

# **Submission to the House of Lords Science and Technology Committee**

**Inquiry:** Life Science and the Industrial Strategy

**Call for evidence:** Paper for consideration by the House of Lords Science and Technology Committee

**Submitted by:** Hedley Rees, Managing Consultant, PharmaFlow Ltd., UK

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CURRICULUM VITAE– HEDLEY REES, MANAGING CONSULTANT, PHARMAFLOW LTD

## **1.0 ABSTRACT**

- 1.1 *“The inquiry is an opportunity to learn from the successes and failures of the Government’s 2011 Life Sciences Strategy, in order to properly inform its new strategy.*
- 1.2 This paper is a submission of facts, evidence and expert analysis on the pharmaceutical and biotech industries, as key components of the life science ecosystem. This is in support of the Committee’s stated aim, outlined in italics above.
- 1.3 The paper recounts the industry chronology, from the early days of penicillin, up to present day. From that, a careful and measured analysis is carried out, supported by appropriate references. It explains the reasons for the following Industry issues:
  - 1.3.1 Weak engagement with NHS and healthcare professionals (HCPs)
  - 1.3.2 Low R&D productivity
  - 1.3.3 ‘Patent cliff’ issues
  - 1.3.4 The unacceptably high price of drugs
  - 1.3.5 Dismal failures rates in clinical and non-clinical development
- 1.4 The paper then advocates a revolutionary new approach to product development and commercialisation in life sciences. This is based on replacing the current three stage model with a two stage model which places patients and healthcare professionals at the core. This has the potential to brand the UK as ‘THE Global Powerhouse in Life Sciences.’<sup>i</sup>

## **2.0 BACKGROUND AND INTRODUCTION**

- 2.1 The US National Institutes of Health (NIH) invests nearly \$33 billion annually in medical research for the American people. As the annual rate of increase has flattened off in recent years, Asian countries have taken up the mantle and powered ahead with massive investment. If success is all about funding, what hope does the UK have of becoming a world force in life sciences?
- 2.2 This paper asserts that the future of life sciences is NOT in increased funding, more and better science, health economic outcomes research (HEOR) or any of the solutions presented by the industry today. The secret of success lay in moving to a new paradigm for developing products, as the reigning paradigm is broken, irreparably. Most enlightened commentators on the industry recognise this. Until now, however, there has been no obvious alternative.
- 2.3 The evidence of a 'broken system' first surfaced from the US Government Accountability Office in 2006, in a damning report titled "NEW DRUG DEVELOPMENT: Science, Business, Regulatory, and Intellectual Property Issues Cited as Hampering Drug Development Efforts". The report indicates that 'Only one in 250 development programs succeed'. This is a huge cost to society, in terms of \$Bns wasted, fruitless testing in animals and patients hopes dashed.<sup>ii</sup>
- To identify those 250 molecular candidates, the report states that 10,000 must be researched, screened and patented. Again, this is a shocking attrition statistic.
- 2.4 In 2012, Joseph A. DiMasi, PhD, of Tuft's University, reported failure rates in clinical trials had worsened. As a practical example, over the last 15 or so years, nearly thirty drugs have failed in late-stage clinical trials for Alzheimer's.<sup>iii</sup>
- 2.5 The following analysis of facts and evidence begins with an industry chronology below.

## **3.0 INDUSTRY CHRONOLOGY**

1928 - Alexander Fleming discovers mould in agar plate, but unable to identify active ingredient.

1939 - Howard Florey et al, at Oxford University, purify enough penicillin to run pre-clinical studies.

1941 – Florey et al run clinical studies, but fail to make penicillin in any quantity.

1945 - Andrew J Moyer, working at US Dept. of Agriculture, devised the process to make penicillin in sufficient quantity to meet the needs of World War II.

1948 - Moyer awarded patent for penicillin production process.<sup>iv</sup>

1976 – 1<sup>st</sup> blockbuster (≥ \$1 Bn annual sales), Tagamet, launched by Smith Kline & French (SK&F).

1981 – Glaxo launch competitor product, Zantac

1982 (to date) – Pharma strategy to focus on discovery research and sales & marketing

1985 (to date) – Pharma strategy to outsource facilities, people and drug development

1987 – Glaxo’s Zantac becomes biggest-selling prescription drug, outstripping Tagamet 3:1

1994 (May 17<sup>th</sup>) – Tagamet patent expires.<sup>v</sup>

2006 – US Government Accountability Office (US GAO) issues damning report on failure rates.

2012 – Joseph A. DiMasi, PhD, of Tuft’s University, reports failure rates in clinical trials worsened

2013 – Oxford BioMedica (OXB) Wins Significant Funding via a Competitive Award from UK Government’s Advanced Manufacturing Supply Chain Initiative.<sup>vi</sup>

2014 - EU marketing authorisation for Glybera (gene therapy), at \$1M per treatment, not renewed.<sup>vii</sup>

2017 (Aug 28) - Gilead Sciences to Acquire Kite Pharma for \$11.9 Billion<sup>viii</sup>

2017 (Aug. 30) – US Food and Drug Administration (FDA) approve 1<sup>st</sup> gene therapy product, Novartis’ Kymriah—\$475,000 per single treatment. (OXB supply viral vector)<sup>ix</sup>

## **4.0 ANALYSIS**

### **4.1 The Myth of Penicillin**

4.1.1 It is a widely held belief, both inside and outside the industry, that the mother of all antibiotics was discovered by ‘accident’, in 1928, by Alexander Fleming. Not commonly known is that this is a complete myth. What Fleming actually discovered was a mould in one of his agar plates where bacteria had not grown.

4.1.2 However, Fleming did not have the wherewithal to properly identify the mould strain, or make it. It took a team at Oxford University, headed by a gentleman named Howard Florey, to purify enough penicillin to run pre-clinical (1939) and clinical (1941) studies. They were a great success, but they didn’t know how to make sufficient quantities for wider patient use.

4.1.3 In 1941, Florey and a fungal expert, Norman Heatley, visited the US and the scenario was put to a microbiologist named Andrew J Moyer, an expert in moulds, working at USDA’s Northern Regional Research Laboratory in Peoria, Illinois. He and his team

came up with the idea “to culture the penicillin in a mixture of corn steep liquor and lactose, thereby greatly increasing the yields and production rate.”

4.1.4 Moyer applied for a patent in May 1945, which was awarded three years later. He was inducted into the National Inventors Hall of Fame in 1987. The detail and explanation of how the myth persisted can be found in the endnote.<sup>x</sup>

4.1.5 The morale of this story is that the development of a highly differentiated drug is the result of intense collaboration between ALL key stakeholders in the life cycle of a prescription medicine. This includes competent authorities and governments.

## 4.2 Competing stomach ulcer drugs herald the ‘blockbuster era’

4.2.1 The chronology leads on to the battle of the stomach ulcer drugs, Tagamet and Zantac. These two products were phenomenally successful in financial terms, being the first ‘blockbusters’, turning over many \$Bns during their in-patent life.

4.2.2 Tagamet was first to market, having taken 12 years to develop. Zantac came to market some five years later, reportedly having ‘cleaned up’ the Tagamet production process. With a cleaner process, the side effects were marginally less troublesome to patients. Glaxo targeted this ‘weakness’ with stunning impact on sales. Further detail can be found in the endnote<sup>xi</sup>

4.2.3 This became the model for a new strategy in Pharma; that of patenting thousands of molecules in the hope that sales & marketing expertise would ‘do the job’ for those few that made it to market.

## 4.3 The new strategy for Pharma and Biotech

From mid-1980s onwards, as part of this new strategy, Pharma implemented three significant strategy options:

4.3.1 Focus almost exclusively on discovery research and sales & marketing

4.3.2 Outsource what were deemed ‘non-core’ activities, including drug development, analytical methods, manufacture and product distribution.

4.3.3 Outsource drug development to more nimble ‘biotech’s’

4.4 In summary conclusion, these were massive errors of judgement and have left pharma and biotech companies without the necessary skills or facilities to develop new, differentiated products. The patent cliff was the inevitable result.

4.5 The remaining issues listed in 1.3 above have also been caused by this failed strategy. For example, NHS and its healthcare professionals are excluded from R&D,

with their deep knowledge of a therapeutic area being ignored, until it is all too late to change the *fait accompli* arriving at the hospital gate.

- 4.6 In terms of the patent cliff, where it has become increasingly difficult to bring blockbusters to market, the industry is faced with a conundrum. How does it maintain the financial returns investors have come to expect? In response, it has begun to focus on rare diseases and what are classified as ‘orphan indications’. Both offer less challenging regulatory pathways and crucially, less price sensitivity, at least in theory.

Unfortunately, drugs for such small patient populations must be priced highly for the ‘blockbuster equation’ to work. As an example, the chronology in 3.0 above shows Glybera, a gene therapy drug, being priced at £1,000,000 per patient treatment. Not surprisingly, it did not sell and was withdrawn from the market.

- 4.7 Whilst the Glybera price tag proved too much for the EU healthcare system to bear, the high price strategy still persists, especially in the advanced therapy domain. Advanced therapies (gene & cell) have become the next target for Big Pharma companies. The power of these therapies is that they offer cures rather than disease modification, and as such have tremendous potential.

Following the launch of Novartis’ Kymriah last August, a myriad of Pharma companies have entered the arena and have made major investments. For example, Gilead paid £12Bn for Kite Pharma, a small company with expertise in gene therapy, just a few days before Kymriah launched. The departing CEO of Kite received \$610M in compensation.<sup>xii</sup>

However, these therapies require an order of magnitude greater degree of skill and resource to bring to market successfully; and evidence suggests that Pharma and Biotech companies do not have the necessary translational skills (eg operations, strategic procurement, engineering, supply chain management and information systems) in abundance.

- 4.8 How could this situation be reversed?
- 4.8.1 It should be clear from the foregoing, at the root of all this is pursuit of the monopoly or oligopoly position afforded by the award of a patent for a molecular structure. It has turned the industry blind to the fundamental principles of sound product development methodologies. The evidence is clear, if 9,999 out of every 10,000 molecules fail something is amiss with the prevailing model.
- 4.8.2 Since the days of penicillin, technologies to predict the potential for molecules to be converted into a working drug have moved on unrecognisably, but pharma and biotech have not. Why not? Because there is no incentive to change, as the current system delivers the goods for their investors.
- 4.8.3 Ironically, if we look back to where this all started, with Tagamet and Zantac, it was not the molecule that was patented, it was the processes to produce them. The same with penicillin; and of course, the polio vaccine was never patented!

4.8.4 This analysis therefore reveals that global life science has gone backwards over the last 50 or so years. The UK is no better or worse off than any other developed nation when it comes to life sciences. All are deeply troubled by the outcomes of the incumbent process for developing prescription medicines.

4.8.5 The way to reverse this is to adopt a product development process employed by almost every other industry sector, that of two broad stages:

- Design of prototypes
- Commercial manufacture and supply

The prototype stage would be characterised as follows:

- Identification of the key stakeholders (eg NHS, manufacturers, service providers, regulators, HEOR, process designers etc)
- Deep engagement with UK NHS healthcare professionals (HCPs) and patients, on specific disease indications
- Screen prospective compounds using state-of-the-art in silico, in vitro and ex vivo methods.
- Define prototype supply-chain(s) that are simple, effective and robust.
- Select prototype development candidates for 'pressure-testing' as commercial propositions.

4.8.6 There would clearly need to be extensive consultation with key stakeholders in the industry as to the feasibility of this approach, but not embark on an assessment of an alternative life sciences path could risk missing major opportunities for the UK.

## 5.0 **WHAT SHOULD UK LIFE SCIENCE STRATEGY LOOK LIKE?**

5.1 Firstly, UK policy makers should refer to the development of penicillin and Tagamet, both of which were exemplars of collaboration and innovation in life sciences product development. Penicillin we have discussed above, and as for Tagamet, the American Chemistry Society (ACS) commented on the development effort thus:

“[this] is a story of single-minded commitment by a group of creative scientists working in close collaboration in the United Kingdom. The process of research and development for economical production of the resulting drug, cimetidine [Tagamet], was the work of equally creative scientists working in the United States.”

The head of the cimetidine programme, Sir James Black, later received the Nobel Prize for his drug research. Sir David Jack, who was responsible for Glaxo's development effort in bringing Zantac to market in only 5 years, was quoted as saying:

“the development of Zantac had not been in the same order of inspired breakthrough as the research which produced Tagamet... It's not necessary to shake the earth on

its axis to make money in this industry. We simply improved on James Black's product by choosing a substance with a cleaner reaction."

5.2.1 Policy makers should then seek to create a UK environment whereby companies engaged with a new model for product development could flourish. This could be achieved by (non-exhaustive list, for illustration purposes):

- Facilitating a deep dialogue between NHS and large pharmaceutical companies (Big Pharma), on the impact of moving from a 'patent focus' to a 'patient focus'. This would include the trade organisations ABPI, BIA etc and NHS healthcare professionals. The question would be "How to engage healthcare professionals (not just study investigators) in the drug development process, at inception. This will firmly place those developing and selling prescription medicines alongside those using them. It should not include other stakeholders, such as regulators or government agencies, so that the dialogue remains 'on point'. This is de rigueur in almost every other sector.
- Incentivising investment in prototyping technologies in the UK, especially those that reduce animal testing to an absolute minimum. These are termed *in silico* (computer simulation), *in vitro* (test tube), and *ex vivo* (tissue).
- Drawing the focus of university spin-outs and small drug developers (biotech) towards the prototyping stage, where so much of the benefit exists. Small, or even medium sized companies, do not have the critical mass to carryout the vital foundational work required for successful commercialisation of a drug.
- Encouraging Big Pharma companies based in the UK, to recognise the crucial importance of this early, foundational work in the lifecycle of a prescription drug. Incentivise them to make both financial and 'people resource' commitments to these smaller companies.
- Building on MHRA's Innovation Office, which is highly novel in concept. Since being established, effective 'less formal' communication routes with key stakeholders have been put in place. This would provide an ideal platform for MHRA to evaluate, for example, 'predictive technologies' that could be exploited by UK plc drug developers.
- Encouraging universities and colleges to re-balance their life science curricula so that far greater coverage is given to engineering and applied technology. Science is a 'reductionist' discipline and must be accompanied by translational 'systems thinking' in order to bring products to market.
- Reviewing UK patent laws that apply to prescription medicines. There is already a strong, global undercurrent challenging the present system, with Brazil in particular now involving their regulatory authority, ANVISA, in patent applications.

## APPENDIX

### CURRICULUM VITAE– HEDLEY REES

Hedley Rees has been researching, educating and advising in the pharmaceutical and biotech industries since 2005, having previously been employed in senior positions at Bayer UK, British Biotech, Vernalis, Ortho-Clinical Diagnostics and OSI Pharmaceuticals. His Twitter account @hedleyrees, describes him as ‘laying out #facts, compiling #evidence, shaping #change in #pharma #BigPharma #biotech’.

His skill set covers the range of competencies of strategic procurement, production and inventory control, distribution logistics, information systems and transformational improvement. His early career was spent as an industrial engineer in the automotive, consumer durables and FMCG sectors.

Clients range from large pharmaceutical companies to emerging biotech, and also include investors, lawyers, other consultancies, facility design & build specialists and third party logistics providers (3PLs). Assignments span early stage clinical trial supply chains up to complex multi-product supply networks covering global territories.

As an expert in Lean Thinking and Production Systems, Hedley is a zealous advocate of the regulatory frameworks of US FDAs 21st Century Modernization, penned by Dr Janet Woodcock, Director, Center for Drug Evaluation and Research (CDER) in 2002; also, of the EU modernisation initiatives from The International Council for Harmonisation

Hedley graduated from the University of Wales as a production engineer and holds an Executive MBA from Cranfield University School of Management, is a corporate member of the Chartered Institute of Purchasing and Supply (MCIPS) and an Advisory Board Member of the International Institute for Advanced Purchasing & Supply (IIAPS)

#### **Key career milestones include:**

1995 – Spearheaded supply-chain launch of Alka Selzer in Japan while at Bayer in the UK

2004 – Led manufacturing supply-chain launch of Tarceva in the US (drug for non-small cell lung cancer) in partnership with Genentech, South San Francisco, when at Oxford based OSI Pharmaceuticals

2007 – Joined UK BioIndustry Association’s (BIA) Manufacturing Advisory Committee, serving for three years

2010 – Co-chair of the highly regarded US FDA/Xavier University co-sponsored PharmaLink Conference (formerly FDA/Xavier Global Outsourcing Conference) held in Cincinnati annually. Served for four years.

2011 – Published “Supply Chain Management in the Drug Industry: Delivering Patient Value for Pharmaceuticals and Biologics”, J Wiley & Sons, Hoboken, NJ<sup>xiii</sup>



2012 - Advisory Board Member of Marken, the only supply chain service provider dedicated 100% to the pharmaceutical and life science industries, operating globally.

2013 – Sourced candidate company (Oxford BioMedica, OXB) for UK’s advanced manufacturing supply chain initiative (AMSCI) Round 3, at the request of UK HealthTech and Medicines KTN (Mark Bustard). Recruited consortium members (Cranfield University and Heart of England NHS Foundation Trust (HEFT)). Shaped the innovations within the bid, liaising with BIS representatives to achieve the first successful AMSCI award for life sciences (£7.1M).

2013 - Selected as a Founding Member of Expert Industry Panel for CPhI Worldwide

2015 – Published “Find It, File It, Flog It: Pharma’s Crippling Addiction and How to Cure It”

2017 – Published second edition “Find It, File It, Flog It”<sup>xiv</sup>

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<sup>i</sup> Hedley G Rees, “A new model for product development”, Chemistry Today, Scientific article - Peer reviewed, Jan/Feb 2011

[http://www.pharmaflowltd.com/wp-content/uploads/2017/07/Chem\\_Today\\_Jan\\_Feb\\_2011.pdf](http://www.pharmaflowltd.com/wp-content/uploads/2017/07/Chem_Today_Jan_Feb_2011.pdf)

<sup>ii</sup> “NEW DRUG DEVELOPMENT: Science, Business, Regulatory, and Intellectual Property Issues Cited as Hampering Drug Development Efforts” Report to Congressional Requesters, United States Government Accountability Office (GAO)

<http://www.gao.gov/new.items/d0749.pdf>

<sup>iii</sup> DISRUPTING PHARMA—ONLY POLITICIANS CAN DO IT, HERE’S WHY AND HOW

<http://www.pharmaflowltd.com/disrupting-pharma/>

<sup>iv</sup> Gaynes R. The Discovery of Penicillin—New Insights After More Than 75 Years of Clinical Use. Emerg Infect Dis. 2017;23(5):849-853.

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<sup>v</sup> “COMPANY NEWS; New Drug Era Begins as Tagamet Patent Ends, By MILT FREUDENHEIM, Published: May 17, 1994”

<http://www.nytimes.com/1994/05/17/business/company-news-new-drug-era-begins-as-tagamet-patent-ends.html>

<sup>vi</sup> Oxford BioMedica Wins Significant Funding via a Competitive Award from UK Government’s Advanced Manufacturing Supply Chain Initiative

<http://www.oxfordbiomedica.co.uk/news-media/press-release/oxford-biomedica-wins-significant-funding-competitive-award-uk-government%E2%80%99s>

<sup>vii</sup> “Lack of demand forces uniQure to withdraw Glybera gene therapy in Europe”, PBR, April 24 2017

<http://drugdelivery.pharmaceutical-business-review.com/news/uniquire-to-withdraw-glybera-gene-therapy-in-europe-240417-5794018>

<sup>viii</sup> Gilead Sciences to Acquire Kite Pharma for \$11.9 Billion

<http://www.gilead.com/news/press-releases/2017/8/gilead-sciences-to-acquire-kite-pharma-for-119-billion>

<sup>ix</sup> “FDA approval brings first gene therapy to the United States”. FDA Website

<https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm574058.htm>

<sup>x</sup> EXPLODING THE PENICILLIN MYTH: THE ONLY WAY TO DISRUPT PHARMA

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<http://www.pharmaflowltd.com/exploding-penicillin-myth-way-disrupt-pharma/>

<sup>xi</sup> DISRUPTING PHARMA—ONLY POLITICIANS CAN DO IT, HERE’S WHY AND HOW

<http://www.pharmaflowltd.com/wp-content/uploads/2017/08/Disrupting-Pharma-Only-Politicians-Can-Do-It.pdf>

<sup>xii</sup> “Kite chief Arie Belldegrun up for \$600M-plus payday from Gilead buyout” FiercePharma, August 31, 2017  
<https://www.fiercepharma.com/pharma/kite-chief-arie-belldegrun-up-for-600m-plus-payday-from-gilead-buyout>

<sup>xiii</sup> Rees, Hedley “Supply Chain Management in the Drug Industry: Delivering Patient Value for Pharmaceuticals and Biologics” J Wiley & Sons, NJ, February 2011

<http://eu.wiley.com/WileyCDA/WileyTitle/productCd-0470555173.html>

<sup>xiv</sup> ‘Hedley Rees “Find It, File It, Flog It” Wordcatcher Publishing, December 2017

<https://wordcatcher.com/collections/wordcatcher-politics/products/find-it-file-it-flog-it-hedley-rees>