

The challenges of the changing drug discovery model

The drug development industry is restructuring worldwide. This brings different ways of working and new challenges. As the industry moves away from internally focused research to an external model, project management and communication of science will often be more critical than outstanding science. There is a real danger the key skills will be lost across the world not least in the translation of potential drugs into early clinical trials. Much of the restructuring has been driven by cost by governments such as the UK, often setting a benchmark for others, of delivering best value for the public purse when buying drugs for national healthcare. Ultimately this could be counter-productive. The move towards personalised medicine and smaller potential markets makes many development programmes untenable. The public's view of exceptional risk in drug development research needs to change to address this. Regulation is also critical. It is becoming increasingly clear that one of the world's biggest markets for new drugs is in mental health, an area in which the regulatory requirements are ensuring many potential opportunities are ignored. Professional bodies around the world with their membership drawn from the private, voluntary and academic sectors need to take more of a leadership role in supporting the pharma and biotech development by arguing a rational and reasonable case for regulatory and financing evolution alongside a radically different training agenda.

It is widely recognised that drug discovery has changed. The last five years has seen significant restructuring of Big Pharma around the world with the model of large organisations retaining all the skills and knowledge they need, becoming redundant. It started with outsourcing to contract research organisations but has now gone much further into a virtual world. In the new world of drug discovery the pathway from concept and target validation through to patient benefit will be a collective effort. Centres of excellence in

large Pharma companies, contract research organisations (CROs), academia and public bodies are becoming increasingly common, and centres dedicated to drug discovery outside of the traditional private sector are starting to emerge. In the UK, organisational structures such as the Institute of Cancer Research Centre for Cancer Therapeutics in London¹, the University of Dundee's Drug Discovery Unit², and in Europe the ESRI Roadmap 2010³ for Biological and Medical Sciences has been implemented, and these, along with The

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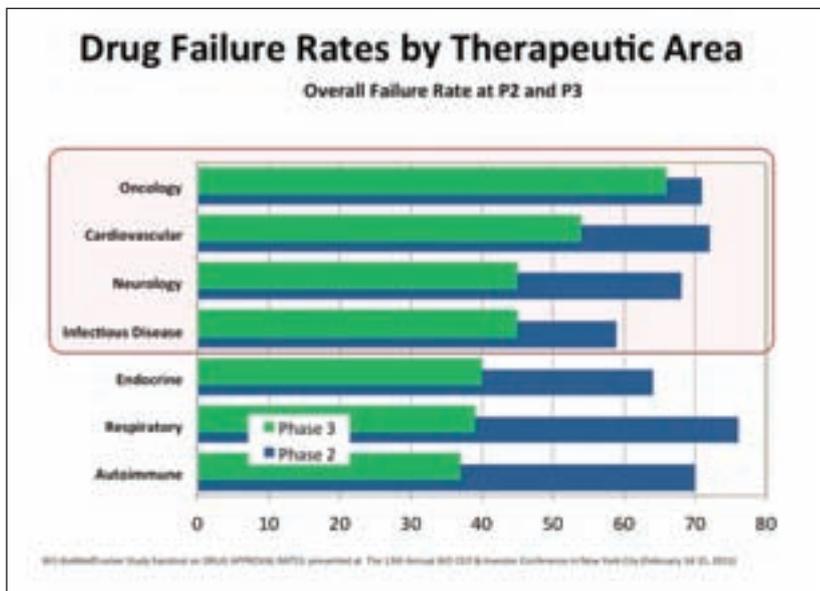


Figure 1 Karolinska Institutet for Innovation⁴ in Sweden, are recent examples of developing research infrastructure and drug development skills. While in the United States, the National Institutes of Health and National Institute of Mental Health (NIH/NIMH) estimates that it costs \$1.8 billion across 25 projects to launch a single drug. The NIMH budget is less than \$1.5 billion, so funding is directed at workgroups and initiatives such as the National Centre for Advancing Translational Sciences (NCATS) to fund and sponsor clinical trails to advance desperately needed and truly transformative treatments⁵. The Critical Path Initiative, the goal of which is precompetitive collaboration to speed up drug development, and the Clinical Data Interchange Standards Consortium⁶ were recently instigated by the NIH Chief Francis Collins. These NIH/NIMH initiatives include soliciting industry to donate compounds with specific mechanisms of action and procedures whereby the Federal Drug Administration (FDA) would release proprietary information on experimental drugs that the drug-makers have abandoned and are willing to donate to the NIH/NIMH pool. Such initiatives are ‘game changers’ and are to be welcomed and applauded in overcoming the obstacles and stumbling blocks of drug research and development. However, one of the key challenges faced by governments, industry and academia is changing the mind-set on intellectual property rights (IP). A patent is valuable only if it can be commercialised into a product. This is a key challenge the NIH and others face in addressing and leveraging collaborative partnerships to attract private and public partnerships that

will finance and run clinical studies. This can only be achieved with greater harmony between national and local government agencies, industry, academia, CROs, patient groups and real estate (for life science R&D) development and investment funds in the US and worldwide. America was once a leader in life sciences and today is clearly not sustaining its historically-strong investments in biomedical research that once propelled it to global life sciences leadership, while other nations are increasing their investments in the field, as highlighted in a report by United for Medical Research (UMR) and The Information Technology and Innovation Foundation (ITIF) in 2012⁷. The report makes a strong case for major, increased federal investment in the NIH and similar agencies. The report states that: “Baseline federal investment in biomedical research through the NIH has decreased in both inflation-adjusted dollars and as a share of GDP nearly every year since 2003,” and goes on to say that: “At the same time, competing nations are significantly increasing their investments in biomedical research, in many cases investing a larger share of their economies than the United States.” The report continues, saying that: “As a share of GDP, Singapore’s funding of pharmaceutical industry R&D was nearly five times greater than that of the United States in 2009, and if current investment trends in the United States and China continue, the US government’s investment in life sciences research over the next half-decade will be barely half of China’s in actual dollars and roughly one-quarter China’s level on a per-GDP basis.” To address this challenge, US and European biomedical research funding agencies, pharma and private investment entities are reaching out from national boundaries into a new approach of emerging collaborative global networks for drug discovery and development.

Clearly, along with national centres of excellence focusing on drug discovery and development, there is a greater need for international collaboration at one end of the spectrum and regionality at the other. Integrating clinicians with access to patients and the drug discovery early-stage research process is also becoming more common, with calls for international centres of clinical studies. Thus, patient centric research looks here to stay. And, according to a recent report by Pricewaterhouse Coopers, by 2020⁸ no pharmaceutical company will be able to “profit alone”. It will, rather, have to “profit together” by joining forces with a wide range of organisations, from academic institutions, hospitals and technology providers to companies offering compliance programmes, social networks,

nutritional advice, stress management, physiotherapy, exercise facilities, health screening and other such services.

This new highly-devolved approach to drug development has significant challenges for the industry. It may no longer be good enough to be an excellent research scientist to work on drug discovery but also 'a jack of all trades'. Of course we need good science, but we also need scientists who have the communication skills and outlook to embrace multi-centred approaches to drug development, and who can manage a more devolved and collaborative way of working. The challenge is to ensure that specific skills are also retained along the way to this new approach. Speciality areas such as medicinal chemistry have traditionally resided within the private sector rather than academia. As restructuring in Big Pharma leads to job losses, it is essential that skills such as these pharmacology/clinical pharmacology, drug metabolism/formulation and *in vivo* capabilities are retained. It will not be possible to simply rely on the academic or public sector to pick up the reins.

Alongside the changing skills agenda there needs to be a continuing public engagement and education process to help the public and government policymakers better understand the challenges which drug discovery now faces across the world.

The profligacy and malpractice of large corporations needs to be urgently addressed in many countries, particularly in G7 major economies. There needs to be a better understanding of the risks and benefits of new medicines and regulatory systems around the world have to be made more fit-for-purpose. It is not that there are fewer potential new targets for drugs; simply that the legal and regulatory framework is making it ever harder to bring a new products to market while, ironically, the regulatory system for the manufacture of generic drugs which are no longer within patent has become easier. British politicians and the media have coined a good phrase for this type of conundrum, 'the double whammy' – reducing profitability in existing drug markets for the original innovators while adding to the costs of new developments. Of course, it is right that patients should get good value for money and that government expenditure on the drugs bill is reduced. But the current solution isn't working. It simply cannot be right that against a backdrop of an explosion of new research publications and an ever-growing knowledge base, that the number of new drugs making the journey all the way to market is reducing. **Figure 1** demonstrates just how high the failure rate can be. In Phase II clinical trials, typically around 70% of

new molecules fail to progress further and a remarkable 50% more fail at Phase III.

International markets vary enormously. But some markets can have a disproportionate impact around the world. This has clearly been the case for the UK where the National Health Service as the largest procurer of drugs around the world has moved to value-based pricing, setting a benchmark process which many have followed. In the short term, the public and private purse of the drug purchaser may well benefit but there are big questions around the long-term impact of this approach.

As advanced economies become ever more knowledge intensive, the stakes involved in intellectual property are rising. Profound and far-from-complete economic and technological changes mean that an appropriate and enabling IP framework has become one of the prerequisites for global prosperity. IP-related spending has come to dominate pharmaceutical and biotech companies, academic institutions, non-profit organisations and investment firms across the developed world. The UK 'patent box' initiative and global policies need to be changed to stimulate and encourage drug development. Research and development tax credits have become popular with some governments as a route to stimulating investment in research and enabling innovation. These are good policies which do help. But they need to go much further, with academia and companies jointly owning patents and profit sharing.

There is no longer value in being second or third in market. To ensure return on investment pharmaceutical companies now need to be best-in-class. This has significant implications for access to the most appropriate healthcare for many. Even for the best-in-class, the market has to be sufficiently large. With the advent of personalised medicine, how can we address the problem of the demand for ever-increasing specialisation of drugs and a smaller number of people as the market? And if this financial model can be made to work, what are the implications for addressing the health challenges of developing countries where the numbers affected may be vast but the capability to pay low? The fact is that emerging economies are now introducing pricing controls and India is planning to follow China and other developing countries in reining-in prices on patented drugs to make medicines more affordable to its population. One recent example is Nexavar, an oral multiple kinase inhibitor for the treatment of patients with unresectable hepatocellular carcinoma (HCC). Earlier this year, Bayer lost a landmark drug ruling in India and was forced to grant a compulsory licence for Nexavar to Natco Pharma (www.natcopharma.co.in), whose price

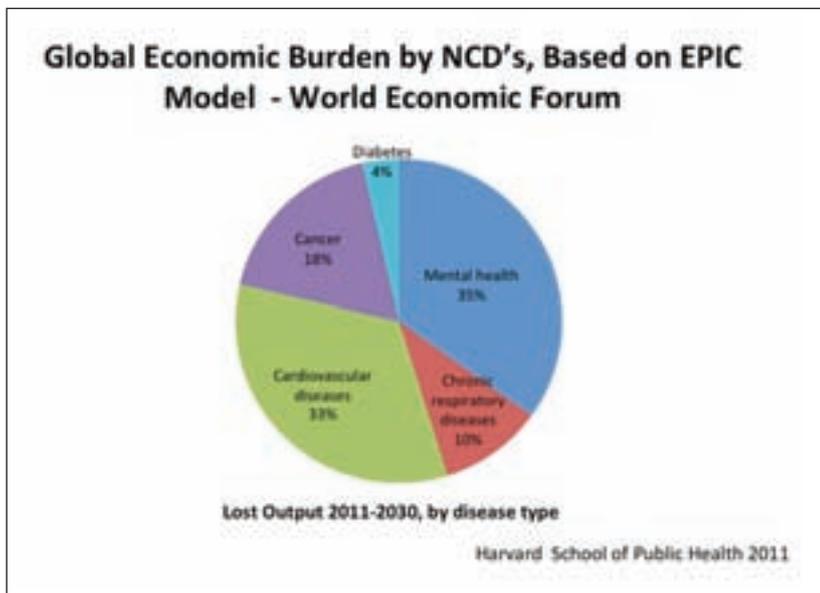


Figure 2 was subsequently under-cut by Cipla (www.cipla.com) by 75%. Novartis is also challenging the Indian Government on the proposed licensing to Indian generic companies of their drug Gleevac, used to treat a type of blood cancer called chronic myeloid leukemia, further highlighting the dangers faced by Pharmas that are hoping to grow branded drugs in emerging economies such as India and China. How new business models will be adapted and develop to address these challenging times for Pharma in emerging markets, will undoubtedly depend on harmonisation of global intellectual property rights and competition policy. An erosion of intellectual property rights would be extremely short-sighted. There is a strong consensus today that a powerful global intellectual property regime is needed to provide an incentive to undertake costly and risky investment in innovative activities, none more so than in drug development.

The route to return on investments is already skewing research focus in a way which is at odds with disease burden. **Figure 2** shows the Harvard School of Public Health's analysis of lost output between 2011 and 2030 by disease type based on the EPIC (which calculates lost output caused through disease) model⁹. Mental health represents 35% of the forecast disease burden and indirect costs of mental illness in 2010 are estimated to have totalled \$2.5 trillion worldwide. Why then are there so few new drugs reaching market to address this significant social challenge when it sits alongside a major market opportunity? The paucity of new innovative medicines for the treatment of mental disorders over the past 20 years is a burden the

pharmaceutical industry has to shoulder despite spending hundreds of billions of dollars on research and development. It is abundantly clear to all that the current animal models, clinical design/testing and 30-year-old diagnosis criteria, together with increasing regulatory demands, are not working.

Alzheimer's disease is a case in point. As **Figure 3** shows, the percentage changes in selected causes of death between 2000 and 2008 chart a dramatic increase (+66%) in Alzheimer's disease. According to the Alzheimer's Association (AA) Fact Sheet in 2012¹⁰, the direct cost of caring for those with Alzheimer's to American society will total an estimated \$200 billion, including \$140 billion in costs of Medicare and Medicaid. These costs will dramatically increase by 2050 to an estimated \$1.1 trillion (in today's dollars), with the cost of Medicare and Medicaid increasing to an unsustainable level of 500%, adding further to the instability of the American economy. Sadly, according to AA, Alzheimer's Disease is the only cause of death among the top 10 in America without a way to prevent, cure or even slow down progression. However, charitable non-for-profit organisations like the Alzheimer's Association are diligently working hard to fund new innovative treatments that one day may lead to advances being made in the treatment of this devastating disease. The recent highly publicised pharma revelations on the Phase III clinical studies with bapineuzmab¹¹ have left patient groups and the public totally bemused and disillusioned in 'what next' in the treatment of Alzheimer's disease?

This highlights the role of other enlightened players in drug discovery – the charitable and professional body sector. The ability of charities to focus exclusively on patient need is a welcome additional dimension to modern drug discovery research. They are increasingly professional, supporting leading-edge research and with the spending capability that is collectively matching many government-funded research programmes. The downside of this approach is it that it does not necessarily match disease burden around the world, although organisations such as the Bill & Melinda Gates Foundation¹² and other similar organisations have made enormous strides in developing countries. Although welcome, it is driven by the organisations' capability to generate funds against the backdrop of fundraising from a public that reacts emotionally in a very different way to different diseases. Mental health is probably a good example. There is a huge need but empathy is often lower than for other health issues such as cancer. In the US and in many industrialised countries, 'deinstitutionalisation' of psychiatric services aimed at

References

- 1 Institute of Cancer Research. <http://www.icr.ac.uk/>.
- 2 Dundee Drug Discovery Unit. www.drugdiscovery.dundee.ac.uk/.
- 3 ESRI Roadmap 20103, for Biological and Medical Sciences http://www.infrafrontier.eu/docs/esfri/BMS_RI_PositionCSF2011.pdf.
- 4 The Karolinska Institutet for Innovation. karolinskainnovations.ki.se/.
- 5 National Center for Advancing Translational Sciences (NCATS) <http://www.ncats.nih.gov/>.
- 6 Clinical Data Interchange Standards Consortium. <http://www.cdisc.org/>.
- 7 UMR/ITIF Report 2012. US Leadership in Decline. <http://www2.itif.org/2012-leadership-in-decline.pdf>.
- 8 Pharma 2020: Challenging Business Models: Pricewaterhouse Coopers, www.pwc.com/.../pharma.../pharma-2020-business-models/index.jht.
- 9 World Economic Forum and the Harvard School of Public Health. The Global Economic Burden of Non-communicable Diseases. September 2011. http://www3.weforum.org/docs/WEF_Harvard_HE_GlobalEconomicBurdenNonCommunicableDiseases_2011.pdf
- 10 Alzheimer Association Fact Sheet 2012. www.alz.org/.../2012_facts_figures_fact_sheet.pdf – United States.
- 11 Bapineuzumab. www.fiercebiontech.com/tags/bapineuzumab.
- 12 Bill & Melinda Gates Foundation for Drug Discovery. <http://www.gatesfoundation.org>.
- 13 Treatment Advocacy Center (TAC) 2012. No Room At The Inn. The consequences of closing public psychiatric hospitals. <http://www.treatmentadvocacycenter.org/>.
- 14 Cockburn, P. 2012. Neglect of the mentally ill is the great scandal of our times. The Independent on Sunday 9 September 36.
- 15 BIRAX Regenerative Medicine Initiative. <http://www.britishcouncil.org/israel-science-birax-main.htm>.

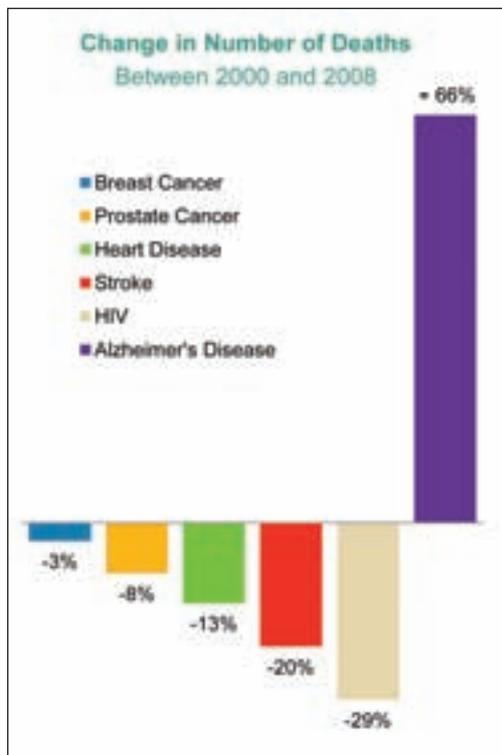


Figure 3

ending unnecessary confinement has led to the mentally ill being confined to the streets or in jail.

A US advocacy group, The Treatment Advocacy Centre (TAC)¹³, recently claimed that US jails have become the nation’s largest psychiatric hospitals. With this in mind, the London 2012 Paralympics helped people and nations to destigmatise physical disability. In the words of Patrick Cockburn¹⁴: “By nature of their disability the mentally ill are voiceless and vulnerable to the inadequacies, responsibilities and culpable actions of governments, and a couldn’t-careless-society for mental illness.”

But there is always light at the end of the tunnel. Pharma, biotech companies and academia are advancing new technologies and are still producing innovative new drugs, albeit at a reduced rate in mental disorders, and other therapeutic areas. Major advances in target identification are accelerating every year, fuelled by tissue engineering, human cell therapies, nano-pills and carriers, gene-based therapies, therapeutic monoclonals, pharmacogenomics, biomarkers, imaging, miniaturisation and automation of assays and a reduction in early-stage animal models in favour of new tools. Advances in ‘virtual modelling’ have a key role to play in the future and the advent of synthetic biology could be another game changer.

Following, unprecedented worldwide restructur-

ing of Pharma, drug development is still thriving in Europe, the US and Asia. But that will not continue to be the case unless some unprecedented changes are made. It is not good enough to park this problem on the doorstep of either Pharma or national governments. Academics, professional bodies, charities and the public all have a role to play. A refreshed and more balanced approach to risk with a more flexible regulatory framework and enhanced incentives around intellectual property are urgently needed. Above all, the skills agenda must be addressed to ensure we retain the benefits of past success while embracing the new more devolved and collaborative approach to drug discovery.

One solution will be to ensure greater permeability and transparency between academia and industry. In other words, making sure people exchange can happen on a significant scale. Universities have to find a way to recognise the value of highly skilled drug development scientists from the private sector who may not have the kudos of a publication record and bring them into academic environments. At the same time, there needs to be a shift in the mind-set of new and existing private sector researchers. A career in drug discovery needs to be seen as one which requires multiple skills, not just science knowledge, and moving between companies, academia, charities and the public sector needs to be expected rather than feared. Universities need to play their role in providing research-ready graduates who should expect to change careers and continually learn new skills, while professional bodies and governments need to provide the mechanisms for continual professional development, easing the movement of people against the backdrop of a sensible and balanced regulatory and fiscal framework.

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