Understanding Big Pharma

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The Open Health Initiative (OHI) is focused on stimulating innovation in the development of viable health interventions that address the neglected portion of the global burden of disease. In recent years there has been a concerted effort involving philanthropic organizations such as the Gates Foundations, a number of pharmaceutical companies and multilateral organizations to tackle the 'Big Three' diseases—malaria, HIV and TB—as well as the neglected tropical diseases, which include Leishmaniasis, Dengue, Sleeping Sickness and River Blindness[1]. Where there is real evidence that progress has been made in the development of interventions (Moran, 2005) it is also clear that there are wider structural issues in the pharmaceutical sector. This sector has seen major consolidation, with a dramatic reduction in the number of 'big pharma' companies, an acute focus on blockbuster drugs to treat, inhibit or limit conditions such as diabetes, heart disease and cancer and an overall decline in the number of drugs that are presented for regulatory approval. Threats to pharma include the rise of generic manufacturers, litigation focused on the safety of the declining number of drugs and a window in 2008-9 where a significant number of high revenue generating drugs come off patent. The purpose of this paper is to summarise some of the structural challenges facing the pharmaceutical sector in order to provide some context for understanding their response to the development of interventions that address the global burden of disease.

Background

For the last fifty years, pharmaceutical companies have been the main driver of innovation in the healthcare sector. The innovation model was based on a tacit contract between governments, the public and society. The contract recognized that

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[1] http://www.who.int/neglected_diseases/diseases/en/

government agencies are poorly equipped, incentivized and financed to innovate in the development of new healthcare interventions. In return for assuming the risk of investing in R&D, companies are granted monopoly control of the intellectual property they generate in order to recover their investment cost and to generate a return on investment that meets the expectations of the financial community[2]. New drug development takes up to 12 years and estimated costs are as high as $800m by some estimates. There are three elements to these costs: the cost of drug development, the costs of R&D investment into failed drugs and the opportunity cost of capital. In a typical drug development process, 10,000 molecules screened, an average of 250 enter preclinical testing, 10 make it through to clinical trials and only 1 is approved by the regulator (Economist, 2005: 8431). Historically the investment community has been rewarded for investing in drug development. With sales of $550bn by the dozen 'Big Pharma' companies representing 50% of the global drug retail market and operating margins of more than 25%, some critics have questioned whether the companies have become too large[3]. In addition, 40% of the market for pharmaceutical companies is in the US. If one of the criteria for a blockbuster drug is that it generates $1bn in sales, then companies will tend to focus on the largest markets, which results in a focus on conditions that are more prevalent in the US market.

While the sector is large and historically has been highly profitable, a number of commentators have pointed to warning signs about the future. Firstly, the pipeline of drugs under development has slowed very significantly over the last decade. While the FDA approved 53 new drugs in 1996, in 2004 they approved just 21 new drugs[4] and by 2007 the figure had dropped to 18. This is in spite of a significant increase in investment; the US pharmaceutical industry group reported a 20%

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[2] In the US, property rights received constitutional protection very early on in the history of the nation.

[3] Prescription for change. Economist, 00130613, 6/18/2005, Vol. 375, Issue 8431

[4] Fixing the drugs pipeline. Economist, 00130613, 3/13/2004, Vol. 370, Issue 8366

increase in R&D spending between 2004 and 2007. Global expenditure on R&D is in the region of $60bn annually[5]. The figures indicate either a decline in the number of products under development or a strategy that focuses on a much smaller number of blockbuster drugs that are expected to generate higher returns overall[6].

Secondly, some of the strongest earning drugs have moved 'off-patent' over the last five years and as a result are facing competition from generic drug manufacturers. GSK lost patent protection on two key drugs in 2004: the antidepressant Paxil and the antibiotic Augmentin. It is predicted that one fifth of the market ($30bn) in the US alone will face competition from generic manufacturers by late 2008[7]. One estimate suggests that in the US in 2009, drugs worth $17bn will go off-patent[8]

Thirdly, the costs associated with the launch of a new drug are high in the first two years and in some cases they represent replacements for existing drugs. This exacerbates what some have called the 'marketing and sales arms race'[9] as companies spend on advertising to compete for the public's attention.

Fourthly, pharmaceutical companies have been placed in a strongly defensive position as a result of a series of legal actions in the US including the ongoing Vioxx case. The strategy of focusing on a smaller number of blockbuster drugs leaves companies vulnerable to both legitimate suits related to the safety of their drugs and more frivolous suits that trade on the willingness of US courts to grant very large damages to patients in the US. A related issue is the emergence of suits that

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[5] Billion dollar pills. Economist, 00130613, 1/27/2007, Vol. 382, Issue 8513.

[6] More R&D: Not Boosting Big Pharma. By: Saftlas, Herman, Business Week Online, 00077135, 10/30/2008

[7] Big trouble for Big Pharma. Economist, 00130613, 12/6/2003, Vol. 369, Issue 8353.

[8] More R&D: Not Boosting Big Pharma. By: Saftlas, Herman, Business Week Online, 00077135, 10/30/2008

[9] Billion dollar pills. Economist, 00130613, 1/27/2007, Vol. 382, Issue 8513

challenge the solidity of the patent on which drugs are based. AstraZeneca faced three patent challenges in the US in 2008; companies face challenges that are legitimate in the face of sloppy patent review and speculative efforts by so called patent trolls who may gamble that it is cheaper for a patent holder to settle than to go through a lengthy court case.[10] In addition, pharmaceutical companies face greater scrutiny from regulators regarding their pricing policy and the safety of drugs[11]

Consolidation

The consolidation strategy acted out over the last eight years has seen the total number of large pharmaceutical companies decline from around 22 key players to around 10 in early 2009. The strategy of merging resources in order to generate economies of scale has forced already large multinationals into almost unprecedented alignments. While the trend towards mergers increased in the nineties there has been so much consolidation that any further activity will be to pick up companies that have been financially weakened in recent years[12].

Drug companies have also responded by reducing their workforce significantly—Abbott Laboratories cut 2000 jobs in 2004 and Merck cut 4000 job—and also by shifting to licensing from smaller or foreign companies[13]. These changes represent the early signs of a shift away from an industry structure that has traditionally been highly vertically integrated. Companies not only seek to buy innovation from

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[10] More R&D: Not Boosting Big Pharma. By: Saftlas, Herman, Business Week Online, 00077135, 10/30/2008.

[11] More R&D: Not Boosting Big Pharma. By: Saftlas, Herman, Business Week Online, 00077135, 10/30/2008

[12] For Drugmakers, There's No Panacea. By: Arndt, Michael, Business Week, 00077135, 1/12/2004, Issue 3865

[13] For Drugmakers, There's No Panacea. By: Arndt, Michael, Business Week, 00077135, 1/12/2004, Issue 3865

smaller startups, but increasingly outsource testing to Contract Research Organisations (CRO) in order to reduce costs. The challenge is that the round of consolidation in the nineties created even larger companies that cut costs in the short term in areas where there was redundancy in their structure, but ultimately created a more unwieldy R&D bureaucracy[14]

Generics in developing countries

The growth of the generic pharmaceutical companies has been identified as a threat to the supremacy of big pharma. While some commentators expected that home-grown companies in India and China in particular, might focus on interventions for conditions that are more common in developing countries, studies have shown that the proportion of R&D investment dedicated to diseases in Less Development Countries (LDC) is around 16% of the total[15]. More recent research suggests the figure in India, where the R&D budgets of the largest ten companies amounts to $170m could be as low as 10% (Lanjouw, 200%). Companies in India such as Nicholas Piramal and Ranbaxy focus on the development, refinement and manufacture of generics for western markets and for growing middle class populations, facing a burden of disease associated with rising affluence. While most health care services are still purchased privately in India and China, constraining the total size of the market, growth rates of 10% and 19% annually still look very attractive to pharmaceutical companies[16]. Ironically, while companies have responded to pressure to make generic drugs available in poorer developing countries that could never afford them at market rates, there is some concern that

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[14] Billion dollar pills. Economist, 00130613, 1/27/2007, Vol. 382, Issue 8513.

[15] Lanjouw, J. 2002, Intellectual Property and the Availability of Pharmaceuticals in Developing Countries, Center for Global Development, Working Paper 5.

[16] The next big thing. Economist, 00130613, 6/18/2005, Vol. 375, Issue 8431

providing 'at cost' or donated drugs to India and China could cannibalise sales to the middle classes[17]

India has been most successful at innovating in the modification of new manufacturing processes for established drugs, while China's growth has been driven by increases in manufacturing capacity for generics, with less modification to the underlying molecules involved. China has also become a key jurisdiction for clinical trials. The implication is that India has a more market driven and entrepreneurial R&D and pharmaceutical sector, while China is inhibited by the dominance of less entrepreneurial state run enterprises in the sector. Part of the reason for India's success was that for many years the IP systems focused on process patents, which encouraged developers to find novel ways of manufacturing an established drug. In 2005, India recognized full product patents, which was one of the conditions of entry to the WTO. This has opened the door to Western investment in Indian pharmaceutical capacity although concerns still remain about whether patents will be enforced. Both India and China have become threats to large pharmaceutical companies, some of which have responded with strategic alliances and by pushing some R&D offshore.

In some cases, upstart companies are tackling Big Pharma head on: India's Ranbaxy challenged Pfizer's patent on Lipitor in the US. In other cases, Indian companies have focused on reducing the cost of manufacturing for drugs that are nearing the end of their patents, so they can compete directly on price[18]

Opening up?

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[17] The next big thing. Economist, 00130613, 6/18/2005, Vol. 375, Issue 8431

[18] The next big thing. Economist, 00130613, 6/18/2005, Vol. 375, Issue 8431. Levy notes 'find this somewhat questionable because manufacturing costs are historically a fairly small proportion of sales costs. Still, whatever you can save on the costs side, the better off you are.'

Despite these changes, pharmaceutical companies remain highly vertically integrated, compared to other manufacturing sectors[19]. Part of what drives this integration is the need to generate and control the core intellectual property at the heart of drug development. Drug companies have also pursued defensive strategies to retain control and to maintain the value invested in their existing drug portfolio. In some cases, there is real concern that defensive approaches block drug development as 'patent thickets' create gridlock. Michael Heller describes treatments for Alzheimers and cancer that have been set aside because any one of a number of patent holders can veto commercialization. These constraints are also likely to frame the kinds of interventions that drug companies will pursue: simple single molecule interventions are less prone to defensive action by other patent holders than complex treatments.

Drug companies have also responded innovatively, or some might say, cynically, by relicensing drugs that are reaching the end of their patent for new conditions, creating a new marketing campaign and promoting a new 'on-label' use. When Eli Lilly's patent expired on prozac, it was suggested that they simply applied for a new patent for a new disorder with the same basic molecule and sold a new treatment for Premenstrual Dysphoric Disorder as Sarafem[20]. In addition, the class of orphan drugs in the US—treatments for conditions that affect relatively small populations—receive expedited approval in order to create incentives for companies to invest in neglected conditions in developed countries (although the original legislation didn't support expedited review). On the one hand, this mechanism has created incentives for companies to increase investment in orphaned diseases like Cystic Fibrosis. On the other hand, there is some evidence that drug companies have targeted orphan

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[19] Billion dollar pills. Economist, 00130613, 1/27/2007, Vol. 382, Issue 8513

[20] Peter Huber, 2006, Of Pills and Profit: in defense of big pharma, Commentary, July-August: while this example reflects negatively on the tactics of big pharma, generally the piece is sympathetic to challenges they face. Comment from Levy: This appears to be mixing up patent and regulatory matters. I should check the ref.

diseases in order to take advantage of the expedited review process, knowing that doctors can prescribe an approved drug for off-label uses, as long as there is good scientific data to demonstrate efficacy.

At the margins, some companies have begun to change the way drugs are created. In an attempt to engage more university academics, Pfizer has published its drug pipeline on the internet in order to attract more researchers. Managers at Eli Lilly created a company called Innocentive which published known challenges or problems in the pharmaceutical sector and beyond to a network of thousands of researchers. The problems are priced according to their difficultly, creating a new incentive structure for innovation, although the IP is owned by Innocentive or the companies it represents.

The broader diagnosis of the challenges caused by IP systems in companies will be dealt with in a separate paper, but it is worth noting the concerns of commentators like Michael Heller, who describe the problems caused by 'too much ownership' resulting in fragmented property claims that stifle innovation as rival and overlapping patent holders create patent thickets around potential drugs.

In the face of heavy criticism of the pharmaceutical industry and its failure to innovate effectively, or to deal with neglected diseases, the key unanswered question is 'who else would take on the risk of drug development in modern industrial societies'?[21] To put it another way, while there have been changes in the processes of drug development for neglected diseases since 2000, when philanthropic public private partnerships appeared on a larger scale, much of the risk taking and research still occurs in large pharmaceutical companies.

Conclusions

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[21] Peter Huber, 2006, On Pills and Profit: in defense of Big Pharma, Commentary, July-August 2006.

Footnotes

"Big Pharma spends as much as it does on pinkand-lavender branding because Vaniqa economics rule; because price discrimination, though economically essential, is difficult to sustain; because big insurers have so much power to flatten prices; and because patent laws are too porous to fend off me-too competitors. Few companies manufacture vaccines because vaccines are so essential that they are sold mainly to the government, at reasonable-and-uniform— which is to say rock-bottom—prices, and because the seller may well be bankrupted by lawsuits if a problem is uncovered only after tens of millions of healthy people have been vaccinated." Huber, 2006