

Covered in this issue:

US Elections

**Exploring the Value of
Pharmaceutical Investment**

Greater Value for Public Safety?

**US Elections: The Impact of
“Change” on Tomorrow**

The 2008 US election results have now sunk in – President Barack Obama will bring a new approach to national policy across a range of issues, and he will enjoy Democratic Party majorities in both houses of Congress. Democrats will control the Presidency and Congress for the first time since the 1992 elections brought Bill Clinton to power. Then, as now, equity in access to healthcare was a burning issue. In the four presidential terms since then much has changed and great advances have been made in the potential of biopharmaceutical management of a myriad of diseases and conditions. Yet – with the notable exception of Medicare Part D, the outpatient prescription drug program for seniors – fundamental questions about lack of insurance, underinsurance, and the Federal Government’s role in ensuring healthcare still loom large. Will the US intervene more heavily in price determination or negotiation? Can a national plan to improve the status of uninsured Americans (whose numbers could swell to 67 million if no action is takenⁱ) be wrought and implemented? How will the pitfalls of the Clintonian healthcare reform plan – which went down in flames a decade and a half ago – be navigated?

Given Obama’s goal of increasing and improving access while controlling costs, government under his direction is likely to play a major role in establishing policies that encourage coverage. (Obama’s proposals technically mandate coverage only for those 25 years old and younger. While requiring employers to provide insurance or else pay the government, they do maintain current tax treatment of insurance premiums and provide subsidies to ensure affordability, with the result that, according to independent

analysis, they will cover 47% of the currently projected uninsured over 10 yearsⁱⁱ). Due to his belief of a failure by markets to operate on the scale necessary to provide broad coverage, tens of millions of individuals would be able to seek coverage through a new national insurance scheme.

The totality of this proposed new program is expected to cost \$1.6 trillion over 10 years, with costs continuing to rise every year. To put that cost in proportion, federal spending on the Medicare and Medicaid programs in fiscal 2008 was over \$660 billion.^{iv}

“The market alone cannot solve the problem – in part because the market has proven incapable of creating large enough insurance pools to keep costs to individuals affordable.”ⁱⁱⁱ

– Obama 2006

The vast majority of that goes to non-drug costs; for example, Medicare Part D (one of several federally supported programs that have a drug budget) came in under budget in 2008 at less than \$40 billion. However, drug prices remain a relatively easy and politically attractive target for management, in comparison to areas such as hospital costs (although the federal and state governments already pay for more than half of hospital spending), notoriously difficult to control issues like fraudulent claims^v, and so on.

While the Obama proposals contain numerous important means by which to achieve cost savings, such as general improvements in efficiency and greater use of technology, there are two that should create significant pause within the biopharmaceutical industry. The first is the potential for the Federal Government to negotiate prices directly with manufacturers for drugs paid for within the Medicare program. The second is the potential creation of a national cost effectiveness evaluation body, a controversial and likely costly step.

Uncertainty in the Markets

Unpredictable forces will continue to be at play in the US economy as the new government takes office in January. On the one hand, it is entirely possible that turmoil in financial markets, economic recession, and growing unemployment will distract policymakers from seeking a solution to the nation’s un/underinsurance and ballooning healthcare budgets. On the other, the same forces may result in an even worse coverage situation and a heightened sense of urgency, as individuals lose jobs and as companies scale back on benefits for employees.

In addition, healthcare equality figures prominently in the Democratic Party's platform^{vi}, and has been a pillar of Obama's campaign. Like other key areas targeted for change^{vii}, the President-elect will seek to maintain momentum on this critical issue. At the same time, there is likely to be a desire to reconcile political differences with the disparate Democratic Party and even to reach across the aisle for some degree of Republican support. In an environment in which federal bailouts are expanding and the government is taking ownership stakes in financial institutions, the possibility of even greater government intervention in free markets through direct price negotiations – which, with the purchasing power of the government behind them will easily become price controls – may hit a sour note among the more non-interventionist members of Congress.

However, the questions of government-led price negotiations and cost-effectiveness evaluations are also linked to the long-term sustainability of advances in healthcare. While history points to the flight of R&D from Europe following the advent of state price controls, current proposals need to be considered in the light of current pressures.

Risk Abounds

Continuing on the current path of healthcare coverage in the United States is not realistic. The worsening economic crisis creates tremendous new risks for individual insurance, and may have ramifications in insurance companies' ability to offer best-in-class benefits. However, the future of drugs' role in healthcare does not solely consist of products that are currently on the market. In fact, their continued use, many of which represent major advancements in therapy, will provide on-going clinical benefits (see accompanying article in this Bulletin) and eventually lead to cost savings due to the generic competition already provided for under US law. The other major value offered by drugs is housed in the industry's pipeline that exists today and will emerge from tomorrow's research. Of course, the sustainability of the industry's ability to deliver new benefits and breakthroughs depends upon the health of that pipeline. It is well recognized that

The last time policy makers waged a concerted effort to control the price of and the access to the most innovative, but expensive new drugs as part of broader health-care reform in the mid 1990s, the percent of venture capital going into biotech fell by almost half in a single year. A lot of that money shifted into Internet companies.^{ix}

many of these future advances will originate not in the labs of big pharma, but in smaller specialty companies that have no product revenue stream.

Given these dynamics, government intervention in drug pricing may have unintended but serious long-term ramifications. Big pharma will indeed view price controls negatively due to the direct impact on profitability, at a time when the industry has already been battered. However, the engine of future development – the small biotechs and specialty pharma companies – face an even more dire situation. Many companies have only 6-12 months' cash on hand. Nearly 200 publicly traded US biotechs trade at nearly no multiple to cash, and with market capitalizations under \$100 million face delisting^{viii}. Considering the current risk avoidance in capital markets, the near-term shakeout in biotech may be startling as new financing rounds and the opportunities to float new shares have, at least temporarily for many companies, nearly dried up.

While this creates an attractive buying opportunity for larger biotech and pharma companies, who may be able to pick up valuable assets at a low cost, the resulting lack of development activity could create a hole in the future pipeline. Government pricing intervention in the world's largest and most valuable biopharmaceutical market could have even more dire implications for asset valuation and funding of R&D through both private and public markets. According to Scott Gottlieb, former Deputy and Acting Chair of the FDA and current Forbes columnist, this is not a spurious argument.

The question of how to offer healthcare to the entire US population has been characterized as much by agreement on the necessity of finding a solution, as by disagreement on the means by which to accomplish the goal (many in big pharma had concerns about Medicare Part D, which were in part resolved by a prohibition on government price intervention; since its inception, the program has proven to be a significant contributor to many companies' growth). Much of the contention hinges on philosophical differences around government's role. It is clear that national policy shifts (as well as initiatives at the state and local levels) will be instrumental in causing change. What is unclear is the position the new administration and Congress will take on the question of value. Steps toward price control and imposed metrics of cost effectiveness create enormous risks for the biopharmaceutical industry, the research and development of which serves as a leading indicator of the nation's long-term health.

For sources, please refer to the full article on www.pricespective.com <<http://www.pricespective.com>>.

Exploring the Value of Pharmaceutical Investment

As governments across the world continue to pour billions into the financial markets to help prevent a global depression, the budgetary pressure on traditional government services will become even greater. This will be particularly true for healthcare, already top of mind for governments and their citizens. Across markets, regardless of their respective methods of healthcare financing, the pharmaceutical industry faces continued scrutiny over its pricing. A clearly earmarked drug spend is an easy target when reviewing healthcare expenditures and is much less politically sensitive than doctors' pay or the amount spent to remedy medical errors. To prepare for the ever mounting pressure to reduce drug prices, industry and healthcare funders alike should ask: what is the true value of pharmaceuticals, and is this a sound investment?

The British Return on Investment

The UK market is one of the most aggressive in defining value thanks to the activity of the National Institute for Health and Clinical Excellence (NICE). The UK's Office of Fair Trade further pressed the value of pharmaceuticals question in its 2007 report. Given this focus on drug value and well reported public data from the Department of Health and OECD, the UK's National Health Service (NHS) can be used as a starting point to review pharmaceuticals as a healthcare investment and question if that investment should continue.ⁱ

To put forward an unbiased review of England's investment in pharmaceuticals, this article looks at three out of the top five therapeutic classes as defined by 2007 global pharmaceutical sales.ⁱⁱ Recognizing that other factors in addition to drug utilization are at play, a comparison of spend over a ten year period in England against changes in both health and quality of life outcomes highlights that pharmaceuticals are a high-return investment that has greatly benefited not only the healthcare system in terms of reduced costs but also – and even more so – patients.



UK drug spend as a percentage of total healthcare expenditure in 2007

■ Drug spend 10.3%
■ Other health expenditure

Oncology

Perhaps one of the most emotive disease areas, cancer is likely the most publically debated. Despite being the disease state with the highest global spend, total expenditures in

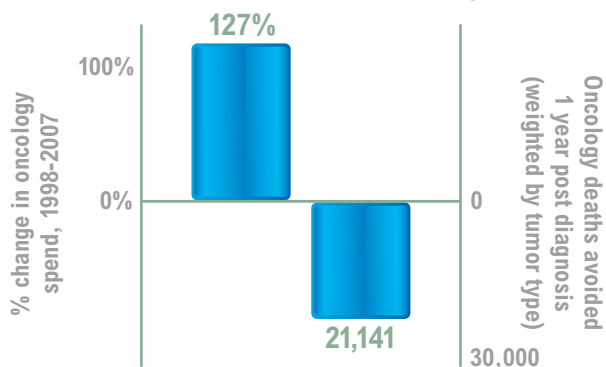
England on cancer drugs are less than other therapy classes such as cardiovascular disease and respiratory disease. NICE has developed over 60 appraisals on cancer, more than in any other disease area. However, the Department of Health is becoming more sympathetic to patients. In response to very public campaigns, the Minister of Health lifted the ban on top-up treatments on 4 November 2008. Previously, patients who paid out of pocket for any non-NICE approved drug were forced to pay for their entire treatment, even for services traditionally provided by the NHS such as chemotherapy.

This focus on and effort to control cancer spend are warranted, but the metrics applied are questionable. The total cost of all cancer drugs prescribed in England increased by 127% (£144.6 million in 1998 to £328.2 million in 2007). This rise in spending is a direct result of the significant investment by the pharmaceutical industry to bring new drugs to the market such as Herceptin and Eloxatin in 2000 and Glivec in 2001. However, other treatments, such as Avastin, which is indicated for use in a number of solid tumors, and targeted kidney cancer therapies including Nexavar, Sutent, and Torisel are generally not funded by PCTs. Given all this, is investment in oncologics prudent?

Patients (and patient groups) say yes. The research and development investment into oncology over the past decade has enabled patients to live longer and better-quality lives. For example, one-year survival rates in England and Wales increased by a weighted average of 2.9% between 1996-1999 and 2000-2001. In other words, more than 21,000 additional patients were alive after one year following diagnosis and treatment. Herceptin can lead to increases of 33% in overall survival and a 50% gain in disease-free survival for breast cancer patients. Even higher results were found for Glivec, a drug for chronic myelogenous leukemia (CML). A New England Journal of Medicine article describes overall survival found to be 95% after excluding causes of death unrelated to CML or prior bone marrow transplantation.ⁱⁱⁱ Meanwhile, the kidney cancer drugs that have been blocked by NICE have demonstrated a potential to increase overall survival by five to six months longer than comparators.

Many may rightly say that the majority of new and high-cost cancer therapies have not cured cancer and only prolong life for a short time. However, this end-of-life period has very high value for many patients, and reductions in mortality rates for patients and shortened average hospital stays should not be dismissed. For example, a study shows that colorectal cancer patients receiving treatment with Xeloda as compared to the previous standard of care not only had improvements in disease free survival and overall survival, but also had fewer hospitalizations and medications that contributed to a cost savings of £3700 per patient for the NHS.^{iv}

Cost and Benefits of Oncologics



Meanwhile, other cancer therapies work to improve quality of life but have no direct impact on the cancer itself. For example, anti-nausea drugs in the NK-1 class such as Emend make chemotherapy more manageable for high-need patients, thereby improving the likelihood of success of the primary therapy. Should supportive care be valued less than improvements in mortality? While NICE has not yet reviewed Emend, the Scottish Medicines Consortium has recommended restricted use which suggests that the SMC and those PCTs who follow its guidance are at least recognizing its value in the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based chemotherapy.

Cancer drugs are costly but valuable, and patient access has traditionally been restricted due to the £30,000 cost per QALY threshold informally imposed by NICE. Without such restriction – based on a figure developed years ago and now applied across all disease states – more value could have been provided to patients who likely place a high premium on additional months of life. In addition, due to the great need for new therapies in oncology, many treatments are studied first in late-stage patients where they may not demonstrate their full long-term potential (e.g., Herceptin has shown significant value in progressively earlier-stage patients in the years since it launched). Perhaps because of significant public scrutiny, the NHS agrees that cancer is a special case and has warmed to the idea of increasing the QALY threshold for cancer. The Minister of Health announced earlier this month that the NICE ceiling may be adjusted up to £80,000 a year.

Cardiovascular disease

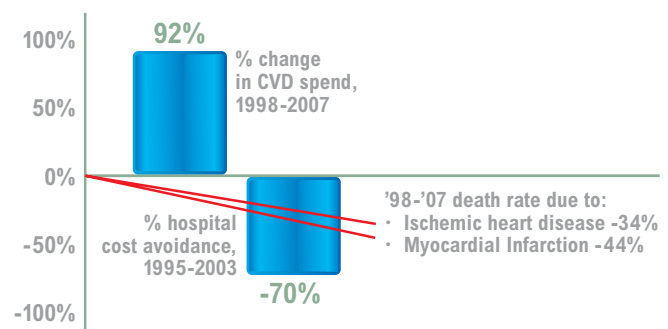
Closely following oncologics, lipid regulators account for over 5% of global sales. It is also an important therapeutic class for healthcare providers as lipid regulators are the primary combatant against cardiovascular disease (CVD), a leading cause of death. From 1998 to 2007, the amount spent on drugs treating CVD increased in England by 93% (from £940.3 million to £1,813.4 million). This trend was fueled by

the launches of blockbusters such as Lipitor in 1997 and Plavix in 1998. Although this was a significant investment, the fundamental question is whether patients and the NHS benefited from this allocation of resources.

In the past decade, the death rates for ischemic heart disease and myocardial infarction in the UK declined by 34% and 44% respectively. Although a decline in national smoking levels also would have contributed to this trend, studies find that pharmaceuticals such as Plavix, ACE inhibitors and statins lead to lower mortality. These positive changes further translate into financial savings for society, especially when considering the production losses from cardiovascular deaths.

Health and societal benefits have been shown to be direct consequences of greater investment in appropriate pharmaceutical utilization. A study based on twenty OECD countries from 1995 to 2003 finds that countries that invested more in cardiovascular drugs had consequently larger reductions in hospitalizations and mortality due to CVD. By not investing in cardiovascular drugs, per capita hospitalization costs in these countries would have been an astounding 70% higher in 2004.^v

Cost and Benefits of CVD Agents



While the case for cardiovascular drug budgets appears very well justified in both healthcare and societal terms, it is also important to note the amount spent on CVD globally has fallen in 2007 by almost 7%. This fall in spend is due to expiration of patents such as Lipostat in 2004 and Zocor in 2006. These agents therefore still represent a valuable investment with an even higher rate of return, but it will be important for the NHS to continue to support new branded agents that offer incremental value in the management of CVD, and not merely to rest on the laurels of the pharmaceutical industry's past drug development success.

Diabetes

While only the fifth largest therapeutic class globally, pharmaceutical management of diabetes is growing worldwide and England has invested heavily in this disease area. Total expenditures on antidiabetic drugs increased by

256% (£167.0 million in 1998 to £594.1 million in 2007). It is easy to associate the dramatic increase in spending on new drugs such as long-acting insulins (Lantus and Levemir), as well as Actos and Avandia in the TZD class. It must also be noted that the patient population has increased by approximately 80% over the same time period and that the use of combination treatment regimens as standard of care has increased.^{vi}

Looking beyond surrogate endpoints such as HbA_{1c} reduction, antidiabetic agents have been successful in controlling and managing this disease. The average length of inpatient stay due to diabetes declined by 19%, and the number of emergency visits and admissions as a percent of patient population declined by 31% and 47% respectively. This substantial decline in hospitalization allows hospitals to shift resources elsewhere, effectively filling budget gaps from the savings created by better management of diabetes.








Conclusion

The focus on the cost of pharmaceuticals continues unabated, but relatively less attention is given to the value they have delivered to individuals, the healthcare system, and all of society over a period of many years. Based on this review, and despite the recognition that many factors can affect the real health outcomes discussed here, investing in pharmaceutical therapy clearly does deliver strong clinical and economic benefits. In this context it is fair to change the familiar question targeting innovative drug manufactures from “should the money spent on drugs be reduced or reallocated?” to “should drug budgets be increased?”

Over the past decade, there have been simultaneous and positive correlations in England between expenditures on pharmaceuticals in high-burden disease areas such as cancer, CVD and diabetes, and important clinical and resource utilization metrics in the same disease states. With the support of objective and rational evaluations such as this, the pharmaceutical industry can seek to shift the debate from overly generalized and ill-informed attempts to curb pharmaceutical budgets and utilization, to widening access to appropriate pharmacotherapy as determined by metrics and outcomes most relevant to each disease state. While the Department of Health and the Association of British Pharmaceutical Industry hammer out the remaining “value” negotiations regarding the Pharmaceutical Price Regulation Scheme (PPRS), it will be to the advantage of both industry and government to take a lesson from the financial markets and to examine real risk-reward profiles prior to allocating finite investment resources.

For sources, please refer to the full article on www.pricespective.com <<http://www.pricespective.com>>.

Greater Value for Public Safety?

Public Intervention	Cost per QALY	Verdict
Avastin – metastatic colon cancer	£62,857	
Sutent – first line renal cell carcinoma, intent to treat population without follow-on therapy (based on NICE’s preliminary decision)	>£30,904	
Taxol (paclitaxel) – adjuvant treatment of women with early breast cancer	£59,431	
Alimta (pemetrexed) – locally metastatic non-small-cell lung cancer	£36,700	
Orencia (abatacept) – severe active rheumatoid arthritis in combination with methotrexate	£55,000	
Airbags	£57,510	
Emergency defibrillators	£41,146	

NICE has come under a fair amount of scrutiny for its £20,000 to £30,000 cost per QALY threshold – and rightly so. It is a measurement nearly always used by NICE in assessing a drug’s worth regardless of the disease area, disease state or type of patient. While the most benign complaints suggest that NICE’s threshold should at least be adjusted for inflation, a more interesting argument is to look at other “life-saving” QALYs that both consumers and government policy makers have deemed worthwhile. Airbags, something many of us look for when purchasing a new car, have a cost per QALY of £57,510. Meanwhile, emergency defibrillators come in at £41,146 cost per QALY according to the Scottish NHS. The next time you walk by a normally discreet, wall-mounted emergency defibrillator, you might ask yourself: “Is this worth more than any medication I may need?”

Editors:

Keiron Sparrowhawk, PriceSpective Ltd, U.K.
+44 (0) 207 832 1086
ksparrowhawk@pricespective.com
Ted Sweeney, PriceSpective, LLC U.S.A.
+1 917 446 2473
tsweeney@pricespective.com
www.pricespective.com