Challenges for pharmaceutical industry: new partnerships for sustainable human health

BY JACKIE HUNTER*

OI Pharma Partners Ltd, Red Sky House, Fairclough Hall, Halls Green, Weston SG4 7DP, UK

The healthcare burden is increasing in both the developed and the developing world and there is widespread acceptance that the historical pharmaceutical business model is not sustainable. In order to meet the healthcare challenge, companies and academia need to develop new business models to increase the probability of success and decrease the cost of failure. New partnerships have already emerged in the area of neglected diseases and other models for diseases of the developed world are emerging.

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1. Introduction

Despite many advances in biomedical research and healthcare technologies, the healthcare burden is increasing globally. Huge challenges in healthcare exist and over the next few decades they are set to increase as the population globally ages; new zoonoses appear; and diseases of the developing world become more prevalent in the developed world owing to climate change and, vice versa, owing to increasing urbanization [1]. For sustainable health in the future, providing new therapies and treatment strategies, there will have to be changes in the current operating models not only for the pharmaceutical industry but also for academics, regulatory agencies, funders and the public.

2. The healthcare burden

There are several reasons for the increases in healthcare burden. The population of the world is increasing significantly and will reach over 7 billion in the next few years, and importantly the percentage of the population over 65 is also set to increase. This increase in the ageing population is occurring in both the developed and the developing world such that, in 2020, the absolute number of people aged over 65 in emerging market economies is likely to be almost double that in 2000. In the developed world, average life expectancy has increased by 2 years.

*jackie@pharmivation.com

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for every decade, but this has not been matched by a concomitant increase in health, leading to an actual increase in the economic burden. There are also key therapeutic areas where the healthcare burden is greatest, such as oncology and central nervous system (CNS), cardiovascular (CV) and infectious diseases. Worryingly, the last three areas are ones where the pharmaceutical industry is disinvesting and reducing effort. Companies are focusing on oncology and immune–inflammation and rare diseases that have a clearer phenotype. However, CV disease, infections and mental disorders, including dementia, will continue to be the leading causes of mortality in the future [2].

Research into infectious disease has received considerable incentives over the past decade, but only two new classes of antibiotics have been introduced during this time [3]. Despite advances in our understanding of the bacterial genome, finding leads remains difficult. Payne et al. [4] reported that Glaxosmithkline (GSK) ran 75 antibacterial screens but were able to find only five leads. Despite a decline in antibiotic usage in some countries, antibiotic resistance is increasing with new strains of resistant bacteria emerging, with some of the key pathogens for which new drugs are most needed being Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumonia and Enterobacter species [3]. Although new drugs have been reported to be in development, there are no phase III drugs currently in the pipeline for these agents. The reliance on effective antibiotics for modern medicine means that everything from hip replacements and complex heart surgery to routine treatments for respiratory and urinary tract infections would be severely affected if resistance became widespread. Other infectious diseases such as tuberculosis and influenza also represent a serious health burden globally. Of course, there are other issues that have led to a decline in antibiotic drug discovery, such as the cost of clinical trials required for regulatory approval and the uncertainties surrounding regulatory requirements for approval [5].

CV disease is a leading cause of death globally and a number of additive risk factors have been identified such as smoking, high blood pressure, raised cholesterol, diabetes and obesity. Although there are treatments and strategies for prevention of CV disease, many patients are still not being treated adequately [6]. Stroke is the fifth leading cause of disability and death globally, with approximately 10 per cent of the 55 million deaths that occur every year worldwide being due to stroke. Despite improvements in stroke care, treatment of the long-term effects remains a major problem. Fifty to seventy per cent of those patients who survive an ischaemic stroke will recover sufficiently to function independently, but 20 per cent will require permanent institutional care. Unfortunately, trials for new neuroprotectants and other agents to treat acute stroke have diminished in the past two decades because of a failure of a number of compounds in the clinic and the large costs of clinical studies.

The same is becoming true of many of the CNS disorders such as depression and dementia that are major causes of mortality and morbidity in both the developed and the developing world. The incidence of dementia, for example, is increasing as the population globally ages so that, within the EU15 countries, Alzheimer’s disease alone accounts for nearly 20 per cent of the total disease burden (acute and chronic disease) of all women over 85 years old [6]. Recent failures of disease-modifying approaches have highlighted the difficulties in therapies aimed at slowing disease progression [7].
3. The current pharmaceutical industry model is not delivering

Figure 1 shows the current timelines for drug discovery and development of new medicines. These are very long and the risk of failure is high such that it has been estimated that over 250 different research programmes are required to result in a single product launch. The early drug-discovery phase identifies leads through either structure-based design or high-throughput screening; the leads are then modified by medicinal chemists to create the optimum, candidate molecule that goes into early preclinical testing. Once a molecule has been shown to be safe and well tolerated in animals, clinical studies can begin. First time in human, phase I, studies are traditionally carried out in normal volunteers but in some instances patients are used, e.g., cancer patients. There has been a growing use of experimental medicine studies in phase I to look for biomarkers of efficacy. The aims of such studies are to reduce attrition in phase II patient studies by either improving dose selection or allowing the selection of the most appropriate patient group for efficacy testing. Phase IIa studies are generally small, single-dose studies to look for signals of efficacy prior to moving to a larger dose-ranging phase IIb study. A positive phase IIb study will trigger large phase III studies which will not only examine efficacy in a broader sample of patients but also examine safety. In parallel to all this clinical activity, long-term toxicology studies are carried out together with other development activities.

This process is essentially linear and has not changed fundamentally over the past 30 years, although the costs of pharmaceutical research and development (R&D) have increased significantly during this time period. It now costs over a billion dollars to bring a new product to market, including the costs of compounds that failed. There are other pressures on the industry, including the need for new outcome measures, comparative effectiveness and other reimbursement requirements, constrained government healthcare budgets and the need for access to medicines by the developing world. Despite these and other pressures, new medicines are urgently needed, and so new models to incentivize innovation will be required.

There are several main areas where innovation will be critical, as follows.

— **New business models.** These will include new collaborative models within and without the pharmaceutical industry, further reshaping of internal R&D and new commercialization models. Much of this activity has started with diseases of the developing world.

— **Adoption of personalized medicine.** Providing healthcare solutions on an individual basis rather than solely on a population basis will require significant innovation not only in terms of technology but also in terms of the understanding and communication of risk–benefit.

— **Systems biology.** Harnessing ‘omics’ knowledge and physiology for better disease understanding and drug development will require integration of knowledge across many boundaries not just between industry and academia.

Fundamentally, advances in the last two will depend critically on advances in the former, and so development of new models is vital to sustainable drug development for the next decades.
Over the last 10 years, there have been many mergers and acquisitions within the pharmaceutical industry, and the central core R&D organizations of industries continue to shrink as companies seek to access expertise and assets outside the company at reduced cost and risk [8]. But the interactions between industry, academia and biotech are no more likely to succeed than they have in the past, if collaborations are undertaken along previous lines. It is clear that academia can provide much more extensive disease understanding and target expertise than exists in many large companies, but it also has to work with companies more flexibly and with a greater emphasis on translation. Industry also needs to be more open and to allow academics and other partners access to tools and technologies and the sharing of intellectual property (IP) and knowledge in drug discovery and development. This means that parties have to accept some compromises that may involve some loss of control, and means that trust between the partners is essential for the optimal functioning of the collaboration. To really drive innovation in healthcare, ideally the customers and payers need to be more involved—patients can have a huge impact in defining unmet needs but, ultimately, the approval of regulators is required and they need to be engaged in biomarker and other precompetitive collaborations to clarify the regulatory requirements.

R&D into the ‘neglected diseases’ has led the way in exploring new business models for broader pharmaceutical R&D. Frequently, such initiatives are accelerated by not-for-profit funding, e.g. Gates Foundation and the Wellcome Trust. Some examples of these include the Medicines for Malaria Venture (MMV), GSK’s Diseases of the Developing World Centre at Tres Cantos, the Open Source Drug Discovery initiative in India and the Drugs for Neglected Diseases Initiative (DNDI).
The MMV celebrated its 10 year anniversary in 2009, having been established in Geneva as a not-for-profit ‘product development partnership’ in 1999. The basic mission of the organization was to discover, develop and deliver safe and effective anti-malarial agents. It was established as a public–private partnership (http://www.mmv.org/), with funding from both public and private sectors. It now has the largest pipeline of anti-malarial drugs, with over 50 projects from discovery through to registration including two projects submitted. It has carried out nine pivotal phase III trials in 3 years with 11 000 patients and remains a flagship public–private partnership for neglected diseases research.

GSK has for many years run a ‘diseases of the developing world’ laboratory at its high-throughput screening centre in Tres Cantos in Spain. This has a number of academic and not-for-profit partners and GSK set up a patent pool in 2009 to facilitate access to IP, industrial expertise and technologies to stimulate research into neglected tropical diseases. This pool was joined by Alnylam Pharmaceuticals and administered by BIO Ventures for global health and it now has a dedicated website (www.ntdpool.org), where academics and others can search the 2300 patents currently deposited in the pool. The Massachusetts Institute of Technology and South Africa’s Technology Innovation Agency joined the initiative, now known as the Pool for Open Innovation against Neglected Tropical Diseases, in 2010. In order to support researchers, GSK also set up laboratories for their use at its research centre in Tres Cantos, Spain. More recently, the data from screens for inhibitors of Plasmodium falciparum, the protozoa that is responsible for malaria, were put into the public domain together with data from Saint Judes Hospital and other collaborators [9,10].

In February 2010, Lilly, Merck and Pfizer, in collaboration with Chinese entities, announced the creation of an independent, not-for-profit company, the Asian Cancer Research Group. The aim of the organization is to study two cancers in the Chinese population—non-small cell lung cancer and gastric cancer. Over 2000 patients and their tumours in each tumour type will undergo phenotypic, genotypic, proteomic and, ultimately, longitudinal analysis. This will provide extensive information about novel cancer pathways, heterogeneity of the diseases and their response to therapy. The final data output will be open for other researchers to use.

The DNDI is a virtual, non-profit drug R&D organization that is developing new treatments for malaria, visceral leishmaniasis (VL), sleeping sickness (human African trypanosomiasis (HAT)) and Chagas disease. It was formed in 2003 by seven organizations: five public sector institutions—the Oswaldo Cruz Foundation from Brazil, the Indian Council for Medical Research, the Kenya Medical Research Institute, the Ministry of Health of Malaysia and France’s Pasteur Institute; one humanitarian organization, Médecins sans Frontières (MSF); and one international research organization, the UNDP/World Bank/WHO’s Special Programme for Research and Training in Tropical Diseases (TDR), which acts as a permanent observer of the initiative. It works in partnership with industry, academia and non-governmental organizations and has built an R&D portfolio for the kinetoplastid diseases with seven clinical/post-registration and four preclinical projects ongoing (http://www.dndi.org/). Companies such as Novartis and GSK are sources of hit and lead compounds, while screening is provided by centres such as the Dundee Kinase Consortium.

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A very different model is the Open Source Drug Discovery Initiative in India (http://www.osdd.net/). It is a community of students, scientists, researchers, academicians, institutions and corporations that are committed to discovery of drugs in an open source mode for tropical infectious diseases. The first pilot project is annotation of the tuberculosis genome and funding is provided by the Indian government.

However, new models are also developing in areas outside of the neglected diseases area. In 2009, GSK and Pfizer announced the creation of a joint venture company to tackle HIV. Subsequently named ViiV healthcare (www.viiivhealthcare.com), the new venture aims not only to develop new medicines for HIV but also to improve access to HIV treatments for patients and provide support for communities affected by HIV. This depth and breadth of approach is greater than could be attempted by any one company individually. Other approaches, involving diseases more aligned to the needs of the developed world, have been taken by companies such as Lilly and Bayer Schering.

For example, Lilly announced in June 2009 that it would make certain assays and expertise available to academia to facilitate the creation of new collaborations and identification of new development compounds. This was called the Phenotypic Drug Discovery Initiative (PD²), which has a stated goal of fostering open collaboration between Lilly and global laboratory researchers in Alzheimer’s disease, cancer, diabetes and osteoporosis (https://pd2.lilly.com). According to Lilly press releases and presentations, academic researchers submit their compound through an automated PD² interface. The compound structure is then evaluated by Lilly scientists using a set of proprietary algorithms that focus on structural novelty and whether the compound meets certain developability criteria. If the compound structure is suitable, the researcher is then invited to submit a physical sample for biological testing. In return for the biological data generated, Lilly has first rights to negotiate a collaboration or licensing agreement. If Lilly decides not to pursue the opportunity, then the researcher is granted ownership of the data report.

Bayer Schering has launched a new initiative to foster research in academia and start-ups into targets of mutual interest and to accelerate the translation of new research into effective treatments (http://www.grants4targets.com). It offers a range of grants that are rapidly peer-reviewed with different options for IP and licensing depending on the nature of the collaboration.

Other companies have begun to make elements of their chemical libraries available to external parties. Pfizer has allowed companies to screen against their internal library, and Astra Zeneca (AZ) recently signed a deal with the Medical Research Council Technology (MRC-T) to screen compounds from AZ’s compound collection and compounds from the MRC-T on targets submitted by both parties. Although compound structures will not be disclosed in the AZ–MRC-T deal, it is another step forward in sharing resources to ‘co-create’ additional value.

As well as these more open innovation-aligned collaborative models, where complementary expertise is shared by industry and academia, industry itself is engaging in more precompetitive consortia, usually with academia and biotech companies [11]. Many of these consortia are focused on safety biomarkers in an effort to make better predictions around the toxicological liabilities of molecules. There are a number though which are also focused on the discovery of new
predictive biomarkers, including those for CNS, infectious and CV diseases. These efforts may lead to a resurgence of interest in drug discovery and development for these disorders as patient populations can be stratified into more homogeneous subsets. The largest of these precompetitive initiatives is the Innovative Medicines Initiative (IMI), which is a 2 billion euro partnership between the members of the European Federation of Pharmaceutical Industry Associations (EFPIA) and the European Commission [12]. Each partner contributes 1 billion euro. There are over 25 different companies collaborating on different projects both with each other and with academia and small- and medium-sized enterprises. The aim is to work pre-competitively to solve the bottlenecks in drug discovery and development across diseases that are relevant to both the developed and the developing world. Projects range from new patient-reported outcomes in chronic obstructive pulmonary disease to expert systems for in silico toxicological prediction, and from new animal models in neurodegeneration to education and training programmes. There are also infrastructure building partnerships such as the Open Pharmacological Space project. This project aims to build open access public informatics resources to support drug discovery. It will focus on developing and applying common data standards to improve the integration of data relevant to drug discovery and also develop tools and web services to aid access and mining of the data. This will enable the transfer of expertise in the use of data for drug discovery from industry into the public domain and will also expand the connectivity between the existing public databases. This project will clearly be of benefit to large companies, biotech and academia.

One of the most important aspects of the IMI is that all the EFPIA companies provide matching funding through in-kind contribution, which can be people, samples, assays, etc. This drives a different level of engagement from the industry participants. The other important aspect to this more applied funding programme is that the call topics announced each year for funding proposals are formulated initially by the EFPIA members and so represent real barriers to drug development in a particular disease area. This also ensures a high level of industry engagement in the resulting consortia.

4. Challenges for new models

There are many challenges to the implementation of these new ways of working. It is essential that there is strong senior management support within the participating organizations. This type of support was vital in ensuring the commitment of companies in the area of neglected diseases and will also be essential if a new more open R&D architecture is to be implemented across the industry for other diseases. Of course, these are challenges for all the other partners, including academia and biotechnology companies. Academics will have to collaborate more effectively not only within their institutions but also across institutions. Biotechnology companies likewise will have to see the value of broader collaborations for validating their platforms and ensuring acceleration to market their products and services.

There is also a need for appropriate metrics that can show the value created by these new ways of working. While all pharmaceutical companies recognize that alliances differ, they can lack useful frameworks for helping them refine
management approaches to alliance requirements. Categorizing alliances by complexity and importance can give executives a portfolio view of their alliances, which looks at managerial aspects as well as financial ones [13]. Companies need to incorporate these measures into an overall system of evaluation that will allow them to capture the additional value contributed by new partnership models. Projects should be viewed more holistically in what they can contribute to the overall innovation within a company—this can include access to different ways of thinking, dormant IP that can be opened up to external collaborators for new innovation and access to talent or new customer insights in emerging markets. There are now more attempts to create such strategic frameworks in order to better assess these new ways of working against more traditional collaborative models [14].

Transparency and clear communication around the objects of the collaborative models are also important. Validation of the data placed in the public domain remains an important issue. For example, there has recently been some controversy about the results put in the public domain by the Open Source Drug Discovery Initiative (http://www.nature.com/news/2010/100609/full/news.2010.285.html), as the data are yet to be peer-reviewed although manuscripts are being submitted for peer-review publication. Even when such efforts are peer-reviewed, as in the case of the deposition of the compounds in the Pool for Open Innovation against neglected tropical diseases [9], they can still raise questions. There were comments that these compounds are not ‘drug-like’, as claimed by GSK [15]. This highlights the need for very clear communication about the value and the nature of what is being shared, as any perceived lack of transparency could easily create a negative impression for the consortia.

There are also challenges on the academic side—the comments with regard to the Open Source Drug Discovery Initiative are a good example. In this very interactive world, sceptical academics could perhaps have found ways of commenting on the annotated data or interacting with the programme to do online peer review, rather than the more traditional journal-based approach. In addition, the incentives in terms of individual recognition and reward are not aligned in academia to a more collaborative approach to industry.

There are also many practical barriers to the formation of the collaborative knowledge platforms that underpin many of these new ways of working. These can include: building a critical mass of contributors, standardization and quality of the data entered, curation of the resulting databases, appropriate tools for analysis and visualization, data protection for clinical samples and issues around IP. Indeed, IP is one of the areas where there is the most active debate and tension when an organization is trying to create a more open, innovative ecosystem.

There is a real need for innovation and innovative ways of working if we are to deliver better healthcare to the population globally. The challenges of integrating information across the whole healthcare sector, whether at the basic level of systems biology, personalized healthcare, new drug development or the development of new markets, are huge. The opportunities that new technologies bring for tackling not only the diseases of today more effectively but also those of tomorrow are also enormous. The challenge for all of us is to match the opportunities with the challenges to drive innovation as efficiently and as effectively as possible. To do this there need to be the appropriate incentives.
in place, the engagement of many different stakeholders including patients and regulators but most of all people with the right expertise and enthusiasm to fully realize the value of new partnering models for human health.

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