech IPOs declined, though were still higher than 2013¹²⁸. But the UK does show a financing gap: in 2014, life sciences companies in the UK accessed US\$883m of venture financing but only 12.2% was directed for “enterprise-size financing rounds”¹²⁹.

SUPPORTIVE SHAREHOLDERS

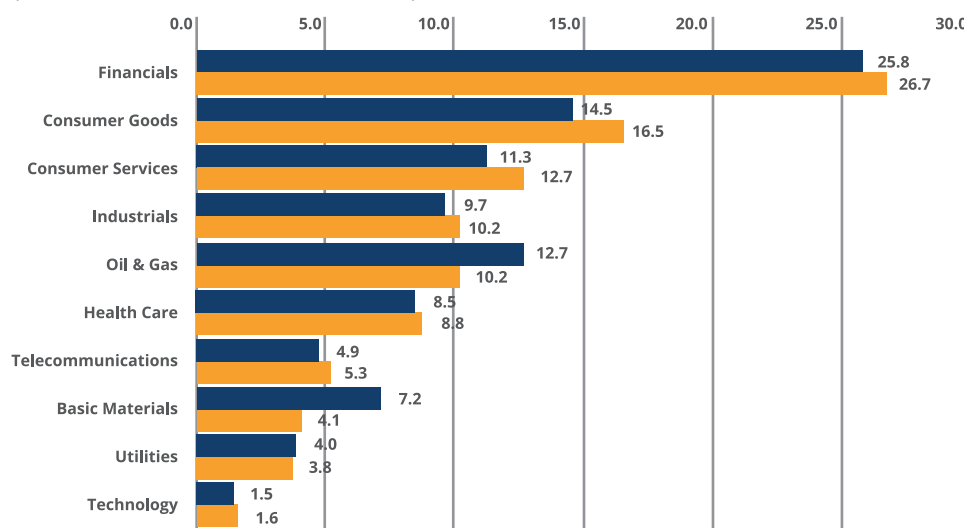
During 2015 global investors became preoccupied with the idea of finding biotech “unicorns” – the star company that can generate a significant investment return to more than compensate for all the losers in the portfolio. But identifying these unicorns is notoriously difficult¹³⁰. We argue that if investors took a stake in many well-managed companies with strong science they would be in the right place at the right time to benefit from a winner/unicorn. Generalist investors need to be persuaded of this strategy. Certain supportive investors in the UK already understand it and they have, often, been critically important for the success in the Case Studies below. For instance, Mark Denham of Aviva Investors recently discussed his strategy for success in the sector, citing clear “business models” and that they are “long-term, active and engaged investors”¹³¹.

These key investors can often take large stakes in

numerous possible winners. Those interested in the IP commercialisation area often invest in both the parent business and their investees (in the belief that the parent has performed due diligence, and installed good management in the investee business). These supportive investors believe that this approach gives them the chance of generating a significant return on investment in the portfolio as a whole, despite the likelihood that a number of the portfolio businesses will fail.

At the same time, the Bioscience sectors are becoming increasingly important contributors to the FTSE All share, and may help drive more generalist investors to invest into the sector. See below.

FIGURE 15: THE SHAPE OF THE FTSE ALL SHARE INDEX CHANGED IN 2015
(Blue: 31/12/2014, Yellow: 31/12/2015)



Source: Woodford Asset Management, Bloomberg

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BRITISH SCIENCE IS IN GREAT SHAPE:

WRITTEN BY NEIL WOODFORD, HEAD OF INVESTMENT, WOODFORD INVESTMENT MANAGEMENT

I have been an investor in the health care industry for practically all of my career and have for a long time been fascinated by the opportunity for innovation in this sector to deliver great returns to shareholders and, in turn, to provide significant benefits to patients, society and the economy more broadly.

Health care businesses can be difficult to value and this has resulted in some extreme valuation anomalies over the years. In the case of pharmaceutical companies, assessing the value of a portfolio of on-market drugs should be reasonably straightforward and is based on calculating the discounted cash flow of a company's on-market drug portfolio. Important variables that influence this number are the length of drug patents, changes to the size of addressable markets, influences on price and the likely path of market shares once competition is introduced. The value of those cash flows can be, and therefore is, disputed.

What has caused analysts more difficulty over the years, however, is putting a value on the pipeline of drugs in development. This involves making assumptions about issues which are very challenging to model but which have a huge bearing on future value outcomes. Assessing the probability of a drug successfully completing clinical trials is fraught with difficulty, as is forecasting the trajectory of growth once it has been approved, and the ultimate scale of the opportunity it is able to address. This process, ironically, involves more art than science, and I prefer to make a cruder judgement about what is, or indeed is not, priced into share prices.

Over the years, the market has at times made it easier to do this by placing the sector and the shares within it on extreme valuations. In the 1990s, for example, valuations were modest at the start of the decade, despite a prolific period of drug discovery. The pace of new drug development was impressive and

steadily increasing through most of the 1990s, as were valuations in the sector. Ultimately, towards the end of the decade, valuations became very stretched as the market became more and more excited about the pace of scientific development and the great promise that it held for the sector. Some of the euphoria revolved around the mapping of the human genome and what it would mean for the process of drug discovery.

What followed, however, in the first decade of the new millennium, was a slump in research productivity. The number of new drugs being approved by authorities such as the FDA collapsed, as did the valuations of pharmaceutical company shares. In the space of less than 10 years, the perception of these businesses changed dramatically. The market moved from viewing research & development as an investment expected to deliver an attractive return, to viewing it as an expense, detracting from shareholder returns.

This led to a great opportunity, in my view, and one which is still unfolding. The process of scientific discovery did not come to an end – far from it. The plunge in R&D productivity is now reversing and, ironically, innovation is increasingly being driven by what was learnt and then built on fifteen years ago with the decoding of the human genome. The market was right to be excited by this important and exciting scientific breakthrough – it was just wrong on the timing.

But the opportunity does not exist only amongst large, mature pharmaceutical companies such as AstraZeneca and GlaxoSmithKline. We are also very excited by the long-term potential in smaller, earlier-stage UK health care businesses. Companies such as Abzena, Cell Medica, Circassia, 4D Pharma, Immunocore, Oxford Pharmascience, ReNeuron, Stratified Medical and many others like them, are at the cutting edge in their respective fields. Meanwhile, companies that enable analysts and technicians

to read and understand genetic information more quickly, insightfully and at lower cost, such as Oxford Nanopore, Horizon Discovery and Genomics, are also well-placed to disrupt this industry and assist its rapid development.

It has taken a long time to fully understand and harness the potential of genomics, personalised medicine and the greater insights that scientific breakthroughs give into the nature of disease. But the health care industry is now starting to do so with profound and positive implications for investors and patients alike. British science is, in my view, in great shape.

IN SUMMARY – THE SECTOR IS A KEY INVESTMENT OPPORTUNITY

THE TRUTH ABOUT THE SECTOR

The evidence presented here shows that the sector is an attractive investment opportunity. It has delivered positive investment returns in key holdings. Although a number of investors have experienced a bumpy ride over the years, those that have retained their faith have started to reap rewards as the UK investment market has improved.

We believe that the environment in the UK is becoming increasingly positive for Life Sciences business, and that the monies coming into the sector from a variety of resources should deliver a virtuous circle of business growth in, what is now, a far more sophisticated business sector than when it first emerged in the late 20th century. We look at five case studies. The companies have been chosen because they represent many of the different areas of the Life Sciences industry in the UK, and range in size from the small to the large and well-established. We have focused on those companies that have found success, in some cases overcoming significant hurdles to do so.

SECTION 5. CASE STUDIES – THE SUCCESS STORIES

LESSONS LEARNED FROM THE CASE STUDIES

What are the criteria for success for businesses in the Life Sciences sector? Is it share performance, dividends, profitability, partnerships or deals? The answer will, in part, depend on your perspective.

- For fund managers, share price performance is key.
- Individual investors with a long term holding may be most focused on income generated from dividends.
- For patients, it may be new therapies to treat disease, or a clean instrument for surgery.
- For the UK government, it could be the number of jobs created.

All the businesses in our case studies have achieved many of these measures of success. The UK Health and Pharma sectors as a whole have delivered profitable, job-creating, sustainable companies that together rival any of the UK's major economic competitors.

Whichever criteria of success you adopt, the fundamental message to take away from the companies reviewed is the importance of having the "right management at the right time"¹³². It is a truism that good companies have good management. But the Life Sciences sector requires a unique set of skills which, unfortunately, are rarely combined in any one individual. All companies face different challenges as

they grow, but the unusual trajectory of Life Sciences businesses – which can exist for years before they become revenue-generating – makes the evolution far more dramatic. In the early stages, the technical nature of most Life Sciences businesses necessitates, in particular, that management have competency in the science. But because finance is so essential in keeping businesses afloat, management have to command respect in investor circles. This, in turn, calls for first-rate communication skills, and the ability to reassure investors that their patience will be rewarded. Crucial strategic decisions – such as which products to focus on, when to IPO and when to engage in M&A – are particularly tough to make in the Life Sciences sector, demanding, as they do, finely-tuned judgements about the balance sheet, the viability of the technology and the market opportunity. There are no off-the-shelf formulae, of course, but in the Life Sciences world, there is one fundamental ingredient to calling these judgements correctly – experience.

Vital, also, are the other pillars of success – a favourable economic environment, and governmental, investor and charitable support. We are fortunate to have that in the UK. It must continue. We should take considerable encouragement from the fact that the current government has recognized the significance of the sector and, for the first time, has created a ministerial post with overall responsibility for it¹³³.

The case studies below highlight the importance of these lessons.

¹³² Discussion with CEO and CFO of Horizon Discovery 1st October 2015

¹³³ Booth, B. "This time may be different" in Volume 34 Number 1 January 2016 Nature Biotechnology

STATEMENT FROM DAME LOUISE MAKIN, CEO

When I joined BTG in October 2004 its business was acquiring, developing and commercialising early-stage technologies in the life sciences and other sectors. The company had expanded rapidly following a fundraising in 2000 and had over 200 employees, but its growth potential was affected by the downturn in the high-tech and biotech sectors. I was appointed to turn the business around and develop a strategy for sustained growth.

First we cut costs to live within our means, by focusing on our life sciences portfolio, exiting all other activities for value where possible, and reducing headcount to just over 50 people. In 2006 we became profitable, albeit marginally. The next phase was to develop a strategy for growth.

We considered our capabilities, the evolving healthcare landscape, and where in the value chain we should operate. We listened to our shareholders and their ambitions for the business: their understanding and support have been critical to BTG's transformation. We determined that the right path for us was to market our own specialist healthcare products. This led to our first corporate acquisition in late 2008, which brought two established antidote products and the opportunity to de-risk the transition to selling our own products. Over the next 18 months we built a commercial infrastructure in the US and hired our first sales reps, who began selling directly to customers in October 2010.

In parallel, we identified the trend towards minimally invasive treatment of a wide range of conditions as a high-growth area of medicine where we could build leading market positions. In the four years from January 2011 we have made four acquisitions in Interventional Medicine, in the oncology, vascular and pulmonology markets. Each was acquired because it brought an innovative product that advances the treatment of patients, provides new procedures for specialist physicians and has the potential to reduce overall healthcare costs. During the same period, we received FDA approval for and launched our novel varicose veins treatment in the US.

We now employ around 1300 people including four US, two European and one Asian sales force. We have a platform for sustained growth. Our target is to take revenues from approximately \$600m today to around \$1.5bn by our 2021/22 financial year, by reinvesting some of our Specialty Pharmaceuticals and Licensing revenues into product innovation, geographic expansion and indication expansion within our Interventional Medicine business. We will also continue to explore M&A opportunities.

FACTS & FIGURES

BTG is one of the largest businesses in the UK (the eighth largest listed Life Sciences stock in the UK¹³⁴). It was created from the privatisation in 1992 of the merged National Research & Development Council and the National Enterprise Board. BTG, or the British Technology Group as it was then, was designed to generate income from UK intellectual property through licensing technologies¹³⁵ and to rectify what was perceived to be a significant problem: the UK had had a number of instances where it had lost value from its innovation through a lack of commercial understanding.

At the time it floated on the stock exchange, it had revenues from patents on the MRI¹³⁶ and the Oxford three-part knee. Early investors included Invesco Asset Management, which at one time had a holding of nearly 30% and now has c.22% holding¹³⁷.

However, the business lost its way. At the beginning of this century, the company had a portfolio of 10k+ patents with around 130+ inventions being added each year, a partnership with the Royal Bank of Canada, and with Varithena in a wholly owned subsidiary – and by 2004 it had raised £161m from shareholders including the IPO. But with high development expenditure and delays to the Varithena development programme¹³⁸, profitability was not expected until FY2010. Some costs were starting to be taken out of the business at the end of FY2003, but it was only with the arrival of new management that the problems were tackled and solved.

New management – Louise Makin (the CEO, who joined in 2004), and Christine Soden (CFO, who joined in 2005 and left in 2009 to be replaced by the current CFO Rolf Soderstrom following the acquisition of Protherics) were instrumental in transforming the business from loss-making and directionless to the well-managed, streamlined, acquisitive, profitable, bell-weather of the UK sector. After their strategic review, a cost cutting programme was rapidly implemented with the support of shareholders and the process of expanding the business through M&A began.

The new approach has resulted in the successful company seen today. The company first became profitable in FY2007, and generated operating profits of c.£63m in H1 FY2016 alone. The business currently has three main revenue-generating businesses, and has ambitions to be generating over US\$1.5bn in revenues by 2021¹³⁹.

Technology/Product Focus

BTG comprises three businesses: Interventional Medicine, Specialty Pharma and Licensing.

Interventional Medicine

This is considered the main long-term growth driver of the business, and is where much of the M&A has occurred. It comprises three units:

- **Interventional Oncology** – which has therapies for the treatment of hypervascularised¹⁴⁰ tumours, mainly liver cancers (hepatocellular carcinoma or HCC), where BTG's products are currently approved, and associated metastasis (e.g. metastatic colorectal cancer) where clinical trials are currently ongoing (see R&D & Pipeline below). Liver cancer is the sixth most common cancer worldwide, but it has a very poor prognosis, making it the third leading cause of cancer-related deaths (c.600,000 p.a.)¹⁴¹. Meanwhile, HCC (hepatocellular carcinoma) is the most common type of liver cancer accounting for 70-85% of cases. Most cases of HCC are caused by hepatitis infection; HCC is endemic in certain countries, such as China. These cancers are often diagnosed at an advanced stage, making an aggressive interventional and directed treatment the best treatment option. BTG's products are designed to prevent tumours from expanding or to shrink them so that they can be removed surgically¹⁴². The portfolio comprises two products:

a. TheraSphere, was acquired in May 2013

from Nordion inc for c.US\$200m. This is a combined radiation and embolisation¹⁴³ therapy consisting of millions of tiny glass beads containing radioactive yttrium-90. Initially, it was approved in the US in December 1999 under an HDE (Humanitarian Device Exemption)¹⁴⁴. The acquisition of this product has helped to expand BTG's geographic footprint.

b. Bead technology, acquired in 2011 from Biocompatibles for c.£177m. Beads can be used either for stand-alone embolisation or as a combined chemotherapy and embolisation. Bead technology consists of thousands of polymer beads, with some products containing a type of chemotherapy such as doxorubicin. Products are currently on sale in 70 countries mainly for the treatment of HCC, mCRC and other liver metastases.

c. Further clinical trials for this portfolio are expected to deliver data in CY2016, and for possible approvals by end CY2018.

- **Interventional Vascular** division is expected to be a major growth driver for the business in the next five years. Sales in H1 FY2016 were £21m, +40% yoy. It comprises two products:

a. Varithena is a foam-based sclerotherapy¹⁴⁵ method to treat varicose veins using polidocanol as the sclerosing agent. BTG acquired the IP to this technology well before the current management took over (BTG has patents around the canister that delivers the sclerotherapy), and launched it in CY2014 after a rocky approvals process. Varicose veins are enlarged veins that are raised above the skin on legs. They occur when there is a malfunction of the valves in the veins that carry blood from the legs toward the heart. Eventually blood pools in the legs and if untreated this can cause Chronic Venous Insufficiency (CVI). In the US, venous ulcers account for 80% of all chronic wounds found on the legs and affect c.500,000 people each year, costing c.\$1bn p.a. to treat¹⁴⁶. There are alternative treatments, but many require longer hospital times and more repeat procedures. Since the recent US launch, it has taken longer than expected to manage the reimbursement process, holding back the roll-out of Varithena. As a result, FY2016 revenue performance is expected to be towards the

lower end of guidance. For many years, BTG has beaten or been at the top end of guidance, so this is an unusual set-back.

b. EkoSonic system, which BTG acquired in May 2013 for US\$180m in cash and an earn-out of up to US\$40m. The system is approved in the US to treat severe blood clots in the pulmonary arteries and peripheral vasculature (veins), by infusing drugs directly into the veins which are then accelerated through ultrasound technology. In the EU it is approved for the treatment of pulmonary embolism patients with >50% clot burden in one or both main arteries and with evidence of heart problems. Trials to date suggest that patients who use this system require far fewer drugs with one benefit being that they then have fewer kidney problems¹⁴⁷. The list price of the control unit is US\$14,500 and each single use catheter costs c.US\$2,295¹⁴⁸. BTG has invested in upgrading the system, reducing its size. It has also improved its portability – which will make it more attractive for other indications such as acute ischemic stroke. The key patents last till 2022; other additional filings will take protection to 2030. BTG believes that there is a market opportunity worth US\$100-200m¹⁴⁹.

- **Interventional Pulmonology.** This division sells RePneu Coils, a minimally invasive device aimed at the improvement of exercise capacity, lung function, and quality of life for patients with severe emphysema. BTG acquired PneumRx, Inc. in December 2014 for an initial consideration of US\$230m and up to US\$245m in performance-related milestone payments. The RePneu Coil has been used in Europe for the treatment of emphysema since 2008. BTG estimates a market opportunity of at least US\$250m, especially as there are limited treatment options for patients at GOLD stage III and IV¹⁵⁰ i.e. severe emphysema. A 315-subject multicentre pivotal clinical trial, RENEW, completed enrolment in early October 2014 and reported mid December 2015, showing that all primary and secondary end points had been achieved. The RePneu Coil is likely to be submitted to the FDA by mid-2016^{151/152}.

Speciality Pharmaceutical

The Specialty Pharmaceuticals division, BTG's second major division, is focused on the Emergency Room anti-toxicity market, with direct selling by BTG mainly

into the USA. (The European market is mostly covered by Clinigen's access programmes). This division contributed £78.2m in revenues in H1 FY2016 (down 7% yoy), with £52.6m of that from CroFab. Much of the growth is expected to come from the newer therapies such as Voraxase. BTG has four products in the Speciality Pharmaceutical division.

- **CroFab** is an antidote to the bites of certain poisonous snakes endemic to the US (crotalids)¹⁵³. 7,000–8,000 people receive venomous bites in the United States¹⁵⁴ each year. BTG estimates that there are c.5500 treatable bites p.a., and that patients receive around 12-20 vials depending on weight, sex, venom etc. BTG needs only a 19 person sales force, as the focus only needs to be on the most populous snake regions, such as the southern USA.
- **DigiFab** is used in the treatment of patients with a life-threatening digoxin overdose. Digoxin is used in the management of chronic heart failure¹⁵⁵.
- **Voraxaze** is for the treatment of an overdose of methotrexate in adults¹⁵⁶ and for children who cannot clear methotrexate due to impaired renal function.¹⁵⁷ Methotrexate is used as a chemotherapy and for the treatment of autoimmune diseases¹⁵⁸. Most cases of toxicity are caused by dosing errors – overdosing can damage the kidneys and can be life-threatening.
- **Vistogard** (Uridine Triacetate) is an antidote to 5-fluorouracil (5-FU). 5-FU is a common chemotherapy mainly used in the treatment of solid tumours. In the US, c.3% of patients have a serious toxic reaction to 5-FU, and c.1300 patients die annually¹⁵⁹. The NDA was submitted to the FDA in September 2015, and was approved by the FDA on 11 December 2015. It is the first and only drug approved in the US for this indication¹⁶⁰.

Licensing

BTG's third division is its original business: out-licensing technologies developed by UK universities. The licensing business generated over £80m in H1 FY2016. Because of expected patent expiration¹⁶¹, the level of income it generates is likely to decline by 2021¹⁶². There are two key licenses in this division: Lemtrada and Zytiga. The vast majority of revenues came from Zytiga (abiraterone for the treatment of prostate cancer, and licensed to Johnson & Johnson). Lemtrada (Alemtuzumab a humanized monoclonal antibody that is directed against CD52, licensed to

Sanofi/Genzyme) is approved for the treatment of adult patients in Europe with relapsing remitting multiple sclerosis with active disease. It was first approved in 2001 under the name Campath for chronic lymphocytic leukaemia (CLL). After some discussions about pricing with the regulators by Sanofi/Genzyme, BTG received further royalties. It is worth noting that the patents in the US are expected to expire in 2017, after which no US royalties are likely to be received.

Both Zytiga and Lemtrada have royalty rates of c.6% for both these products, with net profit contributions of c.50% to BTG (with the other 50% going to the original inventors of the technology).

R&D & Pipeline

BTG has a number of programmes in development. Most of these will deliver data points over the next 2-3 years. We expect BTG to invest further in its portfolio – targeting c.£30m p.a. split equally between support of existing products, clinical trials and studies, and product innovation. A key plank of BTG’s strategy in recent years has been to reduce reliance on outside development.

Figure 16: BTG’s R&D PROGRAMME

Development Programme	Target Indication	Status
TheraSphere	Hepatocellular carcinoma (HCC) and 2nd line metastatic colorectal cancer (mCRC)	Phase III (BTG is currently enrolling patients for three Phase III clinical trials: EPOCH (TS 102 - mCRC), STOP-HCC (TS 103 – unresectable HCC and YES-P (TS 104 – advanced HCC)) Expected to report in FY2017
Embolisation and chemoembolisation beads	Hepatocellular carcinoma (HCC) and 3rd line metastatic colorectal cancer (mCRC)	Combination of investigator-initiated and registration studies planned

Source: adapted from BTG plc interim results presentation H1 FY2016 10/10/2015

Patents

BTG has a large number of patents in its portfolio. These can be categorised into two areas:

- Patents available for out-licensing. Many of these are coming to the end of their life.
- Patents used to protect its portfolio of therapies. Patents in this group are, additionally, protected by substantial know-how. This portfolio of IP protection is expected to last for over fifteen

years. But, as only a small portion of BTG’s therapies are drugs, the company could expect longer term protection, post patent expiry, to be retained through its know-how, branding and manufacturing. For instance, manufacturing CroFab, which involves injecting sheep with venom, is complex. Delivering a consistent product is critical and very few companies would be able to compete.

Management Team

BTG has a highly experienced and committed management team, with innovative ideas. They have transformed the business over the last 10 years.

FIGURE 17: BTG'S BOARD OF DIRECTORS AND LEADERSHIP TEAM

Name	Role	Biography
Gary Watts	Non-Executive Chairman	Garry Watts was appointed in January 2012. He is also Chairman of Spire Healthcare and of Foxtons Group plc, deputy chairman of Stagecoach Group plc. and non-executive director of Coca-Cola Enterprises, Inc.
Dame Louise Makin	Chief Executive Officer	Dame Louise Makin, MA, PhD (Cantab), MBA, DBE, joined BTG as Chief Executive Officer in October 2004. She is a non-executive director of Intertek Group plc and the Woodford Patient Capital Trust, a Trustee of the Outward Bound Trust and an Honorary Fellow of St. John's College, Cambridge.
Rolf Soderstrom	Chief Financial Officer	Rolf Soderstrom, BA, ACA, joined BTG as Chief Financial Officer in December 2008 from Protherics PLC, where he was Finance Director from August 2007.
Dr. Susan Foden	NED	Susan joined BTG in March 2015 and is a member of the Remuneration Committee.
Giles Kerr	NED	Giles joined BTG in October 2007 and is the Company's Senior Independent Director. He is Chairman of the Audit Committee and a member of the Nomination and Remuneration Committees.
Richard Wohanka	NED	Richard joined BTG in January 2013 and is a member of the Audit Committee. He was CEO of Union Bancaire Privée Asset Management October 2009 to June 2012, and from 2001 to 2009 he was CEO of Fortis Investment Management. Richard is a board member of the Nuclear Liabilities Fund and of Scottish Widows.
Jim O'Shea	NED	Jim joined BTG in April 2009 and he is a member of the Nomination Committee. He is the Chairman of Cardiome Pharma, a director of Zalucus Inc., Prostrakan Group Plc, Trevi Therapeutics, Inc., and Ocular Therapeutic.
Ian Much	NED	Ian joined BTG in August 2010. He is Chairman of the Remuneration Committee and a member of the Audit and Nominations Committees. Ian is currently a non-executive director and the senior independent director of Chemring Group PLC.

Source: BTG PLC

Partnerships

BTG's main licensing partnerships are for its two most important pieces of IP; those related to Zytiga and Lemtrada. The IP on Zytiga is associated with a manufacturing step, and is licensed to Johnson & Johnson; while Lemtrada's IP is around the original compound and is licensed to Sanofi/Genzyme. BTG is hands-off with both licensors. As BTG has no control

over the IP or the activities of these partners, its role is to gather royalties.

It has a more hands-on relationship with its distributors for its other products in countries where it has no direct sales presence. One of the more interesting of these is its relationship with Clinigen (see case study). Clinigen manages the access programmes for the Specialty Pharma products in much of Europe.

FINANCIAL RESOURCES

Current performance

For the first time in a number of years, BTG is not going to be at the top-end or beating guidance for its financial year (ending March 2016). This is mainly because Varithena has been slower to take off than the company expected. The reimbursement structure in the US is proving difficult for physicians to manage – and it's taking longer than anticipated for them to be reimbursed.

BTG ended the first half with cash of £110m, of which £68.1m cash was generated from operating activities. This should allow it to continue its rapid growth and investment phase.

Market Expectations for Financial Performance¹⁶³

BTG gives clear guidance for performance at each results meeting. The financial outlook to March 2016 is as follows¹⁶⁴:

- Revenue Range: £410m - £440m with the Gross Margin expected to be around 70%.
- SG&A is expected to be c.£142m - £148m while R&D spend is expected to be in the range of £75m - £85m
- BTG is expected to have a low effective tax rate at c.3% for the FY with utilisation of significant tax losses.
- However, in the longer and medium term, the company expects an effective tax rate of c.26%.
- Due to exposure to US\$ sales, BTG could see a c.£13m movement in FY Group revenues with a US\$0.05 move in the US\$ rate.

As discussed above, management recently suggested that performance may be towards the lower end of guidance due to the slower than expected uptake of Varithena in the US. This means that consensus estimates are rather conservative for a company that had consistently outperformed expectations.

KEY SUCCESS FACTORS

After its IPO, BTG was the darling of the IP sector, but hit problems when the original management became lax about costs and pursued a flawed strategy which meant they had little control over BTG's revenue stream and were burning cash with no return on

investments. The turnaround and recent success of BTG can be attributed to two key factors.

First, good management. Previous management was overly focused on the performance of a number of products over which it had no control because they were out-licensed. The company also spent far too much money developing its own products such as Varithena. The current management slashed costs and refocused strategy. They have ridden the ups and downs of the regulatory lottery – successfully negotiating the difficulties caused by the delayed approvals process for Varithena – while at the same time making aggressive, and successful, acquisitions. BTG's management have not been averse to making bold moves, and following a med tech strategy, giving it a unique focus in the Bioscience sector. They believe that this will differentiate them from competitors, and allow them to utilise their cash flow to best advantage.

Second, shareholder support. For much of the last fifteen years, the company's main investor has been Invesco. Having a large shareholder has meant that management can make the investments discussed above, knowing that its main investors are supportive.

The company has also been helped by the share price – which has remained reasonably stable despite some bitter disappointments with Varithena along the way.

LESSONS LEARNED

Visionary management is crucial to grow a business such as this, but a bold approach needs to be tempered by a degree of caution, with a close eye kept on costs and strategy. BTG shows that for a company to succeed it helps to have supportive shareholders who are willing to stick with it through short term difficulties. We believe that for Invesco, and the other long term shareholders, patience has borne fruit, and we expect that once the recent Varithena issues are sorted out, and revenues start to accelerate from this product, the share price will improve.

134 Data as of 31 December 2015

135 See company website www.btgplc.com

136 Magnetic Resonance Imaging – a diagnostic technology to see inside bodies 137 See FT.com. As of 4 January 2016

138 Phase III trials were delayed while the FDA asked for additional work

139 BTG plc interim results presentation H1 FY2016 10/10/2015

140 These are tumours fed by numerous blood vessels.

141 Venook, A. P. et al “The Incidence and Epidemiology of Hepatocellular Carcinoma: A Global and Regional Perspective” in *The Oncologist* November 2010 vol. 15 Supplement 4 5-13.

142 Vente, M.A.D et al “Yttrium-90 microsphere radioembolization for the treatment of liver malignancies: a structured meta-analysis “ in *Eur. Radiol* (2009) 19: 951-959.

143 Embolisation is a way of blocking blood vessels. In this case, the aim is to stop the flow of blood to a tumour – in essence “starving” the tumour. The radiation or chemotherapy then helps to kill the tumour.

144 Lewandowski, R. J. & Salem, R. “Yttrium-90 Radioembolization of Hepatocellular Carcinoma and Metastatic Disease to the Liver” in *Seminars in Interventional Radiology*. March 2006; 23(1); 64-72.

145 Sclerotherapy damages the vein so that it is blocked and no longer carries blood, thereby treating the varicosity of the vein.

146 Data from the National Institute of Health.

147 Owens, C. “Ultrasound-Enhanced Thrombolysis: EKOS EndoWave Infusion Catheter System” in *Seminars in Interventional Radiology*, vol 25 (1) 37-41.

148 Owens, C. “Ultrasound-Enhanced Thrombolysis: EKOS EndoWave Infusion Catheter System” in *Seminars in Interventional Radiology*, vol 25 (1) 37-41.

149 BTG plc interim results presentation H1 FY2016 10/10/2015

150 Global initiative for Chronic Obstructive Lung Disease. www.goldcopd.com

151 See BTG press release 14 December 2014

152 Zoumot Z. et al (2015) “Endobronchial Coils for Severe Emphysema Are Effective Up to 12 Months following Treatment: Medium Term and Cross-Over Results from a Randomised Controlled Trial.” In *PLoS ONE* 10(4):

153 Juckett, G and Hancox, J.G. “Venomous Snakebites in the United States: Management Review and Update” in *Am Fam Physician*. 2002 Apr 1;65(7):1367-1375.

154 Downloaded from Center for Disease Control website <http://www.cdc.gov/niosh/topics/snakes/> 10/11/15

155 MHRA Downloaded from <http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con126289.pdf>.

156 >1 mcml/L

157 Lewis, A. From <http://www.pharmacytimes.com/publications/health-system-edition/2013/March2013/Glucarpidase-Voraxaze>.

158 Downloaded from [http://www.rheumatology.org/Practice/Clinical/Patients/Medications/Methotrexate_\(Rheumatrex,_Trexall\)/](http://www.rheumatology.org/Practice/Clinical/Patients/Medications/Methotrexate_(Rheumatrex,_Trexall)/) 10/10/15 159 Mulcahy, N. *Medscape Daily ASCO* 2009: Antidote for 5-FU Overdose Appears Highly Effective. June 17, 2009

160 See press release 11 December 2015

161 The rest of the portfolio are coming to the end of their patent life too. BTG is continuing to generate low revenues levels, from products such as the two-part hip cup, but these are unlikely to continue much past 2017.

162 BTG licensed process patents to Cougar/Johnson & Johnson that are critical for the manufacture of Zytiga which expire in 2026/27. But the drug patent expires in the US in March 2017, so there is possible US generic competition from then. Meanwhile, European exclusivity expires in 2021.

163 BTG plc interim results presentation H1 FY2016 10/10/2015

164 See BTG plc interim results presentation H1 FY2016 10/10/2015

CLINIGEN GROUP PLC

STATEMENT FROM PETER GEORGE, CEO

The catalyst for starting Clinigen five years ago was a “fact” I read and didn’t at first believe; it stated that “80% of the world’s population, some 5.5bn people, do not have access to the medicines they need to treat their disease”. I classified this as a global healthcare crisis and looked for ways to address it. The second catalyst was that my investors at that time in the company I was then running had no desire to address it, so I had to leave and start from scratch to realise my ambitions, hence creating Clinigen.

There are only three ways to get a medicinal treatment into a human subject, during a clinical trial, as a licensed medicine or as an unlicensed medicine, and Clinigen is the only company that focusses globally on these three routes. Unlicensed and clinical trial supply are areas with a high unmet global patient need and many low volume licensed medicines target niche disease areas, which when viewed globally are also defined as a high unmet need. These two elements, high unmet need and niche, and our ability to meet this demand on a global basis have enabled Clinigen to sustain a very successful, fast growing company. Over the five years of operating we have grown to become a publicly listed company with a market cap of over £650m.

Clinigen has a reasonably low dependence on the UK for its customer base, selling its products and services in more than 120 countries worldwide, but a high dependence on the UK for its skill base and credibility. Within the Pharmaceutical sector the UK is highly regarded in both innovation and service provision which has certainly underpinned our ability to succeed. Recently through organic growth and acquisition Clinigen has extended its global footprint and managed to gain global market leadership in two of its service offerings, Clinical Trial Services and Managed Access to innovative new medicines and is targeting market leader position in one other sector over the next two years. Clinigen also has a novel approach to Specialty Pharmaceuticals, where the

focus is the revitalisation of off patent older medicines.

We aim to both keep these essential medicines on the market whilst bringing them back to growth.

Through our range of service and product offerings and our global approach, we have managed to de-risk our business from many economic and market factors meaning we have maintained at least 20% year on year profit growth since our inception and we are a long way from completing our ambitious business plan.

I like to think Clinigen is a good example of a success story in the UK healthcare sector. We targeted an ambitious approach to a global problem and in so doing created a unique company with some of the strongest growth characteristics in this sector. I also believe that the UK supported our ambitions with its unique capabilities like the AIM stock market, enabling Clinigen to achieve its goals.

FACTS & FIGURES

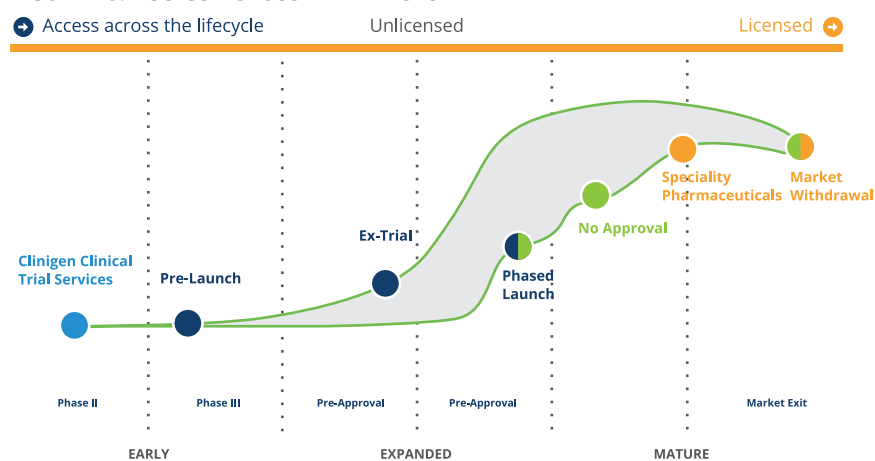
Clinigen is an excellent example of a company with a carefully thought-through business strategy which has been clearly implemented from its inception. It provides drugs to companies for clinical trials, difficult-to-access drugs to patients and doctors, and has a portfolio of its own niche drugs.

Unlike many of its early stage Life Sciences peers, Clinigen grew its business from a profitable base both organically and through acquisition. While maintaining profitability as a clear goal, it did not risk investors’ capital. It wasn’t all plain sailing: the company had to deal with lumpiness in its revenue stream when it first IPO’d. But it clearly communicated these risks to the investment community and its most recent acquisitions have, rather cleverly, both smoothed out the lumpiness and de-risked the business further. The share price reflects the attractiveness of this model for many generalist investors who may feel uncomfortable with the riskier side of the Biosciences sector.

Technology/Product Focus

Clinigen started in 2010 by focusing on the Clinical Trials Services (CTS) and exclusive unlicensed supply, which is now called Managed Access (MA). It evolved by adding a Specialty Pharma business, and then rapidly expanded in 2015 with the acquisition of Idis (April for £225m) and Link Healthcare (October for a maximum consideration of £100m). These extended the customer base and geographic spread of the two original service divisions. In September 2015, Clinigen evolved into a four-part business giving it improved focus and access to customers. Clinigen now has the capacity to offer a service across the whole lifecycle of a therapy:

FIGURE 18: ACCESS ACROSS THE LIFECYCLE



Source: Clinigen plc

Clinigen's four divisions are as follows.

1. Clinigen CTS (Clinical Trial Supply)

Following the acquisition of Idis, Clinigen CTS is now the global leader in the specialist supply and management of quality assured and sourced active comparators, co-therapies and other drugs for patients in clinical trials. This market opportunity is estimated to be worth US\$1.5-2.5bn^{165/166} and to be growing at 8% pa¹⁶⁷.

CTS is the main revenue generator of the Group with 38% of sales (on a pro forma basis for FY2015). However, it has the lowest margin and contributes only 19% of Gross Profit (pro forma 2015). On the plus side, the number of customers now contributing more

than £5m of revenues rose by two during FY2015 to seven.

CTS is developing valued added services in order to improve margins and client retention by addressing unmet or underserved client needs. In FY2016, it plans to launch "Just in Time" smarter supply, labelling (having acquired a plant with the Idis acquisition) and direct-to-site services.

2. Idis MA (Managed Access)

Idis MA is the global leader in the supply of innovative early stage medicines on behalf of pharmaceutical and biotech companies to meet an unmet patient need: for instance, delivery of therapies that are not approved in a particular region. Estimates suggest that Clinigen has a c.30% global market share of a US\$500-600m addressable market¹⁶⁸.

Idis MA delivered annualised c.£120m in sales from 35% pro forma year on year growth, and contributed 30% of Gross Profit (pro forma 2015), the highest of any of the service divisions.

Clinigen plans to increase deliveries further from the 418,000 units in FY2015 (up from 263,000 units in FY2014).

The company now has 99 products under active management and is working with 19 of the top 25 pharma and biotech companies, shipping to 95 countries. It has, for instance, relationships with AstraZeneca across all its service divisions.

3. Idis GA (Global Access)

Idis GA is a new division, purchased with the Idis acquisition. It supplies unlicensed or short supply medicines to patients, prescribed by doctors "on demand". A doctor will prescribe an unlicensed, experimental or short supply drug for a particular named-patient with a rare or life-threatening disease. Clinigen will manage the sourcing and delivery of the

therapy. Management estimate this market to be worth at least US\$5bn¹⁶⁹, and believes that its e-commerce platform will help it gain market share.

Idis GA will be able to work with the newly acquired Link Healthcare to help dominate the ethical on-demand unlicensed supply market across the world. To date, Idis GA has focused on the UK and mainland Europe. Link Healthcare has a strong position in this market in Southern Africa and Australia. Clinigen is also aiming to expand its footprint through Asia-Pacific and Latin America.

Idis GA delivered £61m of sales (on a pro forma basis for FY2015) an 8% decline year-on-year and contributed 17% of Gross Profit (pro forma 2015), the smallest of any of the service divisions. But, Idis GA has been dominated by one key customer with a large, but low margin, contract which contributed to the fall in revenues in FY2015. This relationship is being exited in FY2016, and management expects to replace the lost revenue over the next few years with higher margin contracts.

4. Clinigen SP (Specialty Pharma)

Clinigen SP acquires the rights to, and then revitalises, essential niche hospital-only medicines which have suffered underinvestment by rights holders (perhaps because the product is too small, or needs trials to change indications). It has a portfolio of oncology support and infectious disease medicines acquired over the last five years. It saw sales of £33.7m +25% yoy in FY2015 and gross profit of £29.1m +26% yoy.

Clinigen uses its relationships with Key Opinion Leaders (KOL) to drive and commercialise through prescribers, rather than using big salesforces to promote a therapy.

Clinigen SP has five drugs in its portfolio across four chemical entities:

i) Foscavir (Foscanet Sodium) is the largest revenue contributor to this division now, with a 70% share of SP's sales and profits. It is an antiviral approved for the treatment of cytomegalovirus (CMV) retinitis¹⁷⁰ in HIV patients. Since acquisition from AstraZeneca in March 2010, Clinigen has managed to get it approved for Acyclovir-resistant¹⁷¹ mucocutaneous herpes simplex virus (HSV) infections in immunocompromised patients i.e. transplantation patients. Clinigen supplies Foscavir in 43 global markets. Foscavir is expected to grow in line with

the growth in transplantation patients (the largest market opportunity) at 1-3% pa.

ii) Vibativ (televancin) was licensed from Theravance to treat hospital-acquired pneumonia caused by MRSA (methicillin resistant staphylococcus aureus) when other alternatives are not suitable. Clinigen paid US\$5m in upfronts and was expected to pay tiered royalties on net sales from 20% to 30% over at least 15 years. However, a diagnostic e-test has been difficult to develop for Vibativ – and as a result, the company has impaired the Vibativ Fixed Assets¹⁷² in its accounts.

iii) Dexrazoxane (Cardioxane & Savene). Clinigen has two forms of Dexrazoxane: Cardioxane for cardioprotection¹⁷³ and Savene for extravasation¹⁷⁴. Clinigen will manage the whole of Savene's manufacture, registration, distribution, and commercialisation outside the Americas. Clinigen expects to be able to generate synergies between the two Dexrazoxane-based drugs once revised approval is received for Cardioxane. It's possible, for example, that a combined product could be used to access the US market.

iv) Ethyol (amifostine). Ethyol is a cytoprotective drug acquired in 2014 from AstraZeneca. It is used as an adjuvant therapy to reduce the incidence of xerostomia (dry mouth) which is a significant side-effect in patients undergoing post-operative radiation treatment for head and neck cancer. The marketing authorisations have now been transferred and the final technical transfer of manufacturing will complete in CY2016.

Clinigen recently made a significant move forward with its specialty pharma business. One of the critical issues for the business was access to the US. This might have required Clinigen to build an expensive direct sales team. Instead, in September 2015, the company signed a strategic alliance with Cumberland Pharmaceuticals. Cumberland will provide support for Clinigen products in the US where it is Clinigen's preferred route to market, with Clinigen supporting Cumberland outside the US.

R&D

Clinigen does not undertake early stage R&D and is unlikely to undertake any clinical trials on its own behalf. But it has invested heavily in its businesses.

- **In the Services businesses,** Clinigen has in its own Clinipoint system for ordering and drug management system, and acquired an e-commerce

system with the Idis acquisition. This latter system has a larger database of products and adds significant growth potential to the Idis GA business. The Cliniport system technology comprises an online program management platform which allows physicians to order drugs for their patients, and allows the pharmaceutical or biotech company to monitor sales in real-time. It was developed for Clinigen's GAP (Global Access Program division) which has now been renamed Idis MA. We expect this system to be integrated into the Idis division.

- **In the Specialty Pharma division**, Clinigen has been very effective at working out how to revitalise poorly performing compounds. It does not aim to conduct trials, but engages with key opinion leaders (KOL) and their support work on the drug in question. The company spends relatively modest sums on the revitalisation of each program which vary considerably with each product's requirements. But with this investment it aims to double turnover for the compound over a 3-5 year period.

Pipeline

Clinigen does not have a traditional pipeline – it is not developing NCEs (new chemical entities) on its own behalf. But, following the recent ambitious acquisition for its Services businesses, we expect management to focus, again, on acquisitions for its SP business. At Clinigen's IPO, management expressed an ambition to acquire c.6 new drugs over a 3-5 year period; later the strategy changed to focus on the services acquisitions. However, at the last set of results, management reiterated their desire to expand the drugs portfolio – and discussions are currently underway with a

number of companies. The new drugs are likely to be complementary to the existing portfolio and could include one or more of the following:

- **Drugs supplied or prescribed by specialists**, mainly in hospitals and mainly in Oncology, allowing Clinigen to capitalise on its existing distribution network.
- **Niche drugs**, rarely prescribed at the moment for the main indication (because, for example, they have been contraindicated by the regulators, or superseded by another therapy) but used off-label for another indication or where more recent data suggests the therapy could be revitalised for its original use.
- **Tail-end drugs from large competitors**. A number of the drugs acquired so far have been too small for the original large pharma's portfolios. With the recent deal frenzy in the pharmaceutical industry, some tail-end compounds could be sold inexpensively to Clinigen, especially if Clinigen already has a track record of selling the therapy through either the Idis MA or GA divisions.

Patents

Clinigen owns the IP and know-how for its portfolio of SP products once the products are revitalised. It developed the Cliniport in house.

Management Team

In addition to the senior team shown below, Clinigen has a strong group of highly experienced Managing Directors running each division.

FIGURE 19: CLINIGEN'S BOARD OF DIRECTORS AND LEADERSHIP TEAM

Name	Role	Biography
Peter Allen	Non-Executive Chairman	Joined in August 2012 and is a highly experience NED and Chairman, Is currently Chairman of Future, Advanced Medical Solutions, Diurnal and of Oxford Nanopore Technologies.
Peter George	CEO	Helped form Clinigen in June 2010 and was former CEO at Penn Pharma, having led a £67M management company buy-out in 2007. He has substantial experience in the health and clinical trials industry.
Martin Abell	CFO	Joined August 2015. Prior to Clinigen Martin was Finance Director for the Continental Europe and Rest of World division at Hays plc and has experience at other FTSE 250 businesses in both Finance and Investor Relations.
John Hartup	NED	Joined in May 2011. He has substantial experience as a corporate lawyer. He was managing partner at Ricksons LLP and a partner at DWF LLP. He also has a number of NED roles.

Name	Role	Biography
Ian Nicholson	NED	Joined in September 2012. He is also Chairman of the investment committee of Cancer Research UK Pioneer Fund, CEO of F2G Limited, Director of Casewell Consulting Limited and an Operating Partner at Advent Life Sciences LLP.
Shaun Chilton	Group Deputy CEO	Joined in January 2012. He was previously at KnowledgePoint360 Group, and has substantial experience across pharmaceutical operations and commercial strategy.

Source: Clinigen PLC

Partnerships

Clinigen has a number of partnerships, providing services for numerous businesses across its three service divisions. Its largest (unnamed) client accounts for c.15% of total revenues, mainly concentrated in the CTS business. In addition, it has the formal relationship with Cumberland Pharmaceuticals discussed above.

FINANCIAL RESOURCES

Current performance

Clinigen finished FY2015 (June year-end) with net assets of £204.6m, cash and equivalents of £27.8m, more than offset by Bank loans of £105.8m. Clinigen has a total available bank facility of £140m. This consists of a five-year fixed-term repayment loan of £45m, and a five-year revolving credit facility of £95m. Interest is paid on a tiered scale, but as Clinigen generates cash from its operations and, assuming no further acquisitions, Clinigen is more than capable of servicing and paying back its debt.

The H1 trading update of 19th January 2016 showed that revenue was up 110% for H1 (driven by the acquisitions and organic growth), organic gross profit on a pro forma¹⁷⁵ basis was up 4%, net debt was at £82m with the Link acquisition offsetting the cash flow, and most importantly, management are confident in the integration strategies they have employed so far.

Market Expectations for Financial Performance

The market expects good growth from Clinigen, helped by a full-year contribution from Idis, and a half-year contribution from Link Healthcare. During the analyst call for the H1 FY2016 trading update, Shaun Chilton (the Deputy CEO) discussed the strengthening of the senior executive team and the ambitions for

the business. And, most importantly, that trading for FY2016 is in line with their expectations.

KEY SUCCESS FACTORS

Clinigen has expanded quickly since it was established in 2010. It has grown both organically and through acquisitions, the most ambitious of which were in 2015 with the acquisition of IDIS and of Link Healthcare.

Clinigen has strong management and a supportive shareholder base that has allowed the rapid expansion of its business through acquisition. But, to pursue its ambitious growth strategy, it also needed a solid cash-generative business – this business has also benefited from management’s experience of the pharmaceutical sector.

LESSONS LEARNED

As for many of these businesses, the following have been crucial for its success:

- Experienced management, previously involved in a number of successful business. Many of the team have worked together before.
- Good communication with the shareholder base and the wider investment community. The growth message has been clearly delivered, and the risks not underplayed.
- Supportive shareholder base, who feel comfortable with management’s strategy and growth plans.

165 Lamberti, M.J. et al "Tracking Trial Cost Drivers: The impact of comparator Drugs and Co-therapies" in Pharmaceutical Executive May pg. 34-38

166 Clinigen FY2015 results announcement.

167 Clinigen FY2015 results presentation.

168 LEK Consulting

169 Clinigen FY2015 results presentation

170 Viral disease which can lead to retinal detachment and then blindness 171 One of the most commonly used antiviral drugs

172 "The £3.8m impairment of intangible fixed assets relates to the impairment of the inlicensed product Vibativ which was acquired in 2013. The product's current loss making position and uncertain commercial future has led to the carrying value of the product being fully impaired. The impairment charge includes a full write down of the carrying value of £3.4m, write down of stock of £0.2m and a £0.2m provision for committed future costs relating to the product" Source: Clinigen Annual Report 2015 page 63

173 Acquired in 26th March 2013 for US\$33m from Novartis. It is indicated for use in preventing the cardiotoxicity (damage to the heart) of patients being treated with anthracyclines for advanced and/or metastatic breast cancer. In 2011, the MHRA contraindicated its use in other malignancies or in children after two randomised open studies reported a 3x increase in the incidence of second primary cancers in children compared with controls. However, Clinigen believe that this is a flawed decision and are in the process of compiling information to argue that restrictions should be lifted. It anticipates a response from the regulators in the next six months.

174 Savene was acquired on 31st March 2014 for an undisclosed sum from SpePharm (a majority owned affiliate of Norgine). It is used for the treatment of extravasation (leakage from intravenous chemotherapy from the veins which can cause the surrounding tissue to die) in anthracycline chemotherapy in adults. It needs to be used within six hours of extravasation in order to allow the patient the chance to continue their chemotherapy.

175 From the trading update "Year on year comparisons, referred to as 'pro forma' are calculated from the aggregated unaudited results taken from six monthly management information for Clinigen and Idis, and for Link Healthcare, the two months ended 31 December 2015 and for the two months ended 31 December 2014. Pro forma numbers include Clinigen's 50% share of gross profits from the Joint Venture in South Africa."

HORIZON DISCOVERY GROUP

STATEMENT FROM DR DARRIN DISLEY, CEO

The UK Life Sciences sector is experiencing a renaissance with an integrated policy approach to science, translational research, enterprise, skills development and financing beginning to bear fruit.

Record numbers of start-ups funded by angel, grant and venture capital promise great things for the future of the sector but challenges remain in the scale-up of the most promising businesses; most notably in the lack of sizeable Series C and D level funding and specialist public market investors.

As such the success of star companies like Circassia, Clinigen, GW Pharma, Immunocore as well as emerging stars like Abzena, Midatech Pharma and Retroscreen Virology will be important in underpinning the next wave of IPOs and the re-financing of portfolio-based firms like IP Group, Imperial Innovations, Mercia Technologies and Woodford Investment Funds.

Horizon Discovery's story is an excellent example of this resurgence. Since going public in March 2014, Horizon transitioned from being a private Cambridge Life Sciences firm employing 85 staff to a publicly-listed international Life Sciences group employing over 250 staff in 100,000 square feet of office and laboratory space in Cambridge (UK), Boston (USA), St Louis (USA), Philadelphia (USA) and Vienna (Austria).

We are now established as the world's leading gene-editing company and a go-to provider of integrated product, service and research solutions to over 1200 academic, biotech, diagnostic and pharma customers in 50 countries working at all stages of gen-editing and personalised medicine research. This breadth of offers and strong customer adoption has driven our revenues to £11.9m (up 79%) for FY 2014 and £8.6m for H1 2015 (up 111%). In addition, Horizon is eligible to receive potential future milestones of £208m cumulative plus product royalties.

Our £68.6m IPO on AIM, the largest ever for a Life Sciences company from the Cambridge Cluster, was

6.5x oversubscribed from its £25m target raise, and returned up to 32x for investors who placed out £28.6m in an "old school" exit. Our market capitalisation has since increased from £45m pre IPO.

FACTS & FIGURES

Horizon is an excellent example of a company with high growth, high-tech opportunities, but one with a significantly lower risk profile than a typical biotech company. This is because it is conservative with its cash, has much lower R&D spend, is not reliant on regulatory approvals for revenues, is revenue generating (unlike the majority of biotechs) and has multiple partners across large and small therapy and diagnostics businesses. It has access to some highly inventive and critically important IP, giving Horizon the capability to edit genes. This IP has been important for the company's achievements to date – as have its partnerships, scientific relationships, acquisitions, and focused strategy.

These attributes should drive the ongoing success of the business as it moves rapidly to break even. However, the company's share price does not necessarily reflect the progress the business has made.

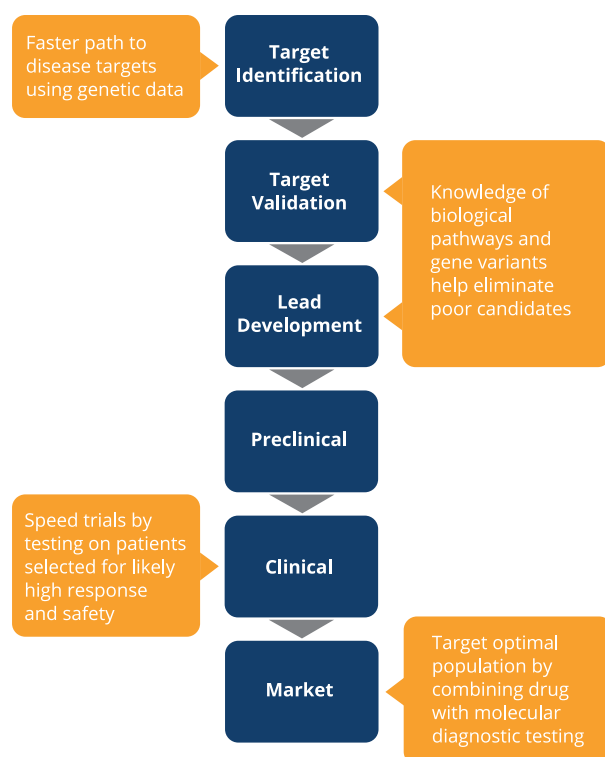
Technology/Product Focus

Horizon focuses on delivering research tools to companies involved in genomics research and the development and implementation of personalised medicines. This is essential to reducing the cost, and boosting the success, of drug development, which has historically taken c.15 years¹⁷⁶ at an average cost of c.US\$2.6bn per drug.

The economics of drug development means expertise has rested with Big Pharma companies. Big Pharma has concentrated on developing and marketing "blockbusters". But treatment of disease is becoming more sophisticated; physicians realise that different patients with different genetics respond differently to different drugs.

A “one size fits all” approach is crude and no longer necessary. Horizon is helping to drive the shift towards “matching the right drug to the right person at the right time.”¹⁷⁷ This approach allows for the lower-cost development of a therapy and a shorter time to market through a tailored research programme. These quicker, better-directed research programmes can use techniques and products sold by Horizon across the whole drug development process. Horizon estimates that its main markets are worth £29bn.

FIGURE 20: WHERE CAN HORIZON DISCOVERY HELP?



Source: Horizon Discovery.com

Horizon has a variety of gene editing tools which it uses to engineer cell lines, in vivo models and derived reagent products. These products are then sold on, utilised in-house within contract research services for its clients, or used to develop drug candidates in its leveraged R&D business. In particular, Horizon believes that delivering services and products to companies at the pre-clinical stage of development is one of its main strengths: it provides genetically-defined cell lines and in vivo models for optimisation of lead candidates, and uses drug combination screening for biomarker

discovery and/or drug positioning.

Gene Editing Tools

Horizon deploys a number of technologies and methods to edit the genes of the cell lines it is interested in: CRISPR, rAAV, and Zinc Finger Nucleases (ZFN), all of which have advantages and disadvantages and deliver subtly different outcomes. Horizon uses whichever approach is most appropriate, and importantly, unlike some of its competitors, has access to, and the IP for, all the most relevant tools to edit genes.

FIGURE 21: COMPARISON OF HORIZON DISCOVERY'S THREE MAIN TECHNIQUES FOR GENE EDITING

Approach	rAAV	ZFN	CRISPR
Control Off-target-effects	✓✓	✓	✓
Targeting Efficiency	✓✓	✓✓	✓✓
Use for Knock-In	✓✓	✓	✓
Use for Knock-Out	✓	✓✓	✓
Complex modifications	✓✓	✓	✓
Hard to transfect cells	✓✓	✓	✓

Source: Horizon Discovery

- rAAV (Recombinant Adeno-Associated Virus)** is Horizon Discovery's proprietary gene editing technology. rAAV has the ability to edit genes, many of which cannot be edited in other ways. It is able to get into cells relatively easily, a key advantage over many other techniques. As rAAV is based on Adenovirus, it uses its naturally evolved method to infect cells efficiently¹⁷⁸ and does not appear to cause any significant side-effects. However, rAAVs have one major disadvantage: they can only take a small amount of genetic information into a cell, limiting their use for gene-editing programmes requiring knock-out of large genes. But the precision of rAAV is excellent, leading to its use as a gene therapy with over 100 on-going clinical trials for various diseases.

- **Zinc Finger Nucleases** are synthetic proteins which have DNA-binding domains that can cut DNA at specific places. But they cut both DNA strands which is not always precise enough for genetic engineering. Using Zinc Fingers is also time consuming and expensive and has been somewhat superseded by CRISPR (see below). On the other hand, the technology is highly targeted and rarely causes off-target alterations. Horizon does not use Zinc Fingers to develop its own products, but offers this technique to clients as a service.
- **CRISPR (Clustered regularly interspaced short palindromic repeats) and CRISPR-associated systems (Cas)**. This is the current technique of choice, and Horizon was one of the first companies to use and offer it. Horizon has relationships with all the original inventors and patent holders, and access to all the relevant IP in this area, though the IP position is complex¹⁷⁹ (see below). CRISPRs were discovered to be naturally occurring in c.40% of bacteria and c.90% of other single-celled organisms such as plasmids and phages.

Business organisation

There is overlap across all the units as Horizon offers services on all of its product offerings, and uses its own products and services for its own Leveraged R&D.

Products

Horizon has three areas from which its product offerings originate:

1. Horizon Diagnostics. Horizon offers reference standards – a critical component of any diagnostic system. It engineers genetically-defined, human genomic reference standards e.g. clinically-relevant cancer genes exactly as they appear in patients' tumours. The manufacturer or clinical researcher can use these to validate diagnostic tests or to compare tests (useful to check the quality of assay results), or to investigate a therapy.

2. Horizon Bioproduction. Horizon offers both off-the-shelf and on-demand CHO¹⁸⁰ based cell lines for bio production. It also offers custom optimisation of CHO platforms, allowing specific and high-value cell lines to be developed according to customer specifications.

Horizon uses all its gene-editing techniques to deliver the cell line required; it can do this more precisely than its competitors. Custom cell lines are critical to the manufacture and development of high-value biological drugs – drugs are unlikely to be approved unless they can be efficiently and effectively produced. Horizon Bioproduction has strong relationships in the industry and, in March 2015, the consortium it is involved in, led by the Centre for Process Innovation (CPI), was awarded a significant share of a £6.2m grant as part of the UK government's Advanced Manufacturing Supply Chain Initiative (AMSCI).

3. Horizon Genomics offers two main products:

a. Cell Lines. Horizon offers a variety of cell line products including its X-MAN cell line catalogue (Horizon Discovery's original product offering). X-MAN cell lines are isogenic human knockout/knockin cell lines i.e. two cell lines are provided to customers, one of which has a specific genetic change, often linked to disease, and the other similar, but lacking that genetic change. The effect of a therapy on the two cell lines can be compared to see whether it treats a disease. Horizon believes that the X-MAN Cell Line library comprising over 20,000 lines (available for sale through its website), is the single largest bank of human isogenic cell lines available. The recent acquisition of Haplogen Genomics, in January 2015, gives Horizon a way of engineering cell lines that is ten times faster and cheaper.

b. In-vivo Models. Following the acquisition of Sage Labs in September 2014, Horizon offers engineered rat (for which it has exclusive IP for ZFN and CRISPR) and mouse models to researchers in pharma and biotech who are looking to use in-vivo models to investigate disease or a therapy. These models are available both off the shelf or on-demand, and are generated using Horizon's full range of gene editing capabilities.

Services

Horizon Research Services include precision gene-editing, isogenic cell line assays, cutting-edge screening platforms and in vivo models to help solve research and drug development challenges. The custom cell line engineering is highly-leveraged as these cell lines are of interest to a wider audience. If

Horizon has not signed an exclusive deal on the line, the cell line or product of interest goes into its catalogue. In addition, Horizon offers services in the following two areas:

1. Horizon Bioproduction. See above. Horizon offers a customisation service.
2. Horizon Genomics. See above. Both cell line and in vivo models are available as a custom on demand service.

Leveraged R&D

Finally, Horizon Discovery also conducts research on its own behalf where it uses the products and services that it offers to external customers too. See R&D & Pipeline section below for more detail on this business.

R&D & Pipeline

Leveraged R&D

Horizon recently raised £25m (July 2015). Management's plan is to invest up to £10m over a 2-year period in its leveraged R&D business in order to identify "Next Generation Molecular Cancer therapies". The business model is similar to Horizon Discovery's HD001 program which is partnered with AstraZeneca. It will use its existing technologies and service businesses to generate a portfolio of interesting therapy candidates (New Chemical/Biological Entities – i.e. completely novel drugs) and targets which it can then out-license to pharma and biotech businesses. The main areas of focus will be in synthetic lethality¹⁸¹ and immuno-oncology. Immuno-oncology is expected to be a key therapy area for treatment of cancers in the future.

Horizon has a track record in this business, having invested c.£4m to date and generating a portfolio of potential milestones worth £208m plus royalties. While not all the programmes will be winners, a large enough range exists for the business to generate an attractive return on its investment.

Critically, because the company only develops its candidates to an early stage, it takes on little clinical development risk.

Other Businesses

Horizon Discovery's other businesses focus on expanding their portfolio of products either through internal development or through acquisition. Horizon Discovery is expected to continue to expand its offering of animal models, cell lines and reference standards, some of which is paid for by clients who might be interested in a particular target or cell line. Horizon Discovery is often able to resell the product through its catalogue at extremely high margins. Margins are expected to continue to rise in the foreseeable future as its network is better utilised.

Patents

The IP position is complex but management have focused on ensuring that the business and its technologies are well-covered by the IP the company has developed or licensed, and it believes that there are no hindrances to its operations.

Horizon Discovery has access to CRISPR in vitro on a non-exclusive basis from the main patent holders including ERS Genomics, Broad Institute, Caribou Bioscience and Harvard University¹⁸². CRISPR IP is spread across several researchers and companies. A number of companies have rights to different parts of the IP portfolio including Life Technologies and Sigma-Aldrich (who are also selling this technology). Horizon Discovery management believe that they are the only company with complete freedom to operate across the whole spectrum of its business. Horizon Discovery has good relationships with all the inventors of CRISPR – and has a number of the key players in this area on its Scientific Advisory Board. In addition, Horizon Discovery has exclusive CRISPR IP (from Caribou via SAGE acquisition) in rats.

At the same time, Horizon Discovery has a strong proprietary position in rAAV (exclusive rights to the IP from the University of Washington until 2018, and for AAV and AAV-DJ from Stanford from July 2014). This, combined with CRISPR, enables it to overcome one of the hurdles in using this CRISPR, namely delivery into a cell.

Horizon Discovery has a non-exclusive in vitro license for Zinc Fingers technology from Sangamo Bioscience patents (through a Sigma-Aldrich sub-license) and exclusive rights for in vivo (animal applications) from the Sangamo Bioscience patents (through a Sigma-Aldrich/SAGE sub-license).

Management Team

The management team is hugely experienced with the executive team having run numerous successful

businesses over the last 10-20 years. The CEO has, rather ingeniously, filled Horizon Discovery's scientific advisory board with many of the originators of its underlying technologies such as rAAV and CRISPR. Some of these people are also paid as formal advisors to the company.

The acquisitions have been fully integrated and management believe that the company is working as a cohesive whole¹⁸³.

FIGURE 22: HORIZON DISCOVERY GROUP'S BOARD OF DIRECTORS AND LEADERSHIP TEAM

Name	Role	Biography
Dr. Ian Gilham	Chairman	Ian is currently the non-executive chairman both of Multiplicom NV, which focuses on DNA sequencing products, and of Biosurfit SA, which focuses on point-of-care diagnostic products. He is also NED on Vernalis, and director of Stowheath Ltd., which offers advisory services to those investing in clinical diagnostics and medical device companies. Ian was formerly CEO of Axis-Shield plc.
Dr. Darrin Disley	CEO & President	Darrin has been involved in the start-up and growth of a number of businesses raising over \$275m and closing over \$450m of commercial deals. He has a PhD in Biotechnology from the University of Cambridge and is an Entrepreneur in Residence at the Judge Business School and Enterprise Fellow at the Department of Chemical Engineering and Institute of Biotechnology, both at the University of Cambridge. He is also Chairman of GeoSpock and Desktop Genetics, NED on Cell Therapy Ltd and is on the Advisory Board of HealX3 Ltd, SimPrints Ltd, the UK Bioindustry Association the Cambridge Phenomenon, the Cambridge Science Centre and Biotech and Money.
Richard Vellacott	CFO	Richard has substantial experience as an accountant, working across the life science sector. He was VP of finance at CSR plc. and was a director in Deloitte's life sciences practice, where he specialised in capital market transactions.
Dr. Jonathan Milner	NED	Jonathan was founder of Abcam Plc and is now involved with a number of companies originating in Cambridge, UK.
Grahame Cook	NED	Grahame is a highly experienced FTSE and AIM non-executive. He has a background in banking, and he has specialised in the life sciences, pharma and biotech sectors. He is chairman of Sinclair Pharma plc and Morphogenesis Inc, and is involved in a number of companies in the sector.
Dr. Susan Galbraith	NED	Susan is currently Senior VP and Head of Oncology Innovative Medicines at AstraZeneca. She was previously at Bristol-Myers Squibb.
Dr. Vishal Gulati	NED	Vishal is a specialist healthcare investor in diagnostics, digital healthcare and biotechnology and has served on the boards of companies across Europe, the USA and in India. He was at Atlas Venture LLP, the Wellcome Trust and has been a practising doctor too. He is on the BioCatalyst awards committee (a UK Government backed £180 million fund for emerging technology companies).

Source: Horizon Discovery PLC

Partnerships

Horizon Discovery has numerous partnerships and relationships, not just in its leveraged R&D business, but for its Services and Products businesses too. It had over 1200 unique customer relationships as of mid-2015, and sells to, or works with, over 30 of the top 50 pharma companies in the world. For instance, in November 2015 Horizon Discovery signed development agreements for reference standards with three major developers of companion diagnostic tests worth c.US\$3.3m. In addition, it is part of over ten grant consortia which are looking at specific business and technology opportunities.

It sells its products either alone or in combination with others through companies such as Abcam¹⁸⁴, ThermoFisher and Sigma-Aldrich, which in some areas are Horizon Discovery's competitors too. These companies are some of the most important providers of product and services into both academic and pharma/biotech company labs.

FINANCIAL RESOURCES

Current performance

Horizon Discovery's interim results showed improved revenue performance +140% (including £0.5m from the Haplogen acquisition) to £8.6m, with products contributing £3m, services £5.4m and leveraged R&D £0.2m. Following the first part of the £10m investment in the leveraged R&D business, the company, as expected, continued to operate at a loss EBITDA of £(4.9m).

The recent FY2015 trading update, meanwhile, indicated that the company continued to perform well in H2. Revenues are expected to be at least 2% ahead of market consensus of £19.8m. Organic growth in the Products business was good, +120% from FY2014 £3.5m of revenues, while the Services business is up 65%, driven by strong demand across its offering.

Market Expectations for Financial Performance

The company is expecting to see declining losses through FY2016 though it will continue expanding its product portfolio, its customer base and its leveraged R&D business. Management are still expecting to reach profitability in FY2017. Horizon Discovery ended FY2015 with c.£25.1m of cash¹⁸⁵ which it can use to invest in its business and to make further add-

on acquisitions to expand its offering. The business is broadly H2 weighted: c.55-60% of revenues traditionally occurring in H2. Management expects this trend to be maintained.

Expected future R&D milestones now stands at £208m plus future product royalties. This is up 32% year-on-year, helped by two new collaborations signed in 2015 with Redx and Servier.

KEY SUCCESS FACTORS

The following are key to Horizon Discovery's success:

- The "right management at the right time"¹⁸⁶ – an aggressive management team targeting a large market opportunity with innovative products.
- Good acquisitions, adding significant products and growth across the whole continuum of drug development at relatively inexpensive prices. A number of the companies acquired had not been performing to their strengths and were priced accordingly. Horizon Discovery's turnaround strategies for these acquisitions are starting to deliver, with impressive revenue growth being seen in these businesses and increased customer numbers.
- Unlike many biotechs, Horizon Discovery is revenue-generating and has £208m in potential milestones plus royalties expected over the next 15+ years from multiple customers. This offers significant upside to investors.
- Horizon Discovery has a low risk approach to R&D with the vast majority of R&D paid for by clients

These attributes means that Horizon Discovery is a relatively low risk, high-tech player in a large and growing market.

LESSONS LEARNED

How do UK investors judge performance? Horizon Discovery's current share price performance may not necessarily reflect that the company has been successful at raising funds (another £25m in 2015), at growing its business consistently and ahead of expectations, at increasing public awareness of the opportunities for its technology, at increasing employment both in the UK and US, at finding and integrating acquisitions, at partnering with some of the largest pharmaceuticals companies in the world, at finding and developing IP, at managing numerous

scientific advisors (some with contentious IP issues), and at developing ground breaking technologies and therapies that will vastly improve lives.

176 This comprises "Average out-of-pocket cost of \$1,395 million and Time costs (expected returns that investors forego while a drug is in development) of \$1,163 million" From TUFTS Center for the Study of Drug Development http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study Downloaded 4/10/2015

177 <https://www.horizondiscovery.com/about-us/our-science/> Downloaded 5/10/2015

178 It always inserting into the same site on a genome, does not cause chromosome breaks but use existing ones, amplifies the gene and does not produce off-target alterations which can be a significant problem.

179 The IP situation for CRISPR has become increasingly contentious over the last few years with one of the developers getting a comprehensive patent, though this is now being contested by the originators of this technique. See <http://www.technologyreview.com/news/536736/crispr-patent-fight-now-a-winner-take-all-match/> [Downloaded 7/12/15] for a review of the issues.

180 "Chinese hamster ovary (CHO) cells are the most dependable host cells for the industrial production of therapeutic proteins." From Abstract Omasa, T. et al "Cell engineering and cultivation of Chinese hamster ovary (CHO) cells" in *Curr Pharm Biotechnol.* 2010 Apr;11(3):233-40.

181 "Synthetic lethality exploits vulnerabilities arising from rewiring of cell signalling pathways by cancer-driving mutations, a strategy recently validated by the approval of AstraZeneca's drug Lynparza for the treatment of ovarian cancer (synthetic lethality also underpins the Group's HD-001 programme). Immuno-oncology can overcome the mechanisms by which cancer cells hide from the immune system, and give long-lasting cancer remission. Immuno-oncology successes include the marketed products Yervoy, Opdivo and Keytruda" From Horizon Discovery Group's press release July 2015

182 Ie from all the key originators Jennifer Doudna, Emmanuelle Charpentier and Feng Zhang.

183 From conversation with CEO and CFO 1/10/2015

184 Press release 9 September 2015. "Horizon exclusively out-license existing human diploid and haploid cell line collection for use in validating the function of Abcam antibodies. Horizon to receive exclusivity payments totalling £660,000 (c\$1,000,000) across an initial three- year term with a further potential £1,275,000 (c\$1,950,000) across years four to six if Abcam extends the exclusive period."

185 See Trading update 18/1/2016

186 A quote from a conversation with the CEO and the CFO 1/10/2015

MIDATECH PHARMA PLC

STATEMENT FROM DR JIM PHILLIPS, CEO

Midatech is rapidly emerging as one of Europe's leading specialty pharma companies. Since our IPO, we have delivered on our strategy due to our novel technology, pipeline, M&A strategy, focus and experienced team. Midatech has a three-pronged business strategy based around our own high value drug pipeline, partnering activities and M&A/ marketed products.

As set out at the time of the IPO, we aim to develop a pipeline of high value product candidates for which there are currently few or no treatment options available. These diseases include diabetes, rare cancers including brain (glioblastoma where we already have a compassionate use programme running in UK), ovarian, liver and pancreatic cancer and neurological/ophthalmologic conditions.

Midatech's core therapeutic focus is oncology. Our in-house product candidates are in rare cancers and with our partners, the pipeline looks at other indications. In order to accelerate the growth of our business we have delivered strategic acquisition of complementary products and technologies. In 2015 we expedited this strategy via the acquisition of DARA Biosciences and Zuplenz® in US taking our marketed portfolio to four oncology products via our own salesforce.

All of our product candidates are based on our two novel platform technologies that can be used alone or in combination to enable the targeted delivery ('right place') and controlled release ('right time') of existing drugs. These technologies are provided through its wholly-owned subsidiaries, Midatech and Q-Chip (acquired in 2014).

Our core platform is a drug conjugate delivery system based on a patented form of gold nanoparticles (GNP) combined with existing drugs for the safe and targeted release of therapeutic payloads at specific organs, cells or sites of disease. Our second platform is a sustained release technology acquired with Q Chip that involves the consistent and precise encapsulation of active drug compounds within polymer microspheres enabling their release into the body in a highly controlled manner over a prolonged period of time.

Our new and rapidly growing structure includes Midatech Pharma US, formerly DARA BioSciences, Inc., which represents the US Commercial arm of Midatech Pharma PLC in US, manufacturing facilities in Bilbao, Spain and an R&D facility in Cardiff, UK. Our corporate headquarters are in Oxford, UK. We would welcome a visit by you in 2016!

FACTS & FIGURES

Midatech Pharma was founded in 2000 using IP from the CSIC (Consejo Superior de Investigaciones Cientificas) in Seville, Spain to develop its main platform technology and associated manufacturing. This technology uses gold nanoparticles designed to deliver therapies to a specific site.

Midatech Pharma IPO'd in 2014, raising £32m¹⁸⁷ and its ADRs are listed on NASDAQ too (from its acquisition of DARA – see below). It is an excellent example of a relatively new specialist pharm business with an experienced management team and a highly acquisitive strategy. Despite ambitious plans it has lower development risk than biotechs as it "redesigns" existing marketed drug molecules using its novel drug delivery technologies, as well as developing its own innovative products. Critically, it is revenue-generating from its portfolio of marketed products in oncology (over £9m is expected in FY2016¹⁸⁸).

Midatech is looking to develop its platform technologies into multiple products and therapy areas. This means that it would not be reliant on any one product and could target multiple revenue opportunities. It plans to grow its business in three ways¹⁸⁹:

- ***“Development and commercialisation of its own products, particularly for rare cancers and cancer care”.*** The company is targeting a quicker and cheaper route to market with Orphan Drugs. An Orphan is defined by the European Union as one that affects fewer than 5 in 10,000 of the general population, and by the FDA as one that affects fewer than 200,000 people nationwide [in the USA]. In 1983 the US Orphan Drug Act gave financial and tax incentives to companies developing drugs for these conditions. Often these drugs are tested on relatively few patients, and come to market much quicker than normal

drugs. For this reason, they are of interest to biotech businesses who are looking to preserve cash.

- *“Development and commercialisation of partner-supported and licensed products, principally in diabetes and neuroscience/ophthalmology”* along with research and collaboration, and possible manufacture of non-competing products
- *“Acquisitions of later stage, strategic and complementary opportunities (products or technologies) that accelerate revenue, and are value accretive”*. In 2015 there were two acquisitions – to some extent, M&A was management’s main focus during this last year.

Midatech’s strategy is to strengthen its revenue-generating and commercially-focused business and to deliver proprietary therapies into the market. At the same time, it aims to become profitable by 2019. The company delivered performance in line with expectations (trading update January 2016).

Technology/Product Focus

Midatech’s main product candidates derive from two technologies (in two subsidiaries). They can either be used separately or together to ensure that drugs are released at the right place and at the right time.

1. **Midatech** drug conjugate delivery¹⁹⁰ system, in which the drug/therapy/cytotoxic agent is attached to another compound, is based on a patented form of carbohydrate-coated gold nanoparticles (GNP). The company believes that these systems confer significant advantages in delivery of certain drugs. These advantages include improved solubility, releasability, mobility due to small size¹⁹¹, targetability¹⁹², stability, excretability, compatibility as they do not cause the immune system to respond, and scalability through Midatech’s cGMP manufacturing facility. Midatech believes that its gold nanoparticle-based system is superior to alternatives which include the use of antibodies and liposomes. Its lead programme is an oral soluble film-based insulin delivery system.
2. **Q-Sphera** sustained release technology. This involves the encapsulation of the drug active in CAD printed polymer microspheres. The drug can be released into the body in a highly controlled manner over a prolonged period of time, even up to 6 months. This business was acquired in 2014.

Analysts estimate that the nanotechnology-based pharmaceutical market is worth more than US\$7bn and Midatech’s main therapy areas have a combined addressable market of over US\$90bn¹⁹³.

Midatech has invested significantly in its GMP manufacturing in Bilbao, Spain. In 2014, capex of €800k upgraded the facility. In addition, Midatech was lead in a consortium which won a €7.9m Horizon 2020 European Union grant to fund manufacturing scale-up for clinical trials and to prepare for commercial production and supply.

Product Portfolio

Midatech has a rapidly growing portfolio of marketed oncology products. Midatech acquired a US presence, salesforce and a product portfolio of oncology supportive care products with the acquisition of DARA in June 2015. The initial consideration was c.US\$24.0 million and an earn out of c.US\$5.7m will be paid over the next few years (through a contingent value rights mechanism) based on the performance of certain DARA products. The acquisition is expected to be cash-flow positive in 2018¹⁹⁴. The DARA portfolio included:

- Gelclair, an oral gel for the management and relief of pain related to mouth problems caused by certain treatments for certain cancers
- Oravig, an orally-dissolving tablet for the local treatment of oropharyngeal candidiasis in adults which launched in Q4 2015
- Soltamox, the only liquid form of tamoxifen which is used in the treatment of metastatic breast cancer

In addition, the company acquired two products co-marketed with Mission Pharmacal: Ferralet 90 (for anaemia), and Aquoral (for chemotherapy/radiation therapy-induced dry mouth).

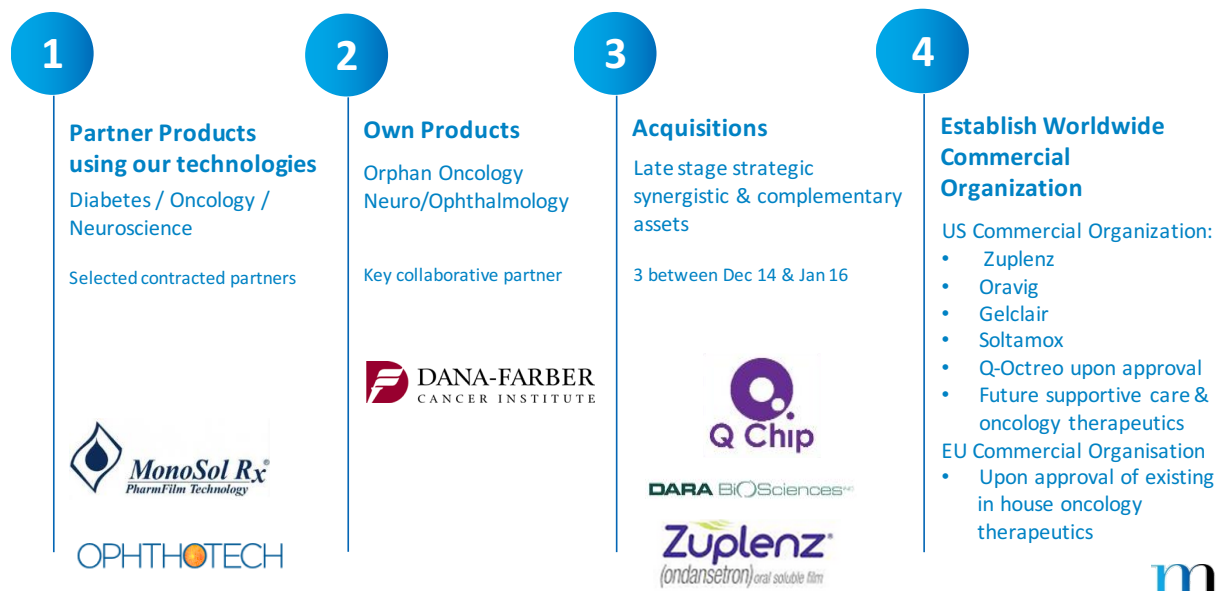
More recently, in December 2015, Midatech added another product to its marketed portfolio which is complementary to Midatech’s three existing oncology products. Zuplenz (ondansetron), a marketed anti-emetic oral soluble film from Galena Biopharma, Inc. for the prevention of chemotherapy-induced nausea and vomiting (CINV), radiotherapy-induced nausea and vomiting (RINV), and post-operative nausea and vomiting (PONV). These acquisitions add to Midatech’s revenue-generating ability but, most importantly, they give it a commercial infrastructure in the US. Midatech expect to have a sales organisation of 32 starting in 2016.

Management expect Zuplenz to target a market worth c.US\$4.6bn by 2018. Midatech paid a total up front consideration of US\$3.75m in cash, and will pay further cash payments, totalling up to US\$26m, dependent on certain milestones being achieved. These are expected to be self-financed by generated cash-flow.

R&D

The company has a number of partnerships with large pharma and biotech companies in diabetes and ophthalmology. The rest of its programme is unlicensed, with Midatech developing these products by itself. The company has an integrated business model made up of four components, all of which will be necessary to hit its strategic targets.

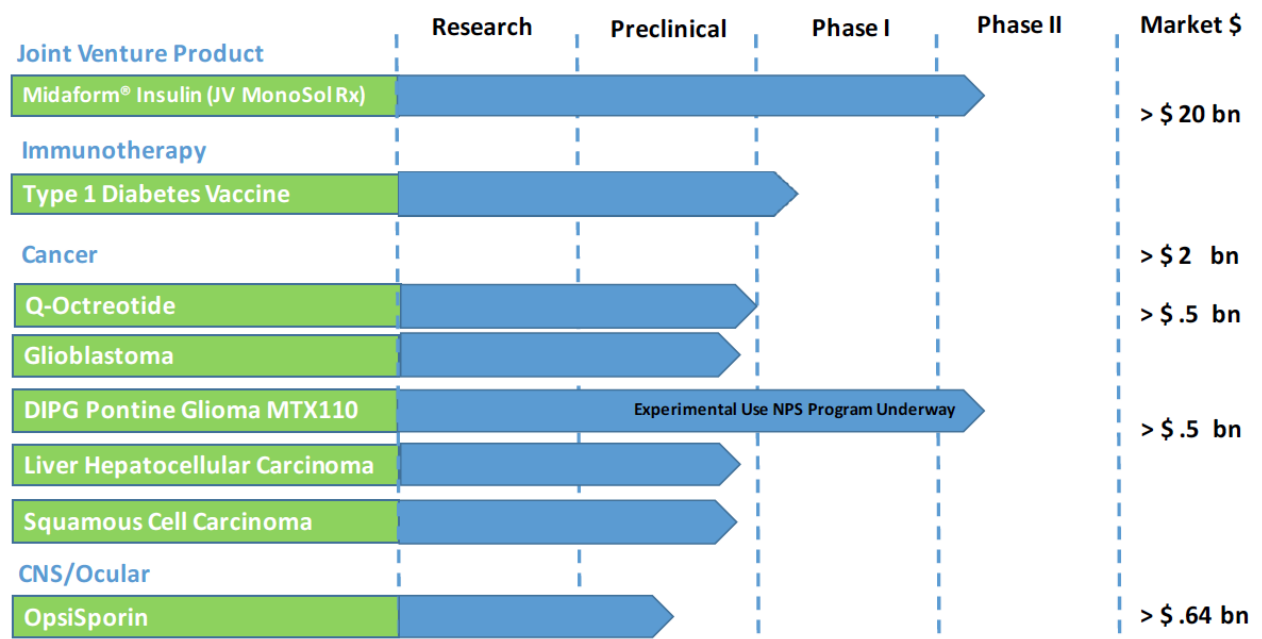
FIGURE 23: MIDATECH PHARMA'S BUSINESS MODEL



Source: Midatech Pharma

Its internal development pipeline is focused on hard to treat cancers. See Figure 24.

FIGURE 24: MIDATECH'S INTERNAL DEVELOPMENT PIPELINE



Source: Midatech Pharma

Focused on Orphan Indications

Its development programme is focused on orphan drugs. These are cheaper and quicker to get to market. They include therapies for Carcinoid Syndrome¹⁹⁵ (already licensed in Turkey¹⁹⁶) and Uveitis¹⁹⁷, as well as Glioblastoma¹⁹⁸, for which Midatech is partnered with the Dana-Farber Cancer Institute, an affiliate of Harvard Medical School¹⁹⁹. The Glioblastoma candidates are now in in vivo testing²⁰⁰.

Type 1 Diabetes Vaccine

The second programme into the clinic is the diabetes vaccine FP7 which has accelerated over the last year and now has two clinical trials starting in 2016. These are both phase 1 trials with multiple biomarkers, the first completes in 2016 and the second in early 2017. It would likely be a short course treatment, turning down the body's own immune system which has attacked the insulin producing cells.

MidaForm

As discussed, Midatech's most advanced programme is its transbuccal insulin (called MSL-001 or MidaForm), which is part of the JV with MonoSol Rx. In July 2015, Midatech initiated its Phase IIa open label, cross-over, seven arm study in type 1 diabetes. The study aims to establish the pharmacodynamic and pharmacokinetic profile, and safety and tolerability of MSL-001 in comparison to an injected human recombinant insulin. There are 12 patients, the study took 5 months, and data is expected Q1 2016. Midatech will look to partner or sell the programme following phase II.

MTX110 for Paediatric Brain Tumour - Compassionate Named Patient Programme in the UK

Most recently, early in 2016, the company was asked by oncologists at the Bristol Royal Infirmary to develop and deliver a treatment for a compassionate use programme for a rare paediatric brain tumour (DIPG Pontine Glioma²⁰¹). This compassionate programme could, if successful, provide part of the data for a

"fast tracked" market approval for a disease with a significant need for a therapy. The treatment is currently getting ready for manufacture. The first treatment may be before the end of March as the company already has a named patient requested.

Q-Octreo for chronic treatment of Acromegaly²⁰²/Cancer

This is a long-acting re-formulation of Octreotide acetate (Sandostatin). It would be a monthly injectable depot with lower cost of goods, and easier to administer, which could cut clinic time by half. It is currently in the final stages of preclinical development, and will be entering bio-equivalence in 2016/7 with a US launch expected in 2018/9. Management believes that it could see peak annual market sales of c.US\$100m.

Patents

The company has invested significantly in its IP portfolio. The combination of both the Midatech gold nanoparticles and Q Sphera technologies could mean that the company can develop a sustained-release, closely-directed therapy for multiple indications.

Management believe Midatech's IP position is critical to its success. The company has a large patent portfolio, considering its size. It has created new composition of matter patents for each product it takes forward to its development pipeline and now has more than twenty patent families and is filing a further 3-4 each year.

In addition, there are foundation patents for each of the main technologies. The original gold nanotech patent will expire in 2021 but, in reality, it cannot be used without the other technologies and processes that Midatech has developed. These are protected well past 2021.

Management Team

Midatech has a highly experienced employee base and board who are helping to drive its aggressive and clever strategy. It employs 105 people across Europe and the

US. Most critically for the company's achievements to date, Jim Phillips has worked successfully with a number of his senior executives before, including the Finance Director, Nick Robbins-Cherry, and the COO/CMO, Dr Craig Cook.

FIGURE 25: MIDATECH PHARMA'S BOARD OF DIRECTORS AND LEADERSHIP TEAM

Name	Role	Biography
Rolf Stahel	Non-executive Chairman	Has approximately 40 years of experience in the pharmaceutical industry with 20 years CEO and Board member of a number of Life Science businesses across the globe. He joined Shire as CEO in 1994 following a 27-years at Wellcome plc (now part of GlaxoSmithKline). In addition, he is non-executive Chairman of Connecious Life Sciences Pvt Ltd and Ergomed PLC.
Dr Jim Phillips	CEO	Dr Phillips has a medical background and founded Talisker Pharma in 2004, which was acquired by EUSA Pharma in 2006. He was involved in the acquisition of OPI and then the Group's acquisition by Jazz Pharmaceuticals in 2012. He is currently a NED of Herantis Pharma plc (listed in Helsinki), Insense Ltd (a private spin-out from Unilever). Prior to that he held senior positions at Johnson & Johnson and Novartis Pharmaceuticals.
Nick Robbins-Cherry	Finance Director	Has extensive commercial and finance in the life sciences, technology and consulting sectors and had roles at CACI Limited, Johnson & Johnson and ICI PLC. He has extensive MA& experience.
Pavlo Protopapa	NED	Mr Protopapa is the founder and managing partner of Ippon Capital, a private equity company based in Geneva, Switzerland. In addition, he is the chairman and CEO of Spacecode Holdings and is NED and lead investor of Socure Inc. Prior to that he was CFO of the Steinmetz Diamond Group from 1997 to 2012.
John Johnston	NED	He is currently NED of Flowgroup plc and Action Hotels. Prior to this, he was MD of Institutional Sales at Nomura Code, was at Seymour Peirce, founded Revera Asset Management, after having spent the previous 20 years in investment banking.
Dr Simon Turton	Senior Independent NED	Dr Turton previously headed Warburg Pincus' healthcare investing activities in Europe and was a Principal at Index Ventures in Geneva. He has a 20-year career in pharma and biotech and was and NED of Archimedes Pharma, Eurand, ProStrakan and Tornier. His most recent roles were Chairman of Q Chip and OpsiRx Pharmaceuticals prior to their acquisition.
Michele Luzi	NED	Was a partner in Bain & Company, having run their EMEA Telecommunications Technology Media Practice for seven years. He was a member of the World Economic Forum Global 36 Agenda Council and of the Web Foundation Advisory Board.
Dr Sijmen de Vries	NED	Dr de Vries has extensive experience in the pharmaceutical and biotechnology industries. He is currently CEO and CFO of Pharming group N.V., and was previously CEO of 4-Antibody and of Morphochem AG.

Source: Midatech PLC

Partnerships & Joint Ventures

The company has a significant number of relationships, a number of which are revenue-generating. Its numerous relationships are impressive for a pharma company at this stage of development and attests to the strong management and also to the technology Midatech has developed. While many of its partnerships cannot be disclosed, the list includes at least three top-ten pharma/biotech businesses and a university hospital. Two of the more significant disclosed relationships are:

1. The 'MidaSol' JV with MonoSol Rx which uses a fast acting transbuccal film-based Insulin delivery platform for type 1 and 2 diabetes. Since a large clinical trial programme will probably be required, the JV programme is likely to be partnered over the next few years with a large Pharma.
2. At the beginning of 2016, Midatech signed an exclusive licensing agreement with Emergex Vaccines which will use Midatech's gold nanoparticle technology to develop vaccines to prevent and treat for infectious diseases. Midatech will also manufacture product for clinical trials. While specific terms have not been released, Midatech will receive initial, milestone and royalty payments.

FINANCIAL RESOURCES

Current performance

At the interims and ahead of the closing of the DARA acquisition, revenue grew from £36k in the six months to June 2014 to £324k. Net cash outflow from operating activities (before working capital) was £4.9m, leaving a cash balance at 30 June 2015 of £24.34m. Since then, Midatech has made further investments, and following the acquisition of Zuplenz, management expects cash to be c.£16m at the end of FY2015, and revenues to be slightly ahead of expectations²⁰³.

Market Expectations for Financial Performance

Midatech has a clear strategic plan; it aims to become profitable by 2019. It will do this by:

- Acquiring at least two value-enhancing businesses/products. (Three were acquired over 2014 and 2015.)
- Establish and expand US commercial presence. US products were acquired in 2015, launches and expansion expected in 2016.

- To have two products licensed to partners. Multiple candidates are in discussion.
- To have marketed one of its own products: Q-Octreo (see above). A US partner for endocrinology is under discussion and the company has signed a deal in Turkey with Centurion.
- To be recognised as a leading emerging specialty pharma company globally.

The recent trading update indicated the company could see stronger revenue growth in 2016, possibly ahead of current market expectations of c.£9m²⁰⁴. The company currently has two years' worth of cash but management does not feel pressure to raise further funds²⁰⁵. Management believes that Midatech could, if they so wish, get to profitability within its cash. However, it may choose to accelerate programmes or make additional deals which may require further funds.

KEY SUCCESS FACTORS

The company has an experienced management team. Both the CEO and the Chairman have run businesses before and have extensive M&A experience, the COO has a background in large Pharma, and the head of manufacturing worked on the scale-up of Avastin²⁰⁶. Many have previously worked successfully together. We believe that confidence in each other's abilities borne from a history of working together has meant the management team has been unafraid to grow the company through acquisition: one of the key reasons for the successful, but aggressive, M&A strategy the company has pursued to date.

Management experience with IP and manufacturing has already borne fruit. For a company, at this early stage, to have a GMP manufacturing facility up and running and available to manufacture product is unusual and more than encouraging.

But the management team has shown they also understand the need to generate revenues, albeit small levels initially, both to reassure investors and to preserve cash. Experience has meant that they have ensured too, that a number of relationships are already in place which could lead to further out-licensing opportunities.

LESSONS LEARNED

Midatech Pharma has an enviable list of long term shareholders – including Woodford Investment Management – investors who invest not just in attractive and potentially valuable technologies but also in experienced management teams. Midatech's aggressive M&A, its well thought-out strategy and its focus on oncology and orphan diseases highlights its clever use of cash which could mean that the company does not have to return to investors for more cash ahead of breakeven. Furthermore, unlike many similar early stage business, the company's revenue-generating strategy is potentially achievable, with its acquisitions in 2015 important in convincing shareholders of the strengths of the business and management team.

187 The funds it raised at IPO have been used for: c.£5.2m to fund a Phase IIa and a Phase IIb clinical trial for MidaForm in Type 1 Diabetes Mellitus, ahead of potential out-licensing; c.£3.9m to fund a pre-clinical programme for the GNP transbuccal application of GLP-1; c.£6.2m to fund the development of the oncology programmes, including pre-clinical trials in glioblastoma, liver and pancreatic cancer; c.£8.3m to fund the development of the neuroscience and sustained release technology activities including Q-Octreo, Q-Cyclosporin; and c.£6.2m for working capital purposes

188 Panmure Gordon

189 See <http://www.midatechpharma.com>. Downloaded 26/12/15

190 Farokhzad, O. & Langer, R. "Impact of Nanotechnology on Drug Delivery" ASC NANO January 2009, volume 3 issue 1 pp16-20

191 3.5 nanometre diameter according to the company. Source: www.midatechpharma.com. This is substantially smaller than the liposome based system employed by a number of competitors, and, management believes, is the smallest in clinical use.

192 "Multiple binding sites mean several therapeutics and targeting agents may be attached to a single nanoparticle" Source: www.midatechpharma.com

193 See Panmure Gordon and Edison initiation 2015

194 See Interim results presentation 2015

195 A syndrome caused by certain tumours of the midgut which can lead to flushing and diarrhoea. 196 See announcement re relationship with Centurion Pharma December 2015

197 Inflammation of the eye that can lead to cataract, glaucoma and on to vision loss.

198 A type of highly aggressive brain cancer.

199 See press release April 2015

200 See Interim results 2015 presentation

201 There are 300 cases per year with no survivors. Source: Midatech's JP Morgan 2016 presentation

202 Can be caused by a benign tumour in the pituitary gland and can cause excess growth hormone production.

203 See trading update 6/1/2016.

204 See trading update 6/1/2016.

205 Conversation with management 15/1/2016

206 Roche drug.

STATEMENT FROM PETER GRANT, CEO

At Skyepharma we are focused on applying our expertise and technologies in inhalation and oral drug development to create products which deliver real benefits to patients, help our partners to achieve their goals and, as a result, deliver value for our shareholders. We see this as a virtuous circle, enabling us to invest using our strong cash generation in the next cycle of innovation whilst also growing profitability.

Our development, regulatory and supply chain expertise has been a critical factor in the success of our asthma treatment *flutiform*[®]. The benefits of this unique combination therapy are being recognised in leading markets around the world, including the UK, Germany, Japan, South Korea and Australia.

Together, our revenues from *flutiform*[®], our milestones and share of sales from Pacira's long-acting surgical analgesic *EXPAREL*[®] and our royalties from the GSK *Ellipta*[®] respiratory range, all with key launches over the last 4 four years, mean Skyepharma enjoys one of the youngest product portfolios in our industry, giving us confidence in the potential for future growth of revenues.

With the increasing cash generated by *flutiform*[®] and our portfolio of 15 other approved products marketed by our partners around the world, we are able to invest selectively in the next phase of innovation.

In SKP-2075 and SKP-2076, we believe we have the opportunity to keep Skyepharma at the forefront of innovation in the global asthma and COPD market. SKP-2075 is a highly promising approach to an increasingly recognised and under-treated group of patients with COPD / smoking asthma. With SKP-2076, which we are partnering with our *flutiform*[®] licensee, Mundipharma, we are seeking a unique position in the new emerging field of triple combination therapies with a novel ICS/LAMA/LABA product. We also continue to build on our heritage of innovation in oral delivery by working on new ways to retain drugs for as long as possible in the upper GI tract, where many are most effective.

Successful partnerships are at the heart of the Skyepharma business model and we are proud to be one of the few remaining independent developers in the respiratory and oral fields. We apply our development expertise and technologies to partners' concepts or take new opportunities identified in-house to key inflection points before partnering them through late-stage development, spreading risk and increasing the potential for success.

Our expertise, combined with constant innovation, has given us a track record of financial growth in recent years that reinforces our optimism about the future. With a healthy balance sheet, Skyepharma is able to make carefully targeted investments to ensure the success of current products and to advance our promising pipeline to continue to drive growth into the next decade and beyond.

FACTS & FIGURES

Skyepharma exemplifies the long-term nature of many biotech stories in the UK as the company has now delivered attractive shareholder value, following a sometimes turbulent time over the last two decades.

Past challenges included delays to various regulatory approvals of key product, closure by the regulators of a partner's factory, and safety concerns leading to withdrawal of a partner's product. This in turn led to an overhang of substantial debt, which was only finally resolved when its lead product *flutiform*[®] (a formoterol-fluticasone combination for the treatment of asthma) made sufficient progress to enable the debt to be repaid in 2014. The shares hit a low in 2010 of 26.5p²⁰⁷ but, with the support of patient investors, approvals of *flutiform*[®] in Europe and Japan, repayment of its debt, a focused strategy, long-term partnerships and strong leadership from its current CEO and management team, the company was named "Turnaround of the Year" and "Best Performing Share" at the 2014 PLC awards²⁰⁸ a year when its share price shot up 235% to 335p.

Skyepharma now has an enviable array of partners, including some of the largest pharma companies in the world (such as GlaxoSmithKline and Sanofi) as well

as medium-sized and regional players (such as Mundipharma and Kyorin). Working with its partners, Skyepharma uses its proprietary inhalation and oral drug delivery technologies to develop both new products and new formulations of existing products to provide new treatment options for patients across the world. The growing financial strength (cash and equivalents at the end of 2015 was approximately £41m), has enabled the company to boost investment in R&D to generate future growth opportunities. Currently, Skyepharma is well-positioned to benefit from the expanding revenues of *flutiform*® and other products, the strength of the pipeline (highlighted in the Q4 2015 Capital Markets day) and the new technologies and products that have the potential to support further growth of the business over the next decade.

Technology/Product Focus

Skyepharma's strategy is to combine scientific expertise with a wide range of validated proprietary inhalation and oral drug-delivery technologies. It has sixteen approved revenue-generating products, nine of which have been launched since March 2012 (accounting for around two thirds of revenues). It has a promising R&D pipeline, and its current portfolio of approved products is expected to grow further. Management believe, therefore, that the company can expect further revenue growth in large and growing markets. Skyepharma focuses on two areas of technology and development – inhalation and oral.

Inhalation

Skyepharma has built its business using its knowledge of inhalation formulation, device and process technologies to develop new products for the asthma and COPD (Chronic Obstructive Pulmonary Disease) markets. Products incorporating its inhalation technologies have been approved in over 60 countries worldwide, including the US, Europe and Japan. The global asthma and COPD market is valued at c.U.S.\$29bn²⁰⁹. Skyepharma's most important product in the inhalation sector is the *flutiform*® pMDI which is approved and marketed in Europe and other leading markets (with partner Mundipharma) and in Japan (with partner Kyorin) for treating asthma. *flutiform*®

has now been launched in 30 countries, approved in a further 8 and is under review in an additional 16.

In-market sales of *flutiform*® in H1 2015 were €65.1m, +129% yoy, and the company has indicated that it has continued to perform strongly for the full year, generating a mix of milestones, royalties and product supply revenues for Skyepharma.

Skyepharma has also licensed a number of its formulation technologies to major Pharma companies, including technologies used in the GlaxoSmithKline Ellipta range of respiratory products. Skyepharma receives a low single-digit royalty from GSK capped at £9m pa, which analysts expect to be achieved in 2017.

But like all similar businesses, there have been a few setbacks. For instance, in the inhalation division, the US FDA required substantial additional work before approving *flutiform*® in the US, which has, so far, meant that this has not progressed. The European filing for paediatric asthma made by Mundipharma in January 2015 was later withdrawn, following questions from the reference member state, although Mundipharma has since indicated that it plans to resubmit the application in due course.

Strong Pipeline

The inhalation pipeline includes several novel developments for both COPD and asthma including SKP-2075 and SKP-2076 (see below), and a proven and growing relationship with Mundipharma as highlighted by Mundipharma's presentation at Skyepharma's Q4 2015 Capital Markets day. Initiatives to further drive the growth of *flutiform*® include:

- good progress on development of a breath-actuated version of the inhaler
- COPD (Europe) trial - recruitment completed in May 2015 in >1,700 patient, 52-week study
- COPD (China / Asia Pacific) trial - recruitment completed in >900 patient, 12-week study
- asthma (China) trial of an investigational new drug; a clinical study is already in preparation for the submission

- additional filings and potential launches in multiple countries

In December 2015, Skyepharma announced it had entered into a feasibility and option agreement expected to lead to Mundipharma (its partner for *flutiform*® in most of the world outside the Americas and Japan) financing the further development of Skyepharma's novel triple asthma therapy, SKP-2076 (an ICS/LABA/LAMA "triple" fixed dose combination product in a pressurised pMDI). Skyepharma is responsible for certain feasibility work, which it expects to complete in Q2 2016. Mundipharma has the option, exercisable until shortly after the end of the feasibility work, to complete the development of, and commercialise, SKP-2076, with Skyepharma providing contract development services. Mundipharma is paying a several hundred-thousand Euro non-refundable option fee. The milestones and royalties, while not disclosed, based on similar deals, could amount to several hundred-million pounds over the life of the product.

Skyepharma is also making good progress with another innovative inhalation therapy, SKP-2075, which combines fluticasone propionate and a low dose of theophylline. A phase 2 study of SKP-2075 in the treatment of patients who demonstrate aspects of COPD and smoking asthma is expected to begin during 2016. This could be one of the first therapies developed specifically for this phenotype, a significant unmet medical need.

Oral

Solid oral dosage formulations are still frequently used for new drugs²¹⁰, and novel technologies could help ensure efficient and effective delivery of the therapy to the patient. Skyepharma's oral products and technologies are now used in ten marketed products which achieved in-market sales of c.US\$3bn over the past five years, according to company estimates. Examples include GlaxoSmithKline's Paxil CR (for depression) and Requip Once a Day (for Parkinson's Disease).

Innovative Pipeline

Skyepharma is working on a number of promising new oral products and oral delivery technologies. These include:

1. **SKP-1052** (for nocturnal hypoglycaemia utilising Skyepharma's Geoclock technology) currently in

phase I. The company is seeking partners to fund further development.

2. **Soctec** (Self-Orienting Capsule technology) designed to retain the drug in the upper GI tract for as long as possible and maximise the potential absorption window. Soctec has a large buoyancy chamber so that the capsule floats upright in the stomach. It uses standard capsules and coating technology. It has the additional virtue of being degradable to support safe emptying of the stomach. The research data on this technology so far has been positive. Additional work is being undertaken to optimise Soctec (gastro-retentive oral drug delivery platform). The next trials are expected to start this year (2016).
3. **Hydrophobic raft technology** for high daily dose needs. This is still at an early stage of development. The technology will also focus on drugs absorbed in the upper segments of the GI tract and on those drugs requiring high therapeutic doses that are not compatible with conventional technologies. Skyepharma is expected to have clinical trial material manufactured with the in vivo proof-of-concept trial planned for H1 2016.

R&D & Pipeline

Skyepharma's R&D strategy is to make measured investment (up to 10-15% of sales annually) in developing new products and technologies through a mix of self-funded development projects, collaborations with partners and targeted in-licensing and acquisitions. The aim is to create a development pipeline with a balanced portfolio of own and partner-funded work while maintaining profitability.

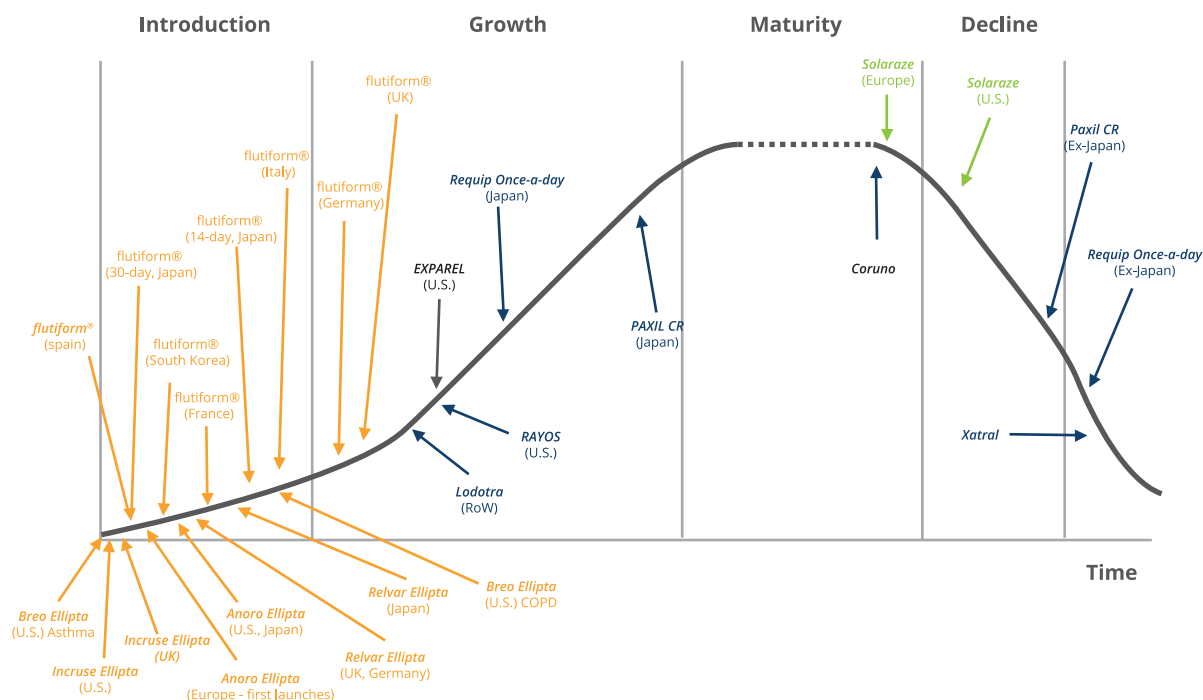
As an example, management believe that a self-funded inhalation project could cost £10-20m, and take several years to reach Phase II proof of concept before partnering. Early partnering, such as the recent Mundipharma for SKP-2076, mitigates risk and preserves cash.

Meanwhile, self-funded oral projects could cost £1-2m, and are mainly focussed on developing Skyepharma's technologies to proof of concept with a view to out-licensing at that point for use in partner-funded developments. Skyepharma could also consider spending a bit more, say £3-5m, to demonstrate the effectiveness of its new oral technologies.

Critical to the company's performance is the long-

term nature of its revenue contributors, and that its pipeline is large enough to replace existing revenues in the future. The curve diagram below shows that this is the case with Skyepharma's more recently approved products replacing declining revenues from its mature portfolios.

FIGURE 26: SKYEPHARMA PORTFOLIO



Source: Skyepharma

Patents and other protections

Skyepharma has a strong patent portfolio built around its inhalation and oral technologies, and is steadily building up new IP around its portfolio of innovative new products and technologies. Additional protections often arise from novel devices, patents around the concept or delivery profile, periods of regulatory marketing exclusivity (10 to 11 years in Europe) and the difficulty of matching product profiles sufficiently

to obtain approval for a generic version.

Management Team

Skyepharma has a highly experienced, long-standing management team, many of whom have been involved with the company for the last decade and have steered it through various challenges to achieve its current success.

FIGURE 27: SKYEPHARMA'S BOARD OF DIRECTORS AND LEADERSHIP TEAM

Name	Role	Biography
Frank Condella	Non-executive Chairman	Frank Condella became Non-Executive Chairman on January 2010, having originally joined as CEO in March 2006. He stepped down as CEO September 2008, becoming a non-executive in November 2008. Prior to that he had over 30 years' experience in the pharmaceutical industry.
Peter Grant	Chief Executive Officer	Peter Grant became CEO on January 2012, having joined as CFO in November 2006. Previously he was an interim CEO of Voice Commerce Group, FD at Eurodis Electron PLC, CFO at WorldPay plc and CEO of Molins plc. He is NED of Abzena plc.

Andrew Derodra	Chief Financial Officer	Andrew Derodra joined as CFO in November 2013. Prior to that he had over two decades working in senior finance and strategic roles within five FTSE100 groups, including Tate & Lyle, SABMiller and Diageo.
Dr Thomas Werner	Non-Executive Director and Chairman of the Remuneration Committee	Thomas Werner joined in May 2009. He is Chairman of the Remuneration Committee and is a member of the Audit and Nomination & Governance Committees. He has over 30 years of experience in the pharmaceutical industry, previously as a Senior VP of GlaxoSmithKline. He is Chairman of the investor advisory committee of Seventure (France) Health for Life capital investment fund and was on the board of trustees of the Paul Ehrlich Foundation and the Robert Koch Foundation.
John Biles	Non-Executive Director and Chairman of the Audit Committee	John Biles was appointed in March 2014. He is Chairman of the Audit Committee and a member of the Nomination & Governance and Remuneration Committees. He is Chairman of the Audit Committee and Senior Independent Director of Sutton and East Surrey Water PLC. He has numerous years' experience on Boards and in finance executive roles.

Source: Skyepharma

FINANCIAL RESOURCES

Current performance

H1 2015 (last published results) saw revenues increase 19% to £40.8m (vs. H1 2014 of £34.4m), mainly due to the good performance of *flutiform*® royalties and product supply revenues. Operating profit was £12.5m (vs £13.2m in H1 2014 which included £7.5m of non-recurring milestones) and net cash at the period end was £20.9m. Skyepharma's 2015 pre-close trading update indicated that overall revenues for 2015 were likely to be ahead of expectations, mainly due to a (non-cash) €10m milestone from Mundipharma. At 31 December 2015, Skyepharma had net cash of c.£35m (up c.£20m in the year). Partners' sales performed well and *flutiform*® saw robust growth during the year. Management "remain confident in the future prospects for the Group"²¹¹.

Market Expectations for Financial Performance

Following the 2015 pre-close trading update, a number of analysts upgraded revenue expectations mainly due to the good performance of *flutiform*®. News flow is expected to be strong over the next few years including:

- The potential approval of breath-actuated inhaler in Europe, the completion of the COPD trial in Europe and China/AsiaPac, the commencement of the Chinese asthma trial and commercialisation in Latin America for *flutiform*®.
- Additional partnering for the rest of the pipeline.
- A further US\$8m milestone for *Exparel*®

(bupivacaine liposome injectable suspension for postsurgical analgesia) is anticipated in 2016 if *Exparel*®, marketed by Pacira, achieves \$250 million of sales on an annual basis. In addition, Pacira expects to make progress in oral surgery (already approved), and the development of indications for nerve block and chronic pain. These initiatives should further support growth in revenues, with Skyepharma eligible for 3% of net sales plus up to \$36m additional milestones.

- Analysts²¹² expect that, subject to the expected satisfactory progress on the feasibility work on SKP-2076, Mundipharma is likely to exercise its option. In this instance it is possible that revenues for SKP-2076 may ultimately exceed those from *flutiform*®.

The M&A strategy

M&A is expected to be a key plank of Skyepharma's strategy: it is looking to identify opportunities across both its technology areas – oral and inhalation. Larger acquisitions would ideally be earnings-enhancing in less than two years, and easy to integrate with the current business. Smaller, bolt-on acquisitions need to have a value inflection point in 3-5 years, be differentiated for competitors and with long IP, be well-positioned for further royalty-based growth, build on current expertise in the business and have global potential.

In H1 2015, a £25m five-year unsecured multi-currency Revolving Credit Facility, with an accordion option to extend the facility up to £35m during the term of the loan, was signed. This will provide funding flexibility.

The cost of borrowing is 1.3% above the relevant LIBOR/EURIBOR rate. There are currently no plans to draw down on the facility, though the company continues to seek opportunities to acquire value-creating products and technologies.

KEY SUCCESS FACTORS

Delays to various product approvals and the Group's substantial indebtedness meant that Skyepharma's shares underperformed for a number of years. On 20 April 2014, Skyepharma successfully completed a capital raise and bond repayment, saving £25m in future bond repayments and at the same time enlarging its shareholder base, leading to a significant rerating of the stock. Skyepharma is a good example of a company that has successfully reorganised its capital structure to take into account its pipeline, product portfolio and revised strategy. Critical to the business has been the support of shareholders, and of advisors and analysts who helped manage the investment community's understanding of the company's product portfolio and debt.

LESSONS LEARNED

The new management has refocused Skyepharma's strategy over the past decade and in so doing has turned the company around. In 2006, the current Chairman, Frank Condella, joined the business as CEO and Peter Grant (CEO from 2012) joined the business as the CFO. Peter Grant's turnaround skills, honed in highly competitive engineering and electronic industries, were instrumental in managing the group's finances and debt and buying sufficient time for key product approvals and growth drivers to be achieved. A key lesson, therefore, has been to ensure that the appropriate skills are brought in to suit the circumstances of the business.

As the ingredients for success emerged, it was important to ensure that this was communicated to the investment community, and Skyepharma has been very successful in achieving this. The second key lesson from Skyepharma is, therefore, to carefully select advisors and implement effective investor and media relations strategies to enable a complex business to become investable by generalist investors.

207 20 June 2010

208 See press release 20th March 2015.

209 Skyepharma capital markets presentation of 26 November 2015

210 Represent 46% of new molecular entities approved by the FDA in 2014; 63% in 2013 – 8 of the top 20 selling prescription drugs worldwide in 2013; 55% of the top 20 prescription drugs by value (\$48.04bn). Source: Skyepharma

211 Skyepharma trading update 11 Jan 2016

212 For instance, see Stifel note 23rd December

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REPORT ENDORSERS



Abzena provides proprietary technologies and complementary services in the UK and US to enable the development and manufacture of biopharmaceutical products. The development of biopharmaceuticals is a growing area and requires specialist technology and expertise.

The Group comprises Antitope, PacificGMP and PolyTherics, which between them have built a global customer base including the majority of the top 20 biopharmaceutical companies as well as large and small biotech companies and academic groups.



It has an 80 year history developing manufacturing and selling allergy vaccines for the treatment of allergic rhinitis. It has treated approximately 225,000 patients in Europe. It was the first to use an adjuvant, reducing the number of injections, and does not use aluminium in its vaccines. Its market is predominately in Europe with Germany being its largest, selling 98% overseas. Revenue has grown to £43.2 million employing a total of 420 people. It is currently undertaking clinical trials in the US with Pollinex Quattro and is also in the early stages of development with a number of new concepts.



Alliance is a publicly owned international pharmaceutical company listed on AIM, part of the London Stock Exchange. We started trading in 1998 and have grown strongly to an annual turnover of over £43 million.

Our expertise lies in the acquisition and licensing of pharmaceutical and healthcare products and delivering these to patients. We look carefully for certain criteria in these products and select for a blend of underlying sales stability and growth potential.

Our International footprint is well established, with offices in China, Germany and France and with the recent announcement of our proposed acquisition we will have a major presence in Italy.



Astex is a leader in innovative drug discovery and development, committed to the fight against cancer and diseases of the central nervous system. Astex is developing a proprietary pipeline of novel therapies and has a number of partnered products being developed under collaborations with leading pharmaceutical companies. In October 2013 Astex became a wholly owned subsidiary of Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan. The Otsuka Group employs approximately 43,000 people globally, and its products are available in more than 80 countries worldwide.



The BioIndustry Association (BIA) is the trade association for innovative enterprises involved in UK bioscience. Members include emerging and more established bioscience companies; pharmaceutical companies; academic, research and philanthropic organisations; and service providers to the bioscience sector. The BIA represents the interests of its members to a broad section of stakeholders, from government and regulators to patient groups and media. Our goal is to secure the UK's position as a global hub and best location for innovative research and commercialisation, enabling our world-leading research base to deliver healthcare solutions that make a real difference to people's lives.



BTG is a growing international specialist healthcare company bringing to market innovative products in specialist areas of medicine to better serve doctors and their patients. We have a portfolio of Interventional Medicine products to advance the treatment of liver tumours, advanced emphysema, severe blood clots and varicose veins, and Specialty Pharmaceuticals that help patients overexposed to certain medications or toxins. Inspired by patient and physician needs, BTG is investing to expand its portfolio to address some of today's most complex healthcare challenges.



C4X Discovery (C4XD) is an AIM listed drug discovery company that uses its proprietary NMR-based technology to measure the dynamic 3D shapes of bioactive ligand molecules. This unique and versatile technology provides high-quality blueprints for rational small molecule drug discovery and design and crucial information for subsequent drug candidate optimisation. C4XD discovery has used this innovative approach to produce a high value drug discovery pipeline containing potential new small molecule therapies for Inflammatory diseases, Diabetes and Addictive disorders. C4XD's lead program is an oral orexin-1 antagonist for the treatment of nicotine addiction and is in pre-clinical development. C4XD also has a number of collaborative partners including AstraZeneca, Evotec, Takeda and the Structural Genomics Consortium.



Global specialty pharmaceuticals and services business, supplying clinical trial, licensed and unlicensed critical, lifesaving drugs.

Four distinct operating businesses which benefit from important synergies between them:

- Clinigen CTS – Global leader in the specialist supply and management of quality-assured medicines for patients in clinical trials
- Idis MA – Global leader in ethical worldwide access to the most promising innovative early stage medicines on behalf of pharma and biotech companies to meet an unmet patient need
- Idis GA – Ethical Supply of unlicensed or short supply medicines to patients via their physicians
- Clinigen SP – SP acquires the rights to and then revitalises essential niche hospital only medicines and has a portfolio of oncology support and infectious disease medicines



Evgen Pharma is a clinical stage drug development company focused on cancer and neurological disease. Our pipeline is based on our proprietary *Sulforadex*[®] technology, and includes a number of synthetic, stabilised analogues of the naturally occurring compound sulforaphane. Many peer-reviewed scientific papers have identified the medical potential of sulforaphane in multiple indications. Our objective is to use our *Sulforadex*[®] technology to turn this scientific promise into commercially successful products, addressing important clinical needs.



More than any other technology, biotechnology has the potential to alter our lives in a positive way. And by achieving this potential, today's biotech companies are delivering new levels of health, prosperity and sustainability — across the world.

But with uncertain capital markets, increasing regulation, growing pricing pressures, competition for acquisitions and an evolving health care environment around the world, this sector faces unprecedented challenges. We have been a pioneering presence in the biotechnology industry.

We were the first professional services firm to build a practice dedicated to serving your industry.



F-star designs and develops bispecific antibody products to improve the treatment of cancer and inflammatory diseases. F-star is the only biopharmaceutical company creating bispecific antibodies by modifying the constant region of an antibody. Our Modular Antibody Technology offers unprecedented ease in the development and manufacturing of genuine bispecific antibody products.



Genomics plc develops and applies sophisticated statistical tools to a unique, integrated platform of genomic and associated phenotypic data, in order to learn about human biology in humans. It applies this approach in clinical genomics through the provision of tools that can be used across healthcare systems, and in drug development, where genetic analysis of targets and biological pathways can materially de-risk development programmes. The company, based in Oxford and founded in 2014 by world-leading academics at the Wellcome Trust for Human Genetics, has four collaborations with major pharmaceutical companies, including Biogen and Eisai, and is a Genomics England Platform Partner.



Founded in 1998, GW is a biopharmaceutical company focused on discovering, developing and commercializing novel therapeutics from its proprietary cannabinoid product platform in a broad range of disease areas. GW commercialized the world's first plant-derived cannabinoid prescription drug, *Sativex*[®], which is approved for the treatment of spasticity due to multiple sclerosis in 28 countries outside the United States. GW is advancing an orphan drug program in the field of childhood epilepsy with a focus on *Epidiolex*[®], which is in Phase 3 clinical development for the treatment of Dravet syndrome and Lennox-Gastaut syndrome and which is also expected to enter Phase 3 clinical trials in the treatment of Tuberous Sclerosis Complex. GW has a deep pipeline of additional cannabinoid product candidates.



Horizon Discovery is a UK Biotechnology company that combines deep scientific experience in translational research with a precision gene-editing platform incorporating rAAV, CRISPR and ZFN technologies. The company provides custom cell line and in vivo model generation services for research and bioproduction applications, molecular reference standards, in vivo disease models, and contract research and screening services to over 1,000 organisations engaged in research; drug discovery and development; clinical diagnostics; and biopharmaceutical process optimization. Horizon aspires to provide science-driven research solutions that lead to better understanding of the genetic basis of disease and better outcomes for patients, from sequence to treatment.



hVIVO is a life sciences company pioneering a technology platform of human disease models to accelerate drug discovery and development in respiratory and infectious diseases.

Through its illumination of the entire disease life cycle from healthy to sick and back to health, the hVIVO platform captures disease in motion and promotes rational selection of drug targets and biomarkers in respiratory and infectious diseases, such as flu and colds. It brings together a revolutionary set of capabilities in product validation testing and the mining of biological insights, in order to tackle the long timeline, significant costs and high risks to market facing drug development and diagnostic organisations today.

IMMUNOCORE targeting T cell receptors

Immunocore is a world leading biotech company focused on the development of a new class of biologic drugs with its proprietary novel T Cell Receptor (TCR)-based technology for immunotherapies. Its lead programme, IMCgp100 is in clinical development in melanoma. Company is primarily focused on oncology – but its technology is also applicable in viral and autoimmune diseases. Immunocore is the first company to enable the engineering of TCRs as therapeutics, targeting a class of antigens (HLA-peptide antigens) on cells which cannot be targeted with antibodies.

Current investors are well-renowned, leading international institutions including Woodford Investment Management, Malin Corporation, Lilly, RTW Investments, Fidelity Management & Research Company as well as other private shareholders.



ImmuPharma plc is one of the leading specialist drug development companies in Europe and is listed on AIM in London (LSE:IMM, LN:IMM) since 2006. ImmuPharma was founded and is led by a commercially focused Board and management team with extensive experience. ImmuPharma is focusing on developing novel medicines with high sales potential in specialist markets with serious unmet need. ImmuPharma has a number of drug candidates in development, two platform technologies and over 70 patents. The company's most advanced drug candidate for Lupus and other potential autoimmune diseases is in phase III with a Special Protocol Assessment and "Fast Track" designation from the US FDA.



London
Stock Exchange

London Stock Exchange is the world's most international exchange. Nearly 2,500 companies from more than 115 countries are quoted across its markets.

London Stock Exchange's markets include the Main Market – London's flagship venue for equity, debt and exchange traded products, offering businesses access to Europe's most liquid pool of capital – and AIM – the world's leading market for small and growing companies. Since its launch in 1995 AIM has helped 3,500 companies raise more than £90 billion.



Midatech is a nanomedicine company focused on the development and commercialisation of multiple, high-value, targeted therapies for major diseases with unmet medical need.

Midatech is advancing a pipeline of novel clinical and pre-clinical product candidates based on its proprietary drug conjugate and sustained release delivery platforms with a clear focus on the key therapeutic areas of diabetes, cancer and neuroscience/ophthalmology. Midatech's strategy is to develop its products in-house in rare cancers and with partners in other indications, and to accelerate growth of its business through strategic acquisition of complementary products and technologies.



MISSION Therapeutics was founded in 2011 to commercialise expert research into the ubiquitin pathway for the treatment of cancers and other diseases of unmet need. It has built a World-leading platform for the discovery and development of first-in-class, small molecule drugs that target deubiquitylating enzymes (DUBs) – an emerging, and hitherto intractable, drug class that is attracting significant commercial interest as the potential 'Next Kinase Area'. The Company has received ~\$40M in venture capital from a syndicate comprising institutional (Sofinnova Partners, Imperial Innovations) and corporate (SR One, Roche Venture Fund and Pfizer) investors, and is based at the Babraham Research Campus.



Oxford BioMedica is a pioneer of gene and cell therapy, with a leading industry position in lentiviral vector and cell therapy research, development and manufacture. Our pipeline of gene and cell therapy products addresses diseases for which there is currently no treatment or that are inadequately treated today, including ocular and central nervous system disorders. Our product candidates have the potential to transform treatment landscapes. The Group's strategy is to develop our product candidates to their next value inflection points whilst continuing to build OXB Solutions into a valuable revenue-generating manufacturing and development services business.



PhoreMost has developed a next-generation phenotypic drug discovery technology called *SITSEEKER*[®], which uses the power of live-cells to discern the best new targets for future therapy and crucially, how to drug them. Based on 'Protein Interference' (*PROTEINI*[®]); a new genome-wide target identification & validation platform created by PhoreMost, *SITSEEKER*[®] can now systematically reveal critical druggable target-sites in any particular disease setting and convert this information rapidly into novel small-molecule therapeutics.



PsiOxus Therapeutics Ltd develops novel therapeutics for serious diseases with a particular focus upon cancer.

We are an Oxford based development stage biotechnology company with world leading scientists and a highly experienced management team.

Our approach is to produce novel patent protected therapeutics based on our platform of tumour-targeted delivery with the oncolytic vaccine, enadenotucirev.

Redx Pharma

Redx Pharma is a drug discovery and development company with a pipeline of proprietary drug candidates targeting significant unmet medical needs in commercially hot areas of infection, immunology and oncology. Redx's focus on improving existing drugs to create best-in-class new drugs provides opportunities to crystallise value through industry partnerships, with Redx also able to retain a greater economic interest in selected development programs. Redx's work has already been endorsed by partnerships with global pharmaceutical companies, including AstraZeneca, and the NHS. Formed in 2010, Redx was successfully admitted to AIM (LSE) in March 2015.



Sareum is a drug discovery and development company delivering targeted small molecule therapeutics, focusing on cancer and autoimmune disease, for licensing to pharmaceutical and biotechnology companies at the pre-clinical or early clinical trials stage.

Sareum operates an outsourced research model, working with a world-wide network of collaborators and research providers. Its development pipeline includes two programmes undergoing preclinical IND-enabling studies.

Sareum Holdings plc is listed on the AIM market of the London Stock Exchange, trading under the symbol SAR.



Scancell is developing novel immunotherapies for the treatment of cancer based on its *ImmunoBody*® and *Moditope*® technology platforms.

Scancell's first *ImmunoBody*®, SCIB1 is being developed for the treatment of melanoma and is being evaluated in a Phase 1/2 clinical trial. SCIB1, when used as monotherapy, has a marked effect on tumour load, produces a melanoma-specific immune response and highly encouraging survival trend without serious side effects. In patients with resected disease there is increasing evidence to suggest that SCIB1 may delay or prevent disease recurrence.

Combining SCIB1 and checkpoint inhibition produces enhanced tumour destruction and significantly longer survival times in pre-clinical studies than when either treatment was used alone.



Skyepharma combines proven scientific expertise with validated proprietary drug delivery technologies to develop innovative inhalation and oral pharmaceutical products. The Group is eligible for revenues from 16 approved products in the areas of inhalation, oral, topical and injectable drug delivery, as well as generating income from the development of further products and technology licenses. The products developed by the Group are marketed throughout the world by leading pharmaceutical companies. More than 50% of revenues are derived from products launched since March 2012, including *flutiform*®, Pacira's *EXPAREL*® and the *GSK Ellipta*® range of products. The Group is investing in developing novel products and technologies to deliver additional growth. Skyepharma is listed on the London Stock Exchange (SKP). Its research and development is based in Muttenz, Switzerland.



Sphere Medical is a medical device company specialising in the development and commercialisation of a range of innovative medical monitoring and diagnostic equipment designed to significantly improve patient care whilst providing efficiencies that result in reduced healthcare costs.

The Company's strategy is focused on developing the Proxima (CE-marked device) platform for measuring blood gases, electrolytes and metabolites at the patient's bedside. Proxima is marketed directly to the critical care market with a dedicated field sales force in the UK, Germany, the Netherlands and Belgium. The Company also proposes to work with partners for the worldwide distribution of Proxima.



Verona Pharma plc is a UK-based clinical stage biopharmaceutical company focused on the development of innovative prescription medicines to treat respiratory diseases with significant unmet medical needs, such as COPD, asthma and cystic fibrosis.

Verona Pharma's lead drug, RPL554, is a first-in-class drug currently in Phase II trials as a nebulised treatment for acute exacerbations of COPD in the hospital setting. Verona Pharma is also building a broader franchise around RPL554 to maximise its value, both to patients and to investors. This includes the very significant markets for COPD and asthma maintenance therapy.



Woodford is the opportunity for Neil Woodford, one of the UK's most highly regarded fund managers, to distil 30 years of experience and learning into a business founded on his own principles.

Too often, investors face noise and complexity in an industry focused on relative returns and short-term pressures. Our approach is different - all of our attention is on providing a positive long-term return for our clients. We only invest when there is a compelling long-term opportunity and we believe in engaging with the companies we invest in to help them fulfill their potential and deliver shareholder value.

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