Shifting paths of pharmaceutical innovation: Implications for the global pharmaceutical industry

TARIQ SADAT, ROSLYN RUSSELL & MARK STEWART
RMIT University, Australia
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ABSTRACT The modern pharmaceutical industry has always been dominated by a few large pharmaceutical companies, or ‘big pharma’. Until recent times, big pharma has enjoyed success through its integrated approach of exploiting growing scientific and technological know-hows and commercialising high value blockbuster drugs. However, a number of external and internal forces are influencing the value of pharmaceutical innovation, and making big pharma’s growth through integrated innovation model, unsustainable. To sustain growth, big pharma is adapting its innovation pathway, and complementing its model of creating value through new drugs and new markets with one that deliver the perceived value to users including patients, physicians, payers and policy makers. This paper maps the shifting paths of pharmaceutical innovation by examining big pharma’s responses to the forces that are affecting their innovation models. The shifting paths of pharmaceutical innovation have important implications for the global pharmaceutical industry which are also discussed in this paper.

Key words: Big pharma, innovation models, open innovation, perceived value

Introduction

This paper examines evolving paths of pharmaceutical innovation models within the current context of healthcare and pharmaceutical industry. It describes various external and internal forces that are affecting the value of pharmaceutical innovation, and how large pharmaceutical companies (or ‘big pharma’) are adapting their innovation models (strategies) in response to these forces. It also discusses the implications for the global pharmaceutical industry. The first part of this paper conceptualises pharmaceutical innovation in the context of technological innovation. It also describes the forces that produce technological innovation and determine its path. Conceptualisation of pharmaceutical innovation helps to identify pharmaceutical innovation models and their evolving paths. The second part sketches the evolution of pharmaceutical innovation models within the historical context. It provides a review of the key historical forces that have shaped the pharmaceutical industry and its innovation models. Analysis of the historical paths of pharmaceutical innovation is important because it provides the context for
mapping the shifting paths of pharmaceutical innovation. The third part provides comprehensive analyses of the external and internal forces that are affecting the value of pharmaceutical innovation, and includes illustrations of how big pharma is transforming its innovation models and creating value. The analyses of the forces and the selective illustrations of big pharma’s activities are drawn from various pharmaceutical and biotechnology industry analyst reports as well as from daily reports on pharmaceutical industry by various industry monitors. The concluding section discusses the implications of the shifting paths of pharmaceutical innovation.

Conceptual framework of pharmaceutical innovation

Classical economist Joseph Schumpeter (1939) describes innovation as a function of economic change or, more specifically, economic evolution. Schumpeter defines innovation as a new function of economic production (producing a new commodity, bringing technological change in the production of commodities already in use, setting up new organisation or new form of organisation, creating new markets or new source of supply) that results from conscious efforts to deal with a given situation or fulfil a need in the realm of economic life. For example, the huge demand for antibiotics during the Second World War brought organisational change to fine chemical manufacturers Merck and Pfizer as they turned to manufacturing of pharmaceuticals (Chandler, 2005). Schumpeter’s ‘theory of innovation’ infers that innovation is the process of giving economic value to an invention that has taken place irrespective of an objective need, such as, Alexander Fleming’s serendipitous discovery of penicillin (McKelvey, 1996), or an invention that has taken place to fulfil a specified need, such as Edward Jenner’s discovery of smallpox vaccine in the course of finding a protective mechanism against smallpox (Riedel, 2005).

Schumpeter’s theory of innovation to a large extent has contributed to the conception of technological innovation. McKelvey (1996, pp. 16), along the Schumpeterian line, defines the ‘technological innovation process’ as ‘the process whereby agents act to transform new knowledge, inventions, and/or scientific techniques into economic value, often through products, production processes, and/or changes to the organisation’. Technological innovation occurs as four sequential activities—research, development, manufacturing and marketing—that together constitute the value chain of technological innovation (Porter, 1985; Walters and Lancaster, 2000; Hamilton et al., 1990). Pharmaceutical innovation (or, drug innovation as the meaning implies) incorporates these four activities of technological innovation. The value chain of pharmaceutical innovation is illustrated in Figure 1.

![Figure 1: Pharmaceutical Innovation Value Chain](image-url)
The ‘research’ activities comprise laboratory experiments involving the identification and validation of a druggable target (e.g. an enzyme causing inflammation) in the body, and identification and optimisation of a lead drug candidate that modulates that target (e.g. blocks the action of the enzyme). The ‘development’ activities include preclinical experimentation of the drug candidate in live cells, tissues or animal models to demonstrate its safety and effectiveness. The drug candidate is then clinically trialled to demonstrate its safety and efficacy in humans (Pisano, 2006).

Phase I clinical trials are done with a small number of people (typically between ten and one hundred healthy volunteers) to examine the drug’s safety. Phase II trials are done with a larger number of patients (between fifty and five hundred) to further examine its safety, and determine effective drug doses. Finally, Phase III trials are undertaken using a very large number of patients (up to thousands of patients in many different sites) to explore its long-term safety and efficacy (Pisano, 2006). At each step of research and development (R&D), knowledge and information are created that translate into a hierarchy of optimisation, improvement and characterisation of the new drug (Nightingale, 2000; Nightingale and Mahdi, 2006).

Value is accrued to the new drug in the form of intangible capital, i.e. drug-specific tacit knowledge. The value is captured through owning the tacit knowledge by means of patent protection, and delivered through commercialisation of the new drug by exploiting specialised complementary capabilities in manufacturing and marketing. Complementary capabilities in manufacturing and marketing also accrue value to the new drug in the form of tangible skills and capital investments (Attridge, 2007). An additional step in the pharmaceutical innovation value chain is mandatory regulatory (marketing) approval of a new drug by country-specific drug regulatory authorities, such as the Food and Drug Administration (FDA) in the US, based on experimental proof of the drug’s safety and efficacy in human (Pisano, 2006).

Technological innovation is produced by two distinct, but sometimes intertwined, forces, ‘demand pull’ and ‘technology push’ (Dosi, 1982). In demand pull, technological innovation occurs in response to ‘recognition of needs’ (Dosi, 1982) in the economic system. The outbreak and recognition of HIV/AIDS (Human Immunodeficiency Virus / Acquired Immunodeficiency Syndrome) in the early 80’s triggered the need for a cure, and subsequently resulted in the search and development of antiviral therapies and vaccines against AIDS in the 90’s (Pickrell, 2006). Development of anti-HIV therapeutic interventions as cures followed the ‘demand pull’ trajectory of technological innovation. AIDS also created a new market for pharmaceutical innovation.

In technology push, technological innovation occurs as a cumulative and continuous process, and follows the evolving paths of scientific and technological paradigms. Accumulation of knowledge (scientific and technological) and subsequent progress along technological trajectories are translated into technological innovation (Dosi, 1982). The first recognition of cancer dates back to 3,000 BC. However, the first understanding of cancer was only possible in the 19th century owing to accumulation of scientific knowledge between these two periods. Radical organ removal surgery, radiotherapy and chemotherapy were the early successful anticancer interventions between late 19th and mid 20th century. Since then, the expanding knowledge of the biological processes of cancer and advancing techniques of cancer imaging and diagnosis have been shaping many
promising anticancer interventions including cancer vaccines, monoclonal antibodies (MAbs) and gene therapies (Sikora, 2007).

Technological innovation can only be understood in the context of technological firms’ innovation activities. Pavitt (1984, 1991) argues that firms are the most important source of technological innovations. Firms use their specific strategies, structures and competencies to produce innovation in order to gain competitive advantage and optimise economic returns (value). Large industrial firms are always at the forefront of technological innovations due to their ability to build and integrate firm-specific competencies, coordinate cross-disciplinary and cross-functional specialisations, absorb technological changes through organisational learning processes such as R&D, experience and competitor information, manage resource allocation decisions, and assimilate multiple technological specialisations. This paper, thus, examines evolving innovation models of big pharma to trace the shifting paths of pharmaceutical innovation.

In summary, (technological) innovation can be conceptualised as a function of the value that is embodied in a new product or market or an organisational change. The value is created by firms through innovation activities along the value chain, and delivered through commercialisation of a new product, penetration into a new market, or implementation of an organisational change. In pharmaceutical innovation, a new drug or a new drug market represents the value that is created by pharmaceutical companies. As we will discuss in this paper, cyclical ‘demand pull’ and ‘technology push’ forces are creating new paths to pharmaceutical innovation. Pharmaceutical companies are adapting their R&D and business models to create value along the new paths. We will also find that new innovation models are either complementing the older ones, or displacing them, a pattern which has been described by Bower and Christensen (1995) as ‘disruptive innovation’.

Evolution of pharmaceutical innovation models—the historical context

The path to prescription drugs—the ‘integrated model’

Though the modern pharmaceutical industry, dominated by a handful of large integrated pharmaceutical companies, began its journey around the Second World War, its origin can be traced back to the mid-19th century in Europe as well as in the US. In Europe, particularly in Germany and Switzerland, chemical companies like Ciba, Sandoz, Bayer and Hoechst led the early European pharmaceutical industry during the second half of the 19th century by leveraging their strengths in organic chemistry based manufacturing (Henderson et al., 1999). In the US, around the same period, specialised pharmaceutical manufacturers, such as Eli Lilly, Wyeth, Abbott and SmithKline, started to produce ‘over the counter’ drugs based on natural sources—plants, animals and minerals. Until the First World War, the US companies relied on the German and Swiss companies for supply of chemically synthesised drugs. Following the First World War, the US companies started to commercialise prescription drugs as well, such as vaccines, vitamins, sedatives, tranquilisers and heart medicines (Henderson et al., 1999; Chandler, 2005). Fleming’s discovery of Penicillin in 1928 and the massive anti-
biotic demands during the Second World War created an antibiotics commercialisation path for many of these pre-war era companies, supported by massive research and production programs from the governments, particularly in the US (Henderson et al., 1999). The path also led fine chemical suppliers in the US, such as Merck and Pfizer, to join prescription drug business and to acquire advertising and marketing capabilities for selling antibiotics and other prescription drugs to doctors and hospitals (Chandler, 2005).

The post-Second World War era was marked by intensified R&D efforts from the pharmaceutical companies to produce more prescription drugs through exploiting new learning bases in microbiology, enzymology and biochemistry (Henderson et al., 1999; Chandler, 2005). The pharmaceutical companies emerged as large integrated companies, representing a maturing pharmaceutical industry. They acquired capabilities not only in pharmaceutical R&D and production, but also in managing large-scale clinical trials and regulatory approvals, as well as marketing and distribution of pharmaceuticals around the globe—the organisational capabilities that acted as barriers to entry into the industry (Henderson et al., 1999), and thus rendered them oligopoly (Chandler, 1990). Driven by advances in basic scientific knowledge, economies of scope in therapeutic categories such as painkillers, anti-inflammatories, cardiovascular and central nervous system drugs, shift in drug discovery techniques from ‘random screening’ to ‘guided discovery’, public and national institutional supports for health research, strong Intellectual Property (IP) regime, and stringent drug approval procedures (Henderson et al., 1999), the pharmaceutical industry turned into a more R&D focused innovative industry dominated by a handful of large integrated and profitable companies.

The path to biotechnology R&D—the ‘collaborative model’

The discovery of the structure of DNA in the early 1950s, and subsequent invention of the techniques of genetic engineering in the 1970s created a new path for pharmaceutical R&D, a path involving knowledge and techniques that became better known as ‘biotechnology’. Biotechnology became a research tool in drug discovery and screening processes based on the knowledge and applications of genetics and molecular biology, such as target-based drug discovery using cloned receptors. Biotechnology also became a production tool for the development of protein-based (recombinant) drugs, e.g. insulin (Henderson et al., 1999; Chandler, 2005; Pisano, 2006). The biotechnology path of pharmaceutical R&D produced a shift in pharmaceutical industrial and commercialisation models.

A wave of university research spin-off companies emerged to commercialise biotechnology R&D. But they lacked the essential capital and organisational capabilities needed to walk the entire commercialisation path. Eventually they relied upon the large pharmaceutical companies to support their commercialisation activities (Pisano, 2006). A few of them, for example, Amgen, Genentech, Genzyme, Biogen, were able to internalise capabilities necessary for developing, manufacturing and marketing their products, and turned into large integrated companies or ‘big biotechs’. They succeeded in becoming large integrated companies, in large part, due to having commercialised high value ‘orphan drugs’ for relatively rare, life-threatening diseases, and, in small part,
due to their successful contractual partnerships with the stakeholder pharmaceutical companies (Chandler, 2005).

However, the majority of biotechnology companies today are small- to medium-sized companies that pursue enabling platform technologies in areas such as structure-based (rational) drug design, high-throughput drug screening, bioinformatics, genomics (structure and functions of genes), genetic engineering, recombinant technology and products, etc. For the pharmaceutical companies, the advantages of partnerships with such biotechnology companies can be found in their ability to access specialised biotechnology knowledge and applications that are essential for drug discovery and development processes, and also in their scope to access the high commercial value of novel biotechnology products. The pharmaceutical companies also adopted their own biotechnology innovation programs based on their core competencies, and also through acquisition of small biotechnology companies, in-licensing novel technologies from them, or forming joint ventures or collaborations with them. By exploiting biotechnology capabilities in ‘guided’ or ‘target-based’ discovery of small molecule and biological drugs, the integrated pharmaceutical companies produced a number of novel drugs that not only generated billion dollar in sales to become ‘blockbuster drugs’ (such as GlaxoSmithKline’s anti-ulcer drug Zantac, launched in 1982), but also helped sustain their dominance of the global pharmaceutical industry (Henderson et al., 1999; Chandler, 2005; Pisano, 2006; Hopkins et al., 2007). This ‘collaborative model’ of pharmaceutical innovation also preserved the ‘integrated model’ of the pharmaceutical companies.

The ‘big pharma’ evolved in the 1990’s in two distinct pathways. In the US, companies like Merck, Pfizer and Eli Lilly became very large through exploitation of emerging technologies in microbiology, enzymology, genetics, molecular biology and genetic engineering, and commercialisation of innovative prescription drugs. In Europe, companies like Novartis, Aventis (now Sanofi) and GlaxoSmithKline achieved their sheer size through series of mergers and acquisitions between national and cross-national pharmaceutical companies. The mergers and acquisitions took place to exploit emerging technologies in drug discovery and development, expand and diversify the product portfolio, overcome competitive challenges in domestic and international markets, and achieve economies of scale and scope in the commercialisation of innovative drugs (Chandler, 2005). These and few other European and American companies dominate the global pharmaceutical industry today, and are commonly referred to as ‘big pharma’.

**Evolution of pharmaceutical innovation models—the current context**

*The path to creating and delivering value—the ‘open innovation models’*

Currently, big pharma’s growth through its integrated innovation model is becoming unsustainable due to a range of internal and external forces. As we will see in the remaining sections of this paper, external market forces such as payers (health insurers), government policies (healthcare reforms and drug price controls), emerging market dynamics, and dominance of low-price generic drugs over patented ones are command-
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ING the value of pharmaceutical innovation. We will also see that internal forces like soaring R&D costs are shrinking R&D productivity and the net value of pharmaceutical innovation. R&D productivity here can be defined as the value created by a new drug against the R&D cost incurred (Paul et al., 2010). These internal and external forces are creating intertwining opportunities and barriers to big pharma’s growth. In response, big pharma is pursuing alternative innovation paths, and these paths are leading to ‘open innovation’ models. In the open innovation model, on the one side, big pharma is bringing many scientific and technological forces together so that the growing scientific and technological knowledge can be exploited to create value through productive R&D; on the other side, big pharma is forming bridges with the market forces through various responses to deliver the value to users. The following sections discuss the external and internal forces that are affecting the value of pharmaceutical innovation, as well as big pharma’s various strategies to create, conserve and deliver the value of pharmaceutical innovation. Based on the reports of company activities from various pharmaceutical and biotechnology industry analysts and industry monitors, this paper selects eleven big pharma companies for its analyses. They are AstraZeneca, GlaxoSmithKline, Sanofi, Roche, Pfizer, Johnson & Johnson, Eli Lilly, Abbott Laboratories, Merck, Bristol-Myers Squibb and Novartis.

Healthcare reforms and drug price controls—benefits and hurdles

Crippled by the ballooning healthcare costs, policy makers (governments) around the world are implementing measures designed to contain public healthcare spending. Many developed as well as emerging countries, as the World Health Organisation’s (WHO) 2010 World Health Report (WHO, 2010) shows, are reforming their healthcare policies so that every citizen can access affordable healthcare services. The report describes the path towards universal health coverage by many countries, and the healthcare reforms they are adopting. Such reforms are extending affordable healthcare services to disadvantaged citizens by means of prepayment of healthcare services, or mandatory and subsidised health insurances. Following are two selective country-specific examples, the US and China, representing healthcare reforms in the developed and emerging markets, respectively.

In the US, the 2010 Health Reform Legislation (Affordable Care Act) will extend subsidised health insurance by 2014 to an additional 32 million citizens. The subsidised health insurance will extend to young adult citizens, low-income earners and citizens who have been rejected by private health insurers due to their pre-existing medical conditions (Tumulty et al., 2010; Pickert, 2010; Ford, 2010). Evaluation of the Affordable Care Act suggests substantial gains for the pharmaceutical industry in the longer term. As millions more US citizens come under mandatory insurance cover by 2014, the pharmaceutical and biotechnology industry will gain from expanded market coverage. Citing a report from London-based research and consulting firm ‘GlobalData’, Forbes (Japsen, 2013) reports that while rebates for prescription drugs through Medicaid programs will cost the pharmaceutical industry $20 billion over the next decade, inclusion of uninsured citizens in insurance programs will create $115 billion in new business opportunities for the pharmaceutical industry, and boost indus-
try profits by up to $35 billion over the next ten years. The Pharmaceutical Research and Manufacturers Association (PhRMA) and Biotechnology Industry Organisation (BIO) spent more than US$110 million during early 2009 campaigning in favour of the Act (Tumulty and Scherer, 2009), and later agreed to a cost of around $90 billion in ten years towards fees and discounts on Medicare and Medicaid drug pricing1.

In China, the government launched an ambitious healthcare reform in April 2009 to bring the entire Chinese urban and rural population under universal primary medical services. An estimated 1.2 billion people are now covered by a basic medical insurance system (Guo, 2011), including over 300 essential medicines (Wang and Li, 2011). This provides the international and local pharmaceutical manufacturers with the benefit of an expanded pharmaceutical market, although government measures to control essential drug prices will partly diminish the benefit of such an expanded market.

Similar to China and the US, a number of African, South American and other Asian countries have also undertaken healthcare reforms to extend healthcare coverage (WHO, 2010). Such healthcare reforms will expand the pharmaceutical market for international and local companies. However, as discussed below, government measures to contain healthcare costs are targeted towards controlling drug prices, which are inhibiting the growth of big pharma.

Traditionally, the regulatory approval of a new drug based on its safety and efficacy has been the biggest barrier to its market entry. But now the biggest hurdle for a new drug’s success is whether it would qualify for reimbursement from the payers (PricewaterhouseCoopers, 2013). The payers are increasingly becoming important in determining the value of new drugs. Rising healthcare costs are forcing governments and payers to drive drug prices down. To qualify for reimbursement, pharmaceutical companies are now required to demonstrate through clinical trial results that their new drugs offer significantly more clinical benefit than existing alternatives (comparative effectiveness), and also reduce the total cost of care (cost-effectiveness) (Ernst and Young, 2010; PricewaterhouseCoopers, 2012a; Burrill, 2013).

According to a 2012 US survey carried out by PricewaterhouseCoopers’ Health Research Institute (PricewaterhouseCoopers, 2013), 40% of customers postponed healthcare services one or more times within a year due to affordability concerns. In response, healthcare providers (hospitals) are finding ways to reduce costs of healthcare services to patients. In October 2012, three physicians at the Memorial Sloan-Kettering Cancer Center in the US decided that they would not prescribe a phenomenally expensive cancer drug, Zaltrap, marketed by Sanofi, to their patients with colorectal cancer, that costs over $11,000 a month but offers no better therapeutic results than another similar drug, Avastin, that costs only $5,000 per month (Bach et al., 2012). Sanofi immediately responded to the resistance by taking 50% off the price of Zaltrap (Palmer and Staton, 2012). This example shows why it has now become paramount for drug developers to demonstrate the superiority of a new drug over available alternatives, especially, when it is priced significantly higher than the alternatives.

Pharmaceutical companies are increasingly losing their control over drug pricing as governments around the world are taking radical measures to gain control over drug prices and determine reimbursement. Following are some selective country-specific

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examples of drug price controls in both developed (the UK, Germany and the US) and emerging markets (India and China).

In the UK, National Institute for Health and Care Excellence (NICE) of National Health Service (NHS) uses clinical data on new drugs to assess their cost and clinical effectiveness (value) and whether they could be reimbursed. NICE incorporates citizen council in this process, so patients also have their voices (PricewaterhouseCoopers, 2012a). In 2009, NICE set up a fee-based scientific consultation service for pharmaceutical companies in relation to their products in development that would be subject to future NICE evaluation (NICE, 2013). Pharmaceutical companies are collaborating with NICE to seek advice on clinical trial design to produce evidence of cost and comparative effectiveness. In January 2012, NICE recommended Tasigna, a leukaemia drug, from Novartis only when it agreed to offer the drug at a discounted price from its original price of £30,000 a year (Taylor, 2012a). In May 2013, NICE rejected Roche’s cancer drug, Avastin, due to the company’s failure to provide clinical data on about one-third of participants, and also due to the drug’s proven benefit not matching its single dose treatment cost of £25,000 (Staton, 2013a). Also, effective from January 2014, the UK government will switch to a ‘value-based pricing’ scheme, whereby medicines will be priced according to the benefits they deliver to patients. The scheme will reward only ‘breakthrough’ medicines rather than ‘incremental’ developments (Cooper, 2012).

In Germany, according to the ‘reimbursement modernisation act’ (2011), the launch price of new drugs fixed by drug developers stays effective for one year, and after that new drugs will be assessed for their extra clinical benefits over reference drugs in the market. If no superior clinical benefit is found, the pricing will be matched with that of reference drugs (PricewaterhouseCoopers, 2012a).

In the US, the Affordable Care Act sets out provisions (e.g. discounts) to reduce out-of-pocket pharmaceutical costs, which means branded drugs could see $97 billion in lost revenue over the next decade despite the gains from expanded health insurance coverage (PricewaterhouseCoopers, 2012b). US President Barack Obama’s budget proposal for the 2014 fiscal year proposes to accelerate the closure of Medicare part D coverage gap (the infamous ‘donut hole’) by 2015 through 75% discounts (a 25% increase from that in 2012) on branded drugs (Staton, 2013b).

India was set to launch from July 1, 2013 new price controls for 652 medicines with 348 of them classified as ‘essential drugs’. The new pricing would apply to drugs having a minimum market share of 1%, with some cancer and HIV drugs facing price cuts of up to 80% (Palmer, 2013a). Recently, India denied patent rights to a number of expensive cancer drugs, including Glivec of Novartis (sold as Gleevec in the US) and Sutent of Pfizer due to concerns that they are not affordable to most of the cancer patients in India. Also, the country is enforcing compulsory licensing of a number of branded cancer drugs (e.g. Roche’s breast cancer drug Herceptin, Bristol-Myers Squibb’s leukemia treatment Spryceel) to generic manufacturers so that cheap generic versions can be produced locally (Staton, 2013c).

China is no exception to such price control measures. In May 2012, China amended its IP law to introduce the provision of compulsory licensing of patented drugs to local generic manufacturers in unusual or emergency situations (Taylor, 2012b). In August
2012, China announced it would double its number of price-controlled ‘essential drugs’ to 700 in pursuit of affordable and universal healthcare for its population of 1.3 billion (Sweeney, 2012). To help reduce healthcare costs and make essential drugs available to a greater proportion of the population with basic medical insurance, in January 2013, the Chinese government announced forced discounts between 15-20% on 400 medicines that include several of big pharma’s biggest products (Staton, 2013d).

Emerging markets—opportunities and challenges

Emerging markets like China, India, Latin America and Africa hold big promises for the global pharmaceutical industry. The rising burden of chronic diseases like diabetes and expanding middle-class affluence in these markets are creating big opportunities for pharmaceutical companies (PricewaterhouseCoopers, 2012b). According to IMS Institute for Healthcare Informatics (IMS Institute for Healthcare Informatics, 2012), drug spending in emerging markets is estimated to increase from 20% of global spending in 2011 to 30% in 2016, whereas US and Europe’s combined share will shrink from 58% to 49%. The current African market size will double to $45 billion by 2020, and chronic non-communicable diseases such as heart disease, lung disorders, cancer and diabetes, are estimated to account for almost half of all deaths in sub-Saharan Africa by 2030 (Berton, 2013).

Big pharma is responding to emerging market opportunities by increasing their stakes in these markets. In 2012, the global pharmaceutical companies invested $20 billion in emerging markets, up from around $12 billion in 2011, and China accounted for nearly one-third of that investment (Hirschler, 2012a). Big pharma is forming joint ventures with local pharmaceutical companies in emerging markets. Between 2010 and 2012, for example, Pfizer, AstraZeneca, Sanofi and Merck formed joint ventures with local companies in China, India and Brazil to gain advantages in areas such as branded generics, vaccines, consumer healthcare as well as from joint clinical development programs (Burrill, 2013). They are expanding their R&D, manufacturing and sales networks in these markets. In December 2011, Merck announced it would establish a $1.5 billion R&D hub in Beijing to steer low-cost drug discovery and development operations (Carroll, 2011). Eli Lilly and Sanofi have slashed their sales forces in the US and Europe while expanding them in China. Novartis and AstraZeneca have also closed their manufacturing and R&D sites in developed markets while building new ones in emerging markets (Staton, 2012a).

But many challenges remain in emerging markets. Weak regulatory regimes and IP protection systems, and underdeveloped infrastructure are some. Also, lack of health insurance for the majority of populations in emerging markets means the patients themselves fund a larger share of drug costs than that of developed markets, and thus cannot support specialised drugs, e.g. biologic cancer drugs, that cost several thousands of dollars each (PricewaterhouseCoopers, 2012b; Burrill, 2013).

Though the middle-class affluence is growing, significant differences in per capita drug spending between developed and emerging markets will remain. According to
IMS Institute for Healthcare Informatics (IMS Institute for Healthcare Informatics, 2012), per capita drug spending in 2016 will be $609 and $91 for developed and emerging markets respectively. Such differences in drug spending capacity mean that big pharma cannot expect to reap much of the value of their high-priced patented drugs in emerging markets, and have to rely on large volume generic drug sales.

Big pharma is taking various strategies to meet these challenges. For example, Novartis signed a deal with Jiangsu provincial government in China on its cancer drug, Glivec. Novartis will donate three doses of Glivec to the government for each purchase of one dose. This will bring the annual Glivec treatment cost to about $12,000, down from the US wholesale price of about $77,000 (Staton, 2013c). GlaxoSmithKline has been pursuing an innovative approach through its 'least developed countries (LDC) business unit' in 40 African and 10 Asian countries. The unit has a 50-50 focus on business and reputation, and focuses on sales volume rather than profit margin. The patented drugs are discounted 75% or more from the UK price. The hybrid model achieved some early success as revenue was estimated to triple from £50 million in 2010 to £150 million in 2012 with 20% profit margin (Hirschler, 2012b). Facing patent attacks in India, recently, Roche devised plans to shift manufacturing of expensive cancer biologics in India through collaboration with a local pharmaceutical company, and also proposed between 30-55% price cuts on a few cancer drugs (Palmer, 2013b).

Healthcare reforms across many parts of the world and growing emerging markets are expanding global pharmaceutical markets and, hence, the value opportunities for pharmaceutical companies. However, the value of new drugs is now determined and perceived by value users, in particular payers and policy makers, based on the performance and benefits the new drugs deliver, and also based on market-specific needs. Therefore, the value of pharmaceutical innovation is no longer embodied in new drugs and new markets alone, or commanded by pharmaceutical companies; rather the benefits of new drugs delivered to and perceived by users in existing and new markets embody the value of pharmaceutical innovation. This can be called the 'perceived value'.

**Patent cliff—the end of 'blockbuster era'**

The patent expiry of many blockbuster drugs, also regarded as the 'patent cliff', is displacing the 'blockbuster era' of big pharma. As many of the blockbuster drugs are crossing the period of patent expiry and generic competition, the pharmaceutical industry is facing $290 billion of global prescription drug sales at risk (the value corresponds to sales in years prior to patent expiry), and $148 billion in potential loss due to patent expiry of branded drugs between 2012 and 2018 (EvaluatePharma, 2012). Pfizer’s cholesterol drug Lipitor which sold around $118 billion between 1996 and 2010, became the top selling drug of all time, and made Pfizer the world’s largest pharmaceutical company, went off-patent in November 2011 (Mehta, 2011). Lipitor, that earned nearly $11 billion in 2010, is projected to earn only $2 billion by 2016 (Datamonitor, 2011). The top ten drugs (according to their annual US sales in 2012) facing patent expiry in 2013, generated combined sales of nearly $15 billion in 2012, and are predicted to lose nearly $8 billion of that value by 2016 (EP Vantage, 2013).
Patent cliff is also changing the drug spending landscape in developed markets. According to forecasts by IMS Institute for Healthcare Informatics (2012), patent expiry of many blockbuster drugs will bring total drug spending in developed markets down by $127 billion from 2011 to 2016. Also, global brand drug spending is forecast to grow by only 8% from 2011 to 2016, compared to nearly 80% growth in global generic drug spending. According to the US prescription data from Express Scripts, a pharmacy benefits management organisation in the US, for the first time in more than 20 years, traditional prescription drug spending for common diseases (cholesterol or heart problems, ulcer, pain, depression, neurological disorders, and infections) fell in 2012 due to increased use of low-cost generics. There was significant increase in the use of these drugs by Medicare and Medicaid patients in many therapeutic areas (e.g. diabetes); however, low-cost generics replacing patented blockbuster drugs brought traditional prescription drug spending down. This trend will most likely continue in the short term, and by 2015, spending on traditional prescription drugs for different diseases in the US is expected to drop between 10-25% (Frazee, 2013; Stettin, 2013).

In contrast, spending on specialty drugs for chronic, rare and complex diseases is increasing. Spending on specialty drugs represented one-fourth of total 2012 drug spending within pharmacy benefits in the US, and is predicted by Express Scripts to grow 67% over the next three years. Specialty drugs treat diseases like cancer, HIV, hepatitis C, multiple sclerosis, and rheumatoid arthritis (Frazee, 2013; Stettin, 2013). They are mostly high-priced drugs prescribed by specialists, and involve ongoing patient follow-up and clinical monitoring (IMS Institute for Healthcare Informatics, 2012). Specialty drugs can be orphan drugs to treat rare diseases such as Novartis' Signifor, approved by the US FDA as an orphan drug in 2012, for treatment of Cushing’s disease (Mullard, 2013). Many specialty drugs are biological drugs (or, biologics) that include vaccines, recombinant proteins, and cell, tissue or gene-based therapeutics produced from microorganism, animal or human sources (FDA, 2010).

To overcome the revenue loss due to patent expiry of blockbuster drugs, big pharma is expanding its pipelines with specialty drugs that not only have high growth potential but also offer a number of advantages over traditional drugs. They are high price drugs for niche markets, their complexity makes them less vulnerable to generic competition than traditional drugs, and they require shorter development timeframe with smaller clinical trials on specific targeted patients than do traditional small molecule drugs (Staton, 2013). Big pharma is making merger and acquisition (M&A) or in-licensing deals with specialty pharmaceutical or biotechnology companies to tap their portfolio of specialty drugs. Pfizer’s $68 billion acquisition of Wyeth in 2009 was aimed at strengthening its pipeline with biologics and vaccines that potentially offer high profit margins but requires only limited marketing expenses (Burrrill, 2011). In 2012, Johnson & Johnson in-licensed leukaemia antibody drug ‘daratumumab’ from biotechnology company Genmab for $1.1 billion (Carroll, 2012), and in 2013 US FDA awarded the drug ‘breakthrough’ designation (Carroll, 2013). According to a new law adopted by the US FDA in 2012, the regulatory agency designates ‘breakthrough’ status to drugs that show significant improvements in treating serious or life-threatening diseases during clinical trials in order to fast-track their development and approval (Loftus, 2013). Very recently, GlaxoSmithKline has acquired Swiss bio-
technology company Okairos for $325 million for its genetic vaccine development platform against hepatitis C, HIV, malaria, tuberculosis and human respiratory syncytial virus (Carroll, 2013b).

Several big pharma companies are also upscaling or commissioning biologic manufacturing operations in both developed and emerging markets. In 2012, Novartis invested $500 million to build a new biologic manufacturing plant in Singapore for supply of biologics in adjacent Asian markets, and AstraZeneca opened a biologic manufacturing plant in China through a joint venture with a Chinese company (Palmer, 2012). Also, companies like Eli Lilly and Bristol-Myers Squibb are expanding their biologic R&D and manufacturing operation in the US (Palmer, 2013c).

To cut back costs and balance the revenue loss from diminished value of off-patent drugs, big pharma is slashing its primary care sales force in developed markets that focused on patented blockbuster drugs, and is keeping the sales force small for specialty drug marketing (Staton, 2012b). Big pharma is turning to emerging markets to grab the share of the market that is predicted to reach as high as $375 billion by 2016. Big pharma is also taking control over many generic manufacturers, primarily in emerging markets through joint ventures, to capture the value of global generic markets that will grow from around $240 billion in 2011 to $430 billion in 2016. In 2012, Pfizer formed joint venture with China’s Zhejiang Hisun Pharmaceutical to develop and manufacture branded generics for China and global markets. In 2010, Abbott became one of India’s largest generic drug manufacturers by acquiring Piramal’s Healthcare Solutions for $3.7 billion (IMS Institute for Healthcare Informatics, 2012, Burrill, 2013).

The path ahead for big pharma is one that encompasses a conglomeration of diversified business models targeted at developed and emerging markets. In developed markets, big pharma will focus on high price specialty drugs for chronic, complex and rare diseases, and low price generics for common diseases to replace the value of blockbuster prescription drugs. In emerging markets, big pharma will extend its value through increasing its stake in branded and low-cost generic manufacturing for both developed and emerging markets.

Soaring R&D costs and declining R&D productivity

In the last decade or so, pharmaceutical companies have experienced phenomenal growth in the cost of bringing new drug candidates from the lab to the market. R&D budgets of pharmaceutical companies climbed as well to manage ever increasing drug development costs. But there has not been concomitant growth in the number of truly innovative or potential revenue-generating new drugs (in relation to R&D expenditures) launched in the market (Paul et al., 2010). A number of studies over the last decade attempted to estimate the average cost of drug development, from discovery through preclinical and clinical development to regulatory approval, based on internal industry data as well as external industry survey data. A 2012 study by London-based Office of Health Economics (Mestre-Ferrandiz et al., 2012) calculated the average out-of-pocket cost of bringing a new drug to market as $900 million (in 2011 dollar prices). This cost includes the costs of all drug candidates that fail at different development stages before one reaches the market. Another 2010 study (Paul et al., 2010) estimated
the out-of-pocket cost of single drug development as $873 million (in 2008 dollar prices). Two previous studies, published in 1991 (DiMasi et al., 1991) and 2003 (DiMasi et al., 2003), determined the out-of-pocket costs per single drug development as $114 million (in 1987 dollar prices) and $403 million (in 2000 dollar prices), respectively.

However, a 2012 Forbes article shows that the amounts of dollars spent on R&D by different big pharma companies to produce a single drug are around four to twelve times higher than the empirical out-of-pocket costs described above (Herper, 2012). In this article, average R&D spending per approved drug of eleven big pharma companies is calculated by dividing each company’s total R&D spending by its total number of drugs approved between 1997 and 2011. This is illustrated in Table 1.

<table>
<thead>
<tr>
<th>Company</th>
<th>Total R&amp;D Spending 1997-2011 ($ billion)</th>
<th>Number of Approved Drugs</th>
<th>Average R&amp;D Spending Per Drug ($ billion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AstraZeneca</td>
<td>59.0</td>
<td>5</td>
<td>11.8</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>81.7</td>
<td>10</td>
<td>8.2</td>
</tr>
<tr>
<td>Sanofi</td>
<td>63.3</td>
<td>8</td>
<td>7.9</td>
</tr>
<tr>
<td>Roche</td>
<td>85.8</td>
<td>11</td>
<td>7.8</td>
</tr>
<tr>
<td>Pfizer</td>
<td>108.2</td>
<td>14</td>
<td>7.7</td>
</tr>
<tr>
<td>Johnson &amp; Johnson</td>
<td>88.3</td>
<td>15</td>
<td>5.9</td>
</tr>
<tr>
<td>Eli Lilly</td>
<td>50.3</td>
<td>11</td>
<td>4.6</td>
</tr>
<tr>
<td>Abbott Laboratories</td>
<td>36.0</td>
<td>8</td>
<td>4.5</td>
</tr>
<tr>
<td>Merck</td>
<td>67.4</td>
<td>16</td>
<td>4.2</td>
</tr>
<tr>
<td>Bristol-Myers Squibb</td>
<td>45.7</td>
<td>11</td>
<td>4.2</td>
</tr>
<tr>
<td>Novartis</td>
<td>83.6</td>
<td>21</td>
<td>4.0</td>
</tr>
</tbody>
</table>

Table 1: R&D Spending by Big Pharma per Approved Drug

According to Table 1, with its lowest number of approved drugs, AstraZeneca spent the highest average of $11.8 billion for each approved drug. In contrast, Novartis’ highest number of drug approvals brought its average R&D spending for each drug to the lowest. Table 1 shows how expensive it is to bring a new drug to the market, and may, therefore, justify the extraordinary high price of many specialty drugs. However, the figures raise the question of why big pharma’s R&D spending for each drug (from $4 billion to nearly $12 billion) is so much higher than the empirical R&D costs (less than $1 billion), and where does big pharma lose its R&D money? Billions of dollars in lost R&D can be attributed to a number of factors. The new drugs being developed are faced with the challenges of demonstrating to regulators and consumers their superiority in safety, efficacy and value over many available therapeutic modalities. Many dec-
ades of scientific and technological advances have resulted in many successful therapeutic modalities for diseases like cancer and diabetes. This, in turn, has raised the challenges for new drugs to prove their superior value. Such challenges have been met by expanding the size, number and duration of clinical trials that have significantly added to R&D costs. Millions of dollars have already been spent before many of the new drug candidates in late development stages fail to demonstrate their superior value. Scientific and technological advances have also increased the precision of therapeutic targets, and the need to show precise effectiveness of new drugs on those targets. Many drug candidates fail such precision tests (Munos, 2009; Paul et al., 2010; Scannell et al., 2012; Northrup et al., 2012).

In order to sustain productivity, big pharma needs to close the gap between what R&D per new drug candidate should cost and what big pharma spends on R&D. This means big pharma’s R&D spending is not significantly higher than the empirical out-of-pocket R&D costs, and thus the value created in new drugs through R&D substantially exceeds big pharma’s R&D spending on new drugs. R&D productivity of big pharma is also declining steadily as high-value brands are increasingly being taken over by low-value generics, high price and other existing brands are facing forced discounts and price cuts, and many drug candidates are failing during development. As the ‘blockbuster era’ is coming to an end, and multi-billion dollar brands are becoming scarce, expensive R&D budgets are becoming unsustainable.

Open Innovation networks and improving R&D productivity

Many big pharma companies are joining forces with leading academic researchers as well as biotechnology and pharmaceutical companies to boost early stage drug discovery research and improve R&D productivity. In November 2010, Pfizer launched ‘Global Centers for Therapeutic Innovation’ in the US to develop an open innovation style network of partnerships with leading academic medical centres in the US to combine their scientific expertise in drug discovery with Pfizer’s drug development capabilities. The purpose is to establish a number of Pfizer funded local research centres at the medical centre sites. At these centres academic researchers and Pfizer’s protein and development scientists will jointly perform early stage discovery and clinical research with Pfizer’s proprietary protein libraries to develop novel and differentiated biologic drugs (Pfizer, 2010; Allarakhia, 2011). Johnson and Johnson is also setting up innovation centres in Boston, San Francisco, London and Shanghai. These centres will be working to find local drug discovery expertise among academic and biotechnology communities and create collaborations with them (Carroll, 2013c).

In August 2012, ten of the large pharmaceutical companies launched a precompetitive and non-profit joint venture in the US, called TransCelerate Biopharma. This initiative aims to facilitate the sharing of capabilities and resources to find and accomplish efficient and cost-effective models of R&D. The ten companies are Abbott Laboratories, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Pfizer, Roche’s Genentech unit and Sanofi. TransCelerate Biopharma initially set the goal of reducing bottlenecks in clinical development such as
cost and length of clinical trials by streamlining and standardising clinical trial functions (McBride, 2012a; Burrill, 2013).

In October 2012, GlaxoSmithKline, in an open innovation approach, announced its intention to publish its clinical data on 200 compounds, with potential anti-tuberculosis (TB) properties, to allow external researchers to use them in TB drug development (McBride, 2012b). In another open innovation approach, in February 2013, seven of Europe’s large pharmaceutical companies, including Bayer, AstraZeneca, Johnson & Johnson group’s Janssen Pharmaceutical, Sanofi, Merck KGaA, in collaboration with 23 other universities, research organisations and small- to medium-sized biotechnology companies, launched a €196 million drug discovery platform, called ‘European Lead Factory’. It was built to boost drug discovery by exploiting cutting-edge academic research, and produce a large library of half a million chemical compounds with therapeutic potentials for screening and development (McBride, 2013). In early 2013, the European Commission launched a $187 million research initiative which brought 300 investigators from academia, pharmaceutical and biotechnology companies across 29 countries under one roof with the plan to find 200 treatments for rare heart, liver and kidney diseases by 2020 (Carroll, 2013d).

Delivering value to users

As payers are taking charge of determining the value of new drugs, big pharma is collaborating with payers to develop models of identifying and pinpointing value users (treatment responsive patients), evaluating comparative effectiveness of new drugs, and delivering perceived value to users. In 2011, Pfizer established a collaboration with Medco Health Solutions, a pharmacy benefits management organisation in the US, to integrate identification of patient subgroups through genomic and phenotypic characterisation that are most likely to respond to new and existing drugs. Pfizer also established collaboration with Humana, a managed healthcare (insurance) company in the US, to identify and implement ways to improve quality and cost-effectiveness of chronic disease management. Also, in 2011, Sanofi formed a collaboration with Medco Health Solutions to precisely identify treatment responsive patient populations, and develop patient care models to improve healthcare practice, treatment adherence and patient outcomes (Burrill, 2013).

Additionally, big pharma is pursuing risk-sharing agreements with payers whereby rebates, discounts or refunds on new drugs are offered by them to cover the cost of drugs having treatment response failure or response rates below expectations compared with existing alternatives. Such agreements include GlaxoSmithKline’s agreement with NICE to offer rebate on kidney cancer drug Votrient if it is found inferior to Pfizer’s similar drug Sutent, and with AIFA (Italian Medicines Agency) to pay for patients not responding to 24 weeks of treatment with Votrient (Ernst and Young, 2013).

To better demonstrate the effectiveness and value of new drugs to regulators and payers, big pharma is focusing on the development of personalised medicines. As the name implies, personalised medicines work on a specific patient subgroup who express a particular disease trait. The disease trait is identifiable by a companion diagnostic test. So, by using the diagnostic test the patient subgroup can be selected for treatment with
personalised medicines. In May 2013, GlaxoSmithKline won US FDA approval for two advanced skin cancer drugs, Tafinlar and Mekinist. The drugs target skin cell tumours with mutations to the BRAF gene. BRAF gene mutation accounts for half of all skin cancer cases. Alongside the two drugs, US FDA approved a molecular diagnostic test, ‘THxID BRAF mutation test’, developed by French company bioMérieux. In clinical trials, the diagnostic test was used to select patients with the BRAF gene mutation and this helped the cancer drugs to produce satisfactory results (Carroll and McBride, 2013; Garde, 2013).

Big pharma is also building innovative healthcare delivery models in many emerging markets through engaging doctors, patients and policy maker stakeholders in various healthcare initiatives. In 2007, Novartis started a program called ‘good health of the family’ in India. As part of the program, Novartis trained 500 people to partner with rural doctors to organise health education meetings for villagers. Also, Novartis representatives were handing out referral cards to patients that they could take to doctors and pharmacies with stocks of Novartis drugs for rural diseases like diarrhoea and pneumonia (Sharma, 2010).

Sanofi, in 2009, also initiated a program in India, called ‘endeavour’. As part of the program, Sanofi engaged volunteer city doctors to mentor rural doctors. By 2010, it had sponsored workshops for more than 5,500 doctors, and planned to include 100,000 doctors by 2015 (Sharma, 2010).

In 2011, Sanofi announced its support for China’s integrated diabetes management program, called ‘China Initiative for Diabetes Excellence’, jointly launched by China’s Ministry of Health, Chinese Center for Disease Control and Prevention, and the Chinese Diabetes Society of the Chinese Medical Association. The program was designed to develop 500 diabetes care and public health experts who would collaborate with grassroots-level doctors to deliver diabetes care. The program also aimed to train 10,000 community and county doctors on delivery of diabetes patient education (Sanofi, 2011).

In April 2013, Sanofi announced the opening of a €20 million new logistics hub in Casablanca, Morocco, for distribution of Sanofi drugs to Moroccan and sub-Saharan African markets. Sanofi also signed three collaboration agreements with the Ministry of Trade, Industry and New Technologies and the Ministry of Health of Morocco with the aim of 1) developing standard care protocols and therapeutic education programs for type I diabetes patients, 2) training neurologists, psychiatrists, general practitioners and nurses, and raising public awareness to facilitate care for patients with mental disorders and epilepsy, and 3) contributing to the development of Moroccan pharmaceutical industry by training people for careers in the pharmaceutical industry (Sanofi, 2013).

Conclusion

The big pharma-dominated pharmaceutical industry has long enjoyed the success of innovation through its integrated model of commercialising blockbuster drugs. The success was achieved through big pharma’s ability to create and command the value that was embodied in its blockbuster drugs. Healthcare reforms in many developed and emerging countries and growing emerging market needs are expanding opportunities.
However, drug pricing and reimbursement pressures from governments and payers, increasing dominance of generic drugs over patented blockbuster drugs and rising R&D costs are impeding big pharma’s growth. Big pharma is responding to these opportunities and challenges by adapting its innovation models. As the analyses in this paper point out, while the value of pharmaceutical innovation is embodied in new drugs, the value of new drugs is now determined by market-specific users based on the benefits of these drugs they can access. The success of new drugs now depends on how users in differentiated markets access and perceive their value. Consequently, big pharma is complementing its model of creating value through new drugs and new markets with one that is focused on making the benefits (value) accessible to users.

In the new model, pharmaceutical innovation is open in the sense that big pharma is pursuing innovation in-house as well as through collaborative networks with external innovators, and commercialising innovation by exploiting in-house capabilities as well as through various external partners. This is consistent with Chesbrough’s (2003, pp. 37) definition of open innovation, ‘a company commercialises both its own ideas as well as innovations from other firms and seeks ways to bring its in-house ideas to market by deploying pathways outside its current businesses’. However, there is another degree of openness in the new model of pharmaceutical innovation. The value is created by big pharma as innovators through new drugs and new drug markets; but, as discussed in this paper, the value is embodied as perceived value in the benefits of new drugs. The perceived value is created by both big pharma and the value users, including payers, patients, physicians and policy makers, through various value propositions such as drug price cuts, discounts, specialty drugs, branded generics, personalised medicines, treatment responsive patient identification and risk-sharing agreements with payers, and joint healthcare delivery initiatives.

Through illustrations of big pharma’s various responses to external and internal forces of innovation, this paper also points toward a new landscape of the global pharmaceutical industry. As healthcare demands of emerging markets are steadily increasing, the long prevailing developed market-centric pharmaceutical industry is becoming increasingly focused on emerging markets. However, a division of value proposition between developed and emerging markets is also becoming evident. In developed markets, big pharma is aiming cumulative returns from multiple niche chronic care markets with its high value specialty drugs by exploiting established healthcare financing systems. In emerging markets, where healthcare financing systems are still in their infancy, big pharma is aiming for low value but high volume returns from a sharply expanding healthcare consumer market with its heavily discounted specialty drugs and low value generics of patented blockbuster drugs. Since the value of traditional blockbuster drugs are diminishing rapidly, big pharma is seeking ways to capture value from new markets, such as specialty drugs for unmet, rare diseases, and drugs for disadvantaged and uninsured consumers in vastly untapped global markets. In the new landscape, the value of pharmaceutical innovation lies in the path towards new opportunities. The path forward for the big pharma-dominated pharmaceutical industry is one that makes a shift from product-centric innovation towards market-centric innovation.

On the one side, healthcare reforms, drug price controls and dominance of low price generic drugs are paving the way for accessible healthcare for the majority of
population in both developed and developing ends of the world; on the other side, the market-centric pharmaceutical innovation models are creating ways to deliver the value to users. In tomorrow’s world, as this paper finds, healthcare will not only be cheap and accessible to all, but also efficient and manageable to healthcare stakeholders.

Correspondence

Tariq Sadat, PhD Candidate
School of Economics, Finance and Marketing
RMIT University, GPO Box 2476
Melbourne VIC 3001
Australia
Email: tariqhai@yahoo.com

Roslyn Russell, Professor
School of Economics, Finance and Marketing
RMIT University
Email: roslyn.russell@rmit.edu.au

Mark Stewart, Senior Lecturer
School of Economics, Finance and Marketing
RMIT University, Email: mark.stewart@rmit.edu.au
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SHIFTING PATHS OF PHARMACEUTICAL INNOVATION


