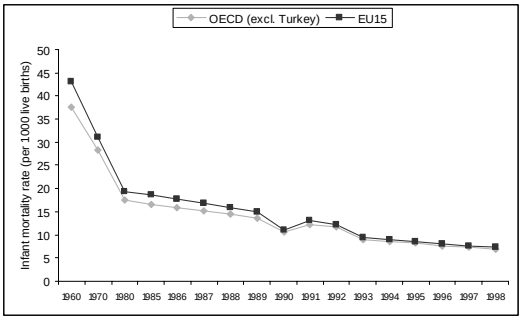
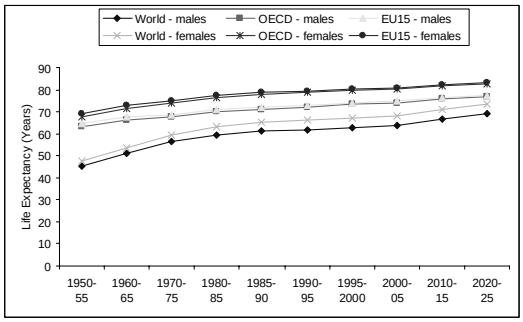
AstraZeneca Submission – The impact of advances in medical technology on healthcare in Australia – The Value of Medicines

People are living longer, healthier lives. Life expectancy has increased and infant mortality has decreased dramatically during the last 50 years (Figure 1). At the beginning of the 1900s, average life expectancy in Western countries was only 47 years. By the beginning of the 21st century, this figure was 76 years. On average, an additional year of life expectancy has been added every five years since 1965.[1] These changes can be attributed to many socio-economic factors such as improvements in housing, sanitation, and living standards. However, the development of new medicines has also played a part.

Figure 1. Infant mortality has decreased, and life expectancy has increased in the last 50 years.[2]





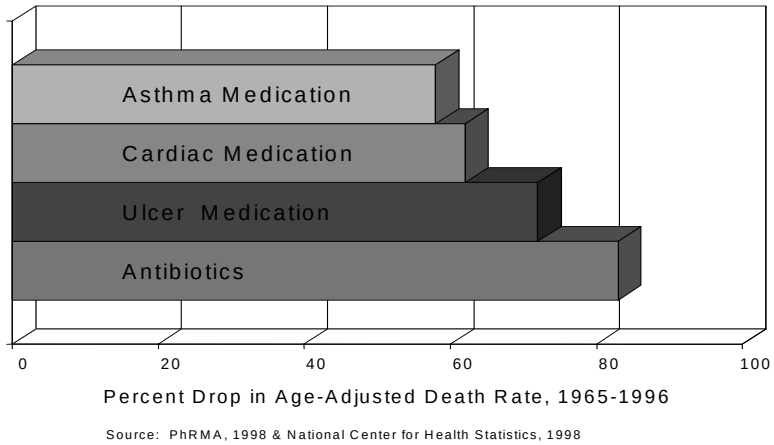
In addition to saving lives, medicines provide value in other ways: they reduce the symptoms of disease, prevent disease occurring or re-occurring, and can improve the quality of life of patients. They can also provide economic benefits by reducing overall healthcare costs, avoiding expenditure in other areas and improving productivity. These aspects are summarised in the sections that follow.

Medicines save lives

One of the most profound effects of pharmaceuticals is saving lives. There are many examples of how medicines have helped reduce mortality in a wide range of conditions, and data from the US, shown in Figure 2, highlights this. Medicines have helped eliminate or significantly reduce the number of deaths due to conditions such as polio, diphtheria, influenza and pneumonia. In many other conditions such as asthma, heart attacks, stroke and

stomach ulcers, appropriate use of pharmaceuticals has helped contain mortality rates, preventing unnecessarily early deaths for many people. [3]

Figure 2. Pharmaceuticals save lives.



Source: PhRMA, 1998 & National Center for Health Statistics, 1998

Much of the fall in mortality is attributable to a variety of factors other than effective medicines. Nevertheless, medicines have made a significant contribution to the decline in death rates towards the latter part of the last 150 years. A good example is the trend in mortality from infectious diseases in the Netherlands before and after the introduction of antibiotics. On average, the annual decline in mortality from all infectious diseases was 4% before the introduction of antibiotics and 10% after their introduction.[4]

Heart disease is one of the world's biggest killers. Cholesterol lowering drugs, particularly HMG CoA reductase inhibitors (statins) have been shown to be effective in the prevention of death due to the consequences of elevated blood cholesterol - events such as heart attacks, or stroke. The Scandinavian Simvastatin Survival Study, a randomized placebo-controlled trial in patients who had experienced angina or a myocardial infarction demonstrated a 30% decline in the relative risk of all-cause mortality and a 42% decline in the relative risk of coronary mortality with simvastatin.[5]

The Prospective Pravastatin Pooling Project estimated, on the basis of three trials of pravastatin (covering those with and without coronary artery disease), a 20% relative risk reduction for mortality and a 24% relative risk reduction for coronary mortality with pravastatin compared with placebo.[6]

In patients with coronary disease, other occlusive arterial disease or diabetes, the Heart Protection study found that patients randomly allocated to a statin experienced significantly reduced all-cause mortality compared with the placebo group (12.9% versus 14.7%).[7]

Pharmaceuticals reduce symptoms and improve quality of life

Many examples describe the impact of new medicines on patient symptoms and quality of life:

- Advanced cancer is incurable. Many medicines for this devastating disease have provided value to patients and their families by improving their quality of life. Drugs to prevent nausea, a common side-effect of cancer chemotherapy, can help make the treatment easier to bear both for patients and their families.

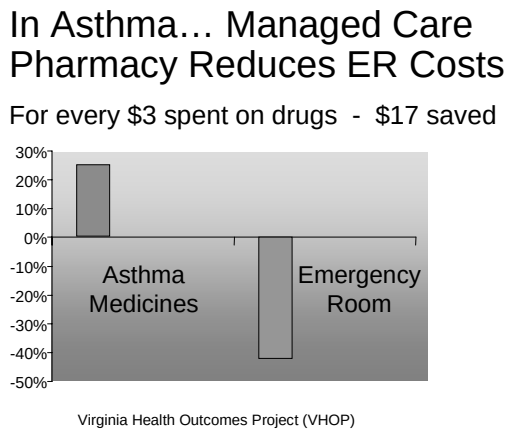
- In patients with moderate to severe migraine, subcutaneous sumatriptan improved quality of life by more than 20% compared to placebo (61.6% versus 20.6%). Patients on rizatriptan show significantly better responses to three domains of the 24-hour Migraine Quality of Life Questionnaire (social functioning, migraine symptoms and feelings/concerns) compared to patients treated with placebo.[8]

- A systematic review of a new schizophrenia medicine - an atypical antipsychotic - found that, compared with typical antipsychotics, it was more effective in improving global state, general mental state and the negative symptoms of schizophrenia, and was as effective as typical antipsychotics with regard to positive symptoms.[9]

Medicines reduce other healthcare costs

There are many examples where appropriate use of medicines has decreased overall costs of care, whilst providing similar or improved outcomes for patients. For example, appropriate use of asthma medications can reduce the number of asthma attacks which would normally result in a need for emergency treatment. For every $3 spent on asthma medications in one US study, $17 was saved due to reduced emergency room visits (Figure 3).[10]

Figure 3. Spending on asthma medicines can save costs of emergency treatment.



Attached are two other papers looking at the cost-effectiveness of asthma medications in mild persistent asthma, including one which looks at country-specific cost-effectiveness and shows that from a societal perspective, the medicine used in the study would be cost saving in Australia, Canada and Sweden (Sullivan SD et al. 2003; Buxton M et al. 2004).

Congestive heart failure is a condition that affects 5 million Americans, causes 45,000 deaths a year, and costs the US $21 billion a year. A major US health plan enrolled over 2000 patients in a disease management programme which focused on education about the disease, and the importance of following treatment regiments including medicines such as angiotensin-converting enzyme (ACE) inhibitors. The programme increased the costs of medicines by over $240,000, mostly due to increased prescriptions for ACE inhibitors. However, this increase was more than offset by a $9 million saving in hospitalisation costs - equivalent to savings of nearly $9,000 per patient.[11] Patient outcomes were also improved - mortality rates were 15% lower than the expected rates, and patient's ability to perform their normal activities increased by 15%.

In Europe, the Cardiac Insufficiency Bisoprolol Study found that, in addition to improved survival, costs of care were reduced by 5%-10% in patients with heart failure treated with the beta-blocker bisoprolol.[12]

In the UK, savings have been made by medicines reducing the need for hospitalisations in many disease areas, as show in Table 1.[2]

Table 1. Estimated savings from reduced use of NHS hospital beds due to medicines since 1957 in 12 disease areas.[2]

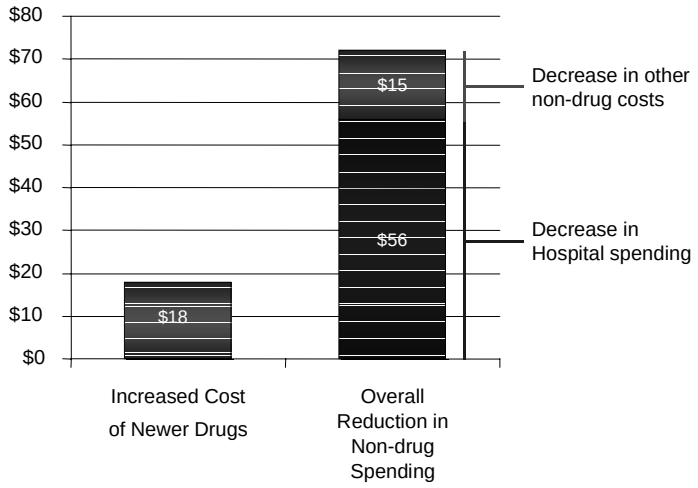
	Estimated saving from reduced hospitalisations (£M)							
	1970	1980	1991/92	1993/94	1996/97	1998/99	1999/00	2000/01
Asthma	0	6	-14	-7	32	35	38	41
Epilepsy	0	10	-2	28	82	83	84	82
Glaucoma	0	2	10	31	56	57	59	60
Hypertension	6	47	318	345	466	467	471	471
Bronchitis	-4	36	175	174	214	215	215	215
Skin disease	0	6	-32	-6	46	46	39	25
Respiratory tuberculosis	54	321	1945	1768	1371	1370	1370	1370
Other infectious diseases	13	106	633	541	445	448	446	440
Mental illness	43	465	2643	5346	6817	7594	7750	7746
Peptic ulcer	7	53	244	251	332	332	330	331
Diabetes mellitus	-2	-7	28	52	90	90	90	88
Rheumatoid arthritis	-5	-8	36	56	125	126	129	134
Total 12 diseases	114	1038	5984	8578	10076	10961	11020	11003

Newer medicines may reduce costs the most

A study of data on prescribed medicines from the 1996 US Medical Expenditure Panel Survey has found that newer medicines have significant benefits over older medicines. Patients consuming new drugs were significantly less likely to die than those consuming older drugs. Moreover, the more recent therapies were associated with the least expenditure elsewhere.[13] Patients who use newer drugs are less likely to lose time at work, and spend time in the hospital. This article is attached (Lichtenberg 2001).

Replacing a 15-year-old drug with a drug aged 5.5 years would entail an additional drug cost of around $18. On a comparable basis, it was estimated that replacing an old drug with a new one was associated with an expected $44 reduction in hospital spending (a regression estimate gave the impact as a $56 reduction). In other words, newer medicines can result in a substantial net reduction in overall costs of treatment (Figure 4).

Figure 4. Newer medicines can reduce overall healthcare spending.[13]

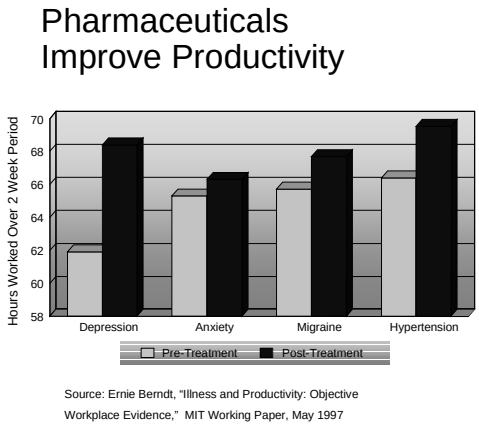


A striking example of newer drugs offering cost savings is in schizophrenia. The majority of economic studies reviewed for the UK National Institute for Clinical Excellence appraisal of atypical antipsychotics showed that the higher costs of purchasing these newer medicines were more than offset by reductions in inpatient stays. Cost savings were generally estimated to average £1000 per patient year, with an approximate range of £250 to £5000 per patient year.[14]

Pharmaceuticals improve productivity

As well as improving outcomes for patients, and helping reduce overall costs of care, pharmaceuticals can offer value in broader ways. By preventing or treating the effects of disease they can help people live normal, productive lives. A 1997 study assessed productivity in employees suffering from various health conditions and the impact of treatment with prescription medicines.[15] Review of pre- and post-treatment work and attendance records found that the number of hours patients were able to work increased following treatment with pharmaceuticals, and this increase was particularly marked for patients suffering from depression (Figure 5).

Figure 5. Pharmaceuticals can increase productivity.



Source: Ernie Berndt, "Illness and Productivity: Objective Workplace Evidence," MIT Working Paper, May 1997

Attached are a number of publications which address the economic costs of peptic ulcer disease and the economic and productivity benefits resulting from treatment of that disease (Henke et al. 2000; Wahlqvist. 2001; Wahlqvist et al. 2002; Dean et al. 2002).

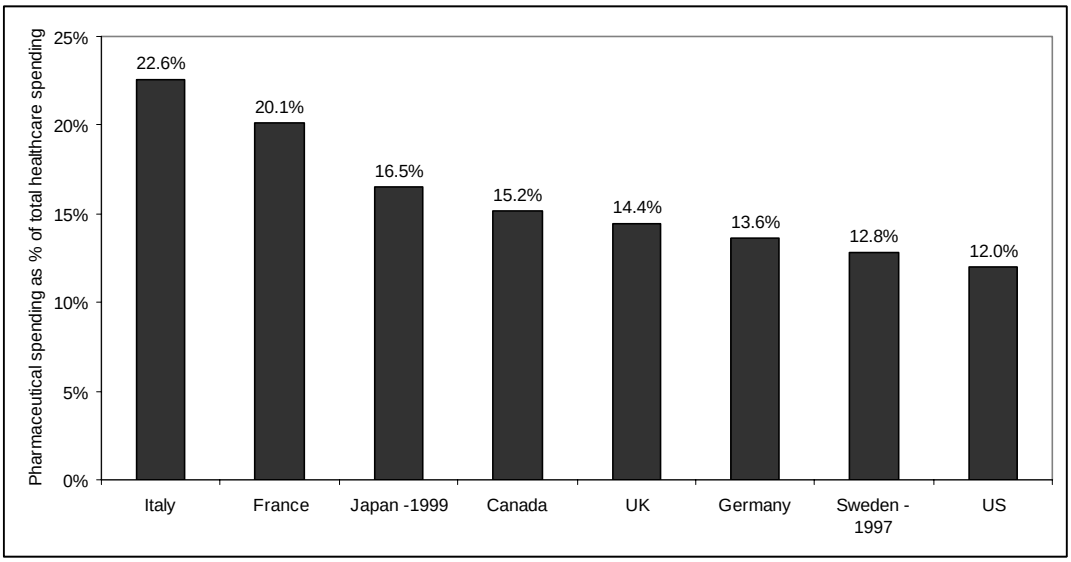
These are just a few examples from an extensive, and growing, body of evidence demonstrating how pharmaceuticals provide value far beyond their cost in a range of different ways. Taken together, this evidence conclusively shows that pharmaceutical expenditure is an appropriate way to allocate healthcare resources - with benefits for patients, doctors and governments.

Pharmaceutical Costs In Context

While the contribution of medicines is clear, the level of investment that is made in them is questioned.

Demographic shifts towards a more elderly population are accompanied by increases in healthcare spending. This is to be expected: more people living for longer coupled with technological advances in medicine mean that there are more opportunities to prevent or treat illness and disease. As pharmaceuticals are the most visible component of healthcare spending the majority of focus on increasing costs has been on medicines. However, medicines comprise only a small component of total healthcare spending across many countries (Figure 6).

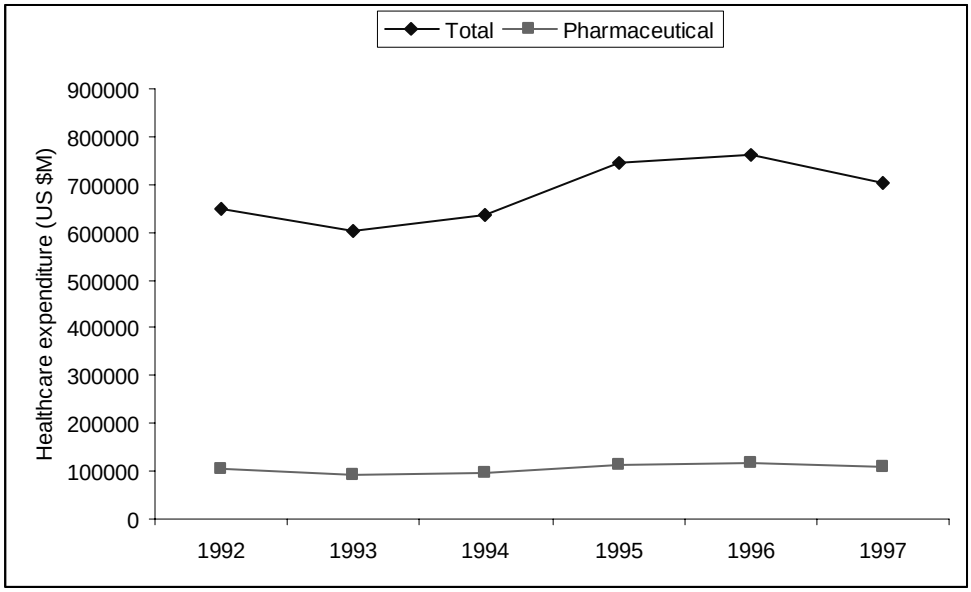
Figure 6. Spending on pharmaceuticals comprised only a small part of total healthcare spending in 2000.[16]



Growth in pharmaceutical expenditure is a concern for many third-party payers but the rate of growth has not exceeded that of other healthcare services. Figure 7 shows the relationship between pharmaceutical expenditure and total healthcare expenditure for the European Union (EU) countries, (excluding Austria for which data on pharmaceutical expenditure were unavailable), from 1992 to 1997. Pharmaceutical expenditure accounted for a reasonably stable share of total healthcare spending over the period, and comprised between 15% and 16%, or less than one-fifth of the total outlay.[16]

In recent years, healthcare expenditure as a proportion of gross domestic product across the EU has remained stable, with the 8.8% share in 1995 remaining similar to the estimated 8.7% for 2000.[2] During this period, the gross domestic product in the EU has been increasing, with the result that expenditure on all kinds of healthcare, including pharmaceuticals has been increasing in real terms. The following sections explore some of the reasons leading to increased spending on pharmaceuticals.

Figure 7. Growth in EU pharmaceutical spending matches that of other healthcare costs.



Why are the costs of pharmaceuticals increasing?

Given the focus that there is on increased medicines spending, understanding what is causing the increase is important. In general, the factors can be put into three categories: increasing number of prescriptions, greater use of innovative (and often higher cost) medicines, and price increases.[17,18] It is likely that different mixes of these same factors are driving increase expenditure in most countries - for example, price increases are a much less important factor outside the US. Growth drivers in the US and Europe are examined in the following sections.

Drivers of growth in the US

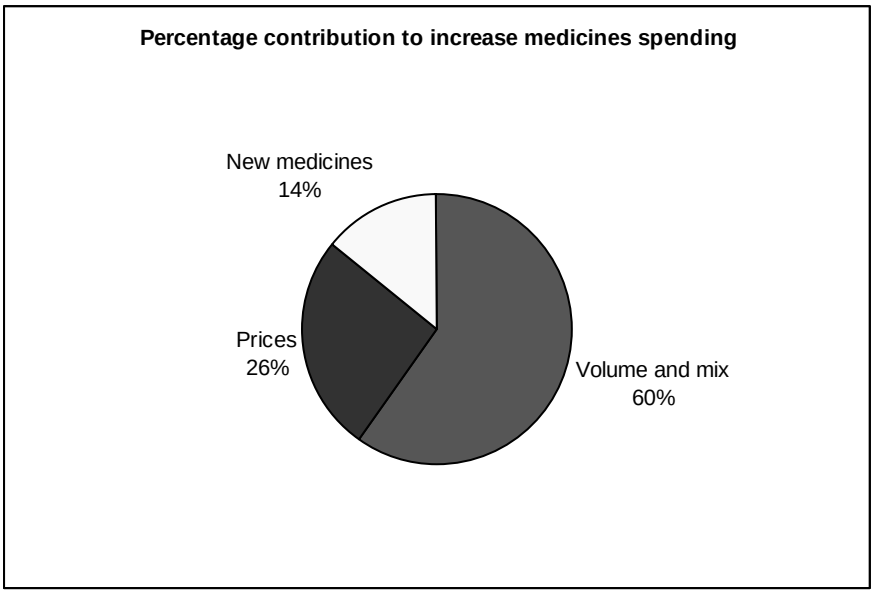
Analysis of prescription drug sales data in the US identifies three factors contributing to sales growth in pharmaceutical expenditure:

- increases in the volume of drugs dispensed (the effects of switching to newer drugs and of increasing prescriptions);
- increases in price;
- introduction of new medicines.

As shown in Figure 8 changes in drug volume and mix accounted for nearly two-thirds of the 14.9% increase in expenditure observed in 2000.[19] Price increases contributed around one-

quarter, and introduction of innovative medicines led to just under one-sixth of the growth in spending.

Figure 8. More prescriptions, use of newer drugs, and price drove the increase in medicines spending in the US in 2000[19]

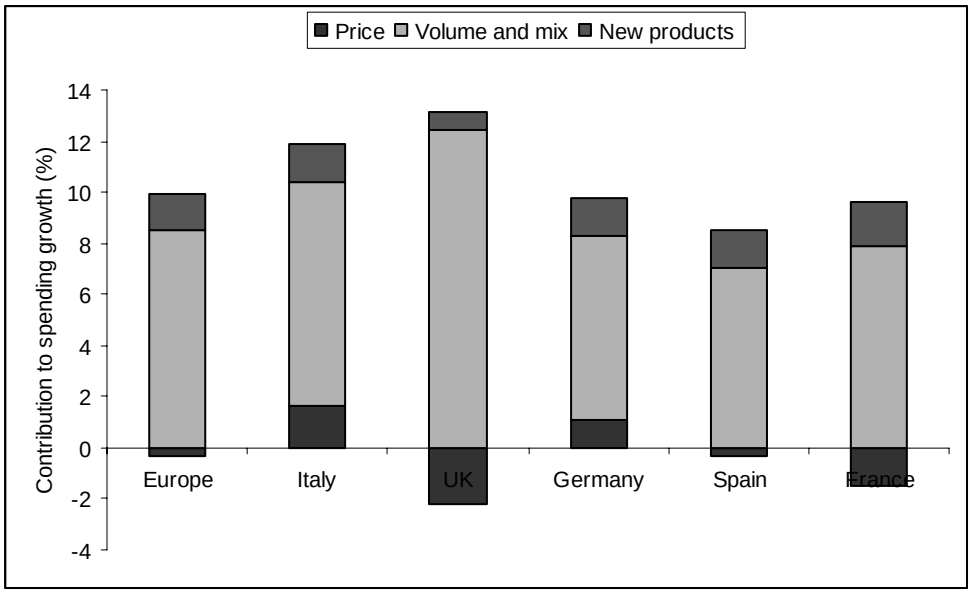


A review of studies examining increases in prescription drug spending in the US during the late 1990s has attributed increases in expenditure to old drugs and new drugs respectively. [20] On the basis of one study using the period 1996-1999, older drugs accounted for 58.6% of the increase in expenditure (utilisation increases 40.3% and cost increases 18.2%) and newer drugs for 41.4% (utilisation 19.9% and cost 21.6%). These results, and those obtained from the IMS analysis above, may be compared with two sets of analyses performed using UK data and evidence from other European countries.

Drivers of growth in Europe

A similar analysis to that presented in Figure 8 is given for several European countries in Figure 9. The picture is markedly different in Europe compared to the US. Increased spending in Europe has been driven by innovation, increasing numbers of prescriptions, and changes in the mix of medicines prescribed. Overall in Europe, there has been a negative impact of price on increases in expenditure - in other words the prices of medicines are falling. This is in contrast to the US, where prices have contributed significantly towards increased spending.

Figure 9. Introduction of new medicines, increased volumes, and changes in the mix of medicines prescribed were the major drivers of increased pharmaceutical spending in Europe in 2001 - price increases had little impact.



Although the relative importance of the three basic influences on pharmaceuticals expenditure (volume and mix, prices and the introduction of new products) will vary between countries, each of these three main drivers of spending are in turn affected by a number of factors (Box 1),[21] and each of the main areas is described in more detail in the following sections.

Box 1. Many factors contribute to increased spending on medicines.

Greater use of medicines

- Increasing population
- Changes in demographics and health status (i.e. more people with increased medication needs)
- Changes in use of drugs on a per patient basis (i.e. more medications per patient per year)

Availability of new medicines

- Changes in prescribing habits (i.e. from older, less expensive medications to newer, more effective & possibly more expensive ones to treat same diagnosis)
- Trends towards using drug therapy instead of other treatments (e.g. as alternatives to surgery and to reduce hospitalisations)
- New diseases to be treated
- New medicines for existing diseases where there was no previously existing treatment
- Old diseases treated better with newer drugs

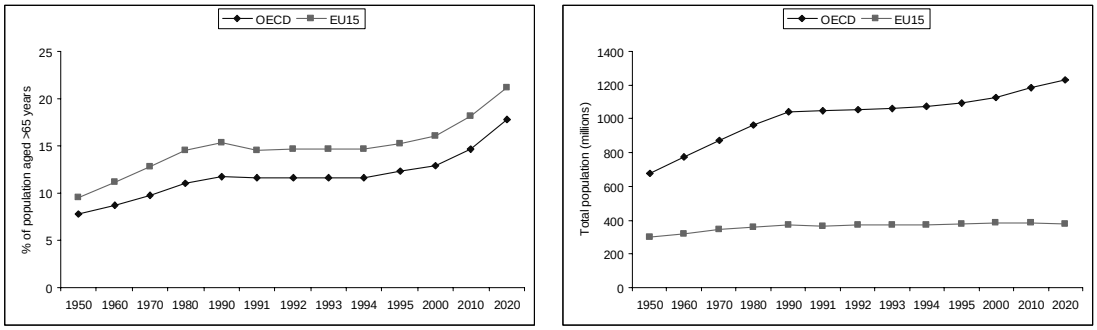
Price increases

- Changes in the unit prices of drugs (both patented and generic)
- Changes in retail and wholesale mark-ups and pharmacists professional fees
- When compared to retail price indices, prices are increasing in US, but stable or declining in EU

Greater use of medicines

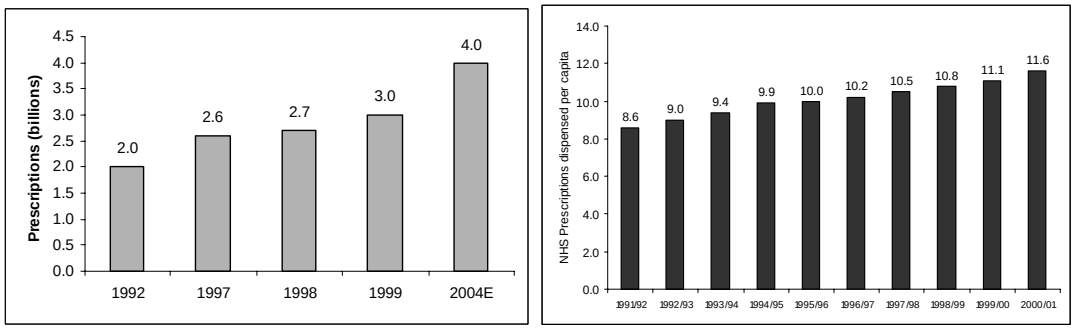
Overall population growth, increasing numbers of older people, combined with new ways of treating or preventing disease are all contributing to the greater use of medicines. There is clear evidence showing that numbers of prescriptions per person tend to increase with age.[22] Figure 10 illustrates the growth in population and in the numbers aged over 65 as a percentage of the total population in OECD and EU countries.

Figure 10. Overall population growth is accompanied by an increase in the proportion of populations aged 65 years and over.



Confirmation that more medicines are now being prescribed[2,23] is provided in Figures 11 and 12 for the US and UK respectively.

Figures 11 and 12. Number of prescriptions dispensed in the US and UK is increasing[23].



Availability of new medicines

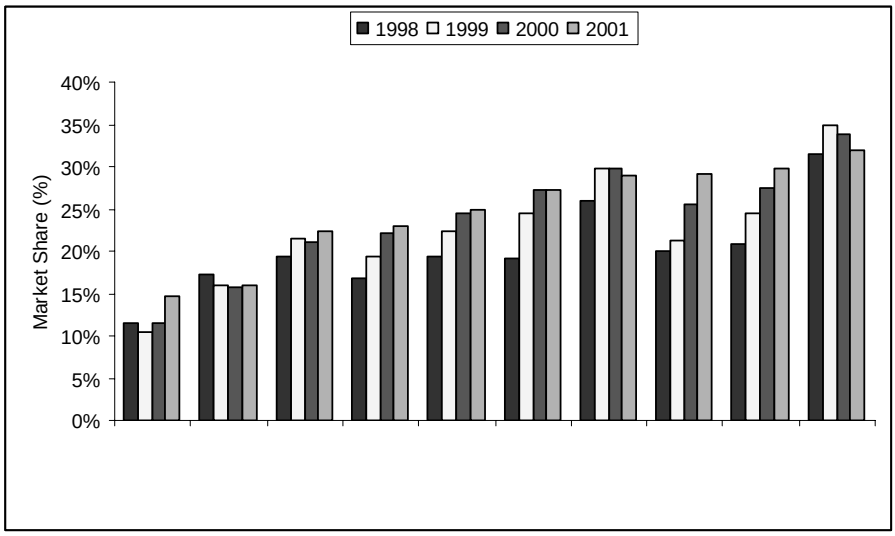
As the US Pharmaceutical Research and Manufacturers Association Annual Report shows, new medicines are being continuously developed.[24] The pharmaceutical industry has over 1,000 medicines in development (in human clinical trials or at regulatory authorities awaiting approval). There are over 400 in cancer, more than 200 to meet the special needs of children, over 100 each for heart disease and stroke, AIDS and mental illness, 26 for Alzheimer's disease, 25 for diabetes, 19 for arthritis, 16 for Parkinson's disease and 14 for osteoporosis.

An important reason for the development of new drugs is the emergence of new diseases, for example, HIV and AIDS. In addition, new medicines may be developed for existing untreated diseases, for example, multiple sclerosis, Alzheimer's disease or erectile dysfunction. Alternatively, new medicines can offer advantages over older medicines in the treatment of established diseases, for example newer treatments for rheumatoid arthritis, depression, or schizophrenia. Moreover, existing drugs may find applications in disease areas not recognised at the time of launch. For example, a study of new indications for drugs classified as 'blockbusters' in the US (according to sales) in 1993 found that secondary uses accounted for more than 40% of total sales by 1995.[25]

Sometimes these new indications may not be appreciated for some time, perhaps not until close to or after patent expiry. For example, it was not until 20 years after the introduction of alpha-adrenergic-receptor antagonists (first tested for hypertension) that their potential application to benign prostatic hyperplasia was recognised. The legacy on innovation represented by generic medicines may have contributed to increases over time in generic prescribing. In the UK, generic prescribing increased from 27% by value to 62% by value between 1991 and 2000.[26]

Not surprisingly, there can often be a rapid uptake of new medicines as they offer benefits over existing therapies or a treatment option where none existed before. This uptake is reflected in the market share that innovative medicines achieve as shown in Figure 13 which details the market share of new medicines for a selection of OECD countries.

Figure 13. Market share of new medicines (launched in the previous five years).

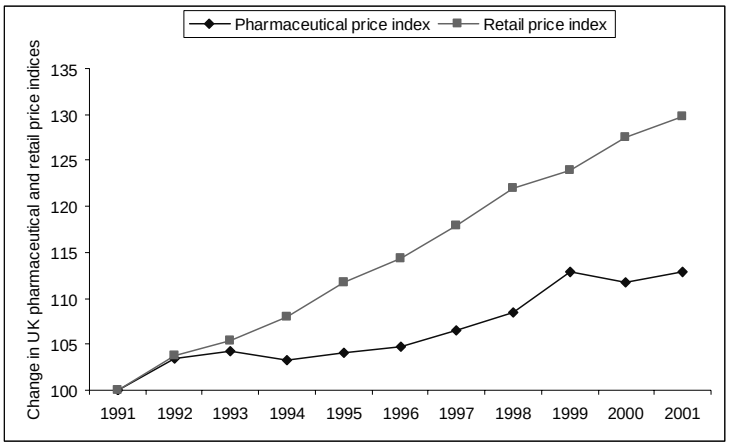


Price increases

As we have already seen, pharmaceuticals expenditure is subject to a number of influences, not all of which act in the same direction. While the overall volume of prescribing increases, price fluctuations may serve to increase expenditure or exert downwards pressure particularly outside the US. There are elements of price-setting which are beyond the control of the pharmaceutical industry, for example, increases in price by wholesalers and pharmacists or price-setting systems used by governments.

Price increases in many countries outside the US are very low. For example, in the UK, increases in the prices of medicines have averaged less than 0.5 percent per year since 1993[27] and, as we have seen, the contribution of price changes in the last ten years has been to restrain expenditure. In many countries, the price of pharmaceuticals are set in agreement with government, which leads to very small increases in price. Figure 14 shows the trend in prices of pharmaceutical products compared with the consumer prices index and an index of pharmaceutical prices relative to the GDP deflator in a number of OECD countries.

Figure 14. In the UK, the prices of pharmaceuticals have risen more slowly than prices in general, as shown by a comparison of the pharmaceutical price index and the retail price index.



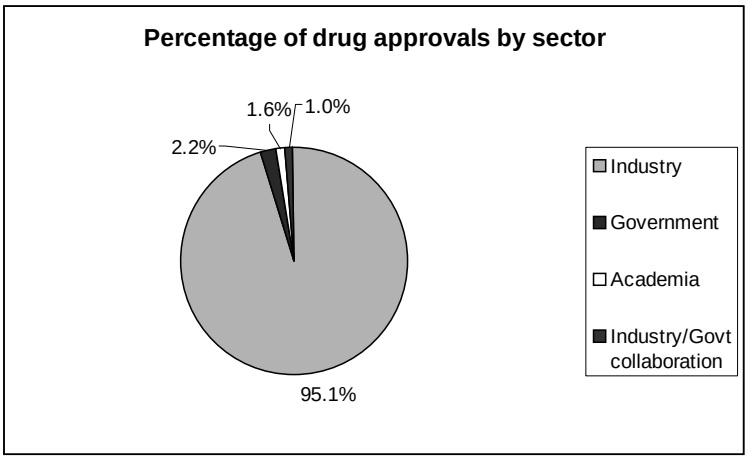
Inappropriate use of medicines

Inappropriate use (under use, overuse, misuse and waste) of medicines can also be an important, and often overlooked contributor to pharmaceutical expenditure. Errors in prescribing are a well established phenomenon. Greater adherence to clinical evidence, treatment guidelines and increased application of evidence-based medicine may help ensure more appropriate prescribing.

Developing new medicines is costly

Any discussion on the worth of medicines should focus primarily on the benefits they deliver to patients, their physicians and healthcare systems. However, it is important to cast a glance to how innovative pharmaceuticals are researched and developed. The majority of innovation in medicines comes from ethical pharmaceutical companies, one of the world's most research-intensive industries (Figure 15).[28]

Figure 15: The research-based pharmaceutical industry is the source of the vast majority of new drug approvals.

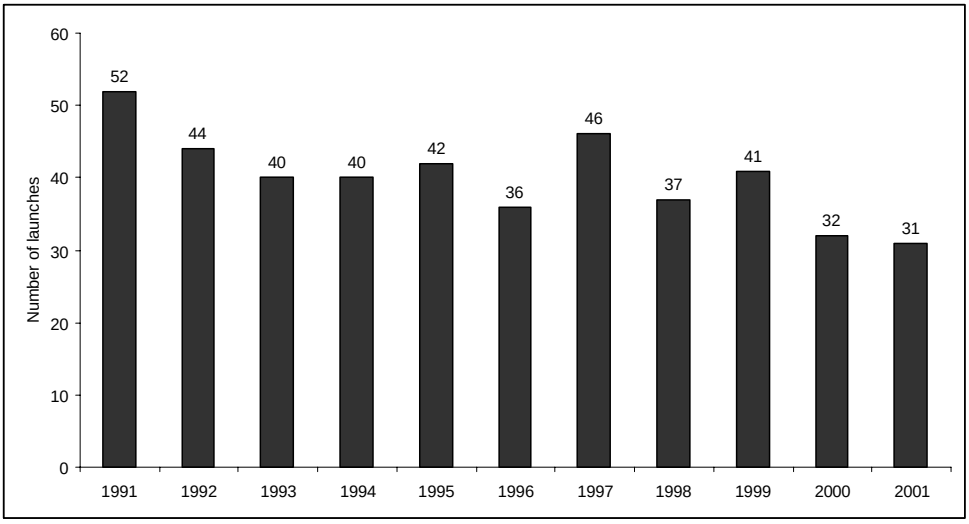


Three clear conclusions emerge when reviewing pharmaceutical research and development:

- Developing new medicines takes a long time and the risks are high;
- Developing new medicines is extremely costly; and
- Only 30% of new pharmaceuticals approved and launched will earn revenues in excess of the average after tax cost of researching and developing new drugs.[29]

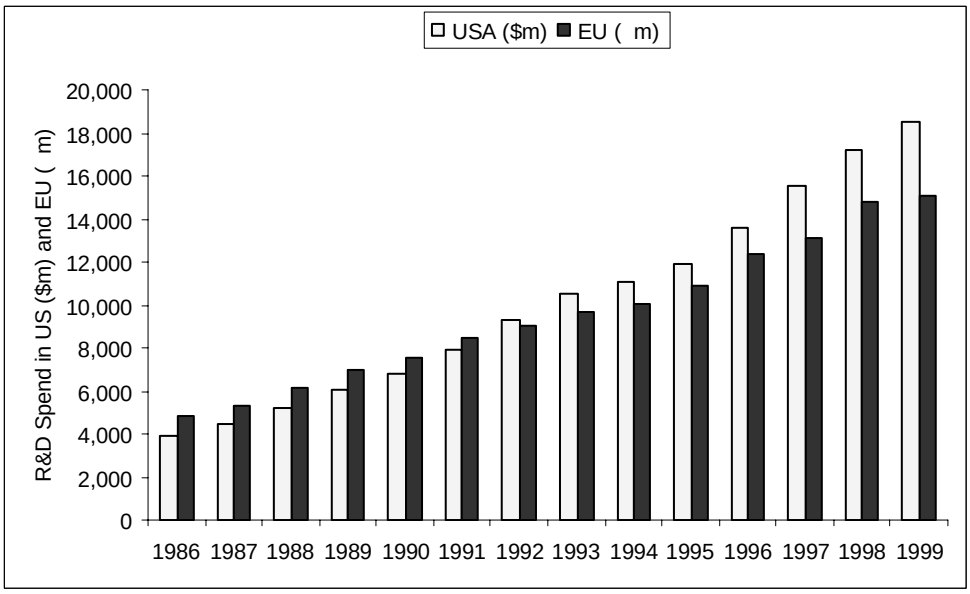
Due to ever higher regulatory hurdles and the time and costs needed to develop truly innovative therapies, it is becoming more difficult to research and develop new medicines. This is reflected in a slowdown in the numbers of new medicines being introduced to the market each year (Figure 16).[30]

Figure 16. The rate of introduction of new drugs is slowing.



It can take 10 - 15 years and hundreds of millions of dollars to develop a new medicine. Most of that time is spent in laboratory and clinical testing with the primary aim of ensuring the safety of the new medicine. For every 5,000 compounds that are assessed for potential as medicines, only a handful will undergo extensive testing in patients. Of the half-a-dozen or so that enter clinical trials, perhaps only one or two will be approved and launched. The difficulties in developing new pharmaceuticals coupled with ever stricter regulatory hurdles for approval have led to major increases in research and development investment across the pharmaceutical industry (Figure 17).[31]

Figure 17: Research and development investments are growing to match difficulty of innovation and regulatory requirements.



Developing new medicines is extremely expensive. Most estimates of the cost of developing one new medicine to the point that it is approved for patient use suggesting the cost runs into many hundreds of millions of dollars. A recent study suggested that this cost may even be up to $800 million.[32] Although it has been argued that this is an excessively high estimate, critics of the study put the figure for after tax actual cash outlay (excluding the value of the lost opportunities to make investments other than R&D) to research and develop a new drug at a still substantial $240 million.[33] The length of time of development, and the need for more and longer clinical trials are factors contributing to these costs.

References

[1] Pharmaceutical Research And Manufacturers of America 2001. The Value of Medicines. Available at http://www.phrma.org [accessed 31 January 2002].

[2] OHE Compendium of Health Statistics 2002

[3] Foundation for Managed Care Pharmacy. The value of pharmaceuticals and managed pharmaceutical care. 2000. [Available at http://www.amcp.org. Accessed *date*].

[4] Mackenbach J, How important have medical advances been, in Sussex J (ed), Improving Population Health in Industrialised Nations, OHE 2000.

[5] Pedersen T R, Coronary artery disease: the Scandinavian Simvastatin Survival Study experience. American Journal of Cardiology 82(10B):5ST-56T, 1998.

[6] Simes J, Furberg C D, Braunwald E, Davis B R, Ford I, Tonkin A, Shepherd J, Effects of pravastatin on mortality in patients with and without coronary heart disease across a broad range of cholesterol levels. The Prospective Pravastatin Pooling project. European Heart Journal 23(3):207-215, 2002.

[7] Heart Protection Study Collaborative Group, MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial, The Lancet 360:7-22, 2002.

[8] Santanello N C, Polis A B, Hartmaier S L, Kramer M S, Block G A, Silberstein S D, Improvement in migraine-specific quality of life in a clinical trial of rizatriptan. Cephalalgia 17(8):867-872 1997.

[9] Mota N E, Lima M S, Soares B G, Amisulpride for schizophrenia. Cochrane Database of Systematic Reviews 2:CD001357, 2002.

[10] The Williamsburg Institute of Virginia Commonwealth University and the National Pharmaceutical Council: The Virginia Health Outcome Project – A Demonstration Project, 1997.

[11] Provide Education about CHF and Pump Up Your Savings. Managed Healthcare. Vol. 8, No. 4 (1998):42-44

[12] CIBIS-II Investigators and Health Economics Group**,** Reduced costs with bisoprolol treatment for heart failure: an economic analysis of the second cardiac insufficiency bisoprolol study (CIBIS-II), European Heart Journal 22(12):1021-1031,2001.

[13] Lichtenberg, FR. Are the benefits of newer drugs worth their cost? Evidence from the 1996 MEPS. Health Affairs Sept/Oct 01. [Available via http://www.healthaffairs.org. Accessed *date*].

[14] NICE Guidance on the use of newer (atypical) antipsychotics for the treatment of schizophrenia, March 2002.

[15] Berndt E, et al. Illness and productivity: objective workplace evidence. MIT Working Paper, May 1997.

[16] OECD Health Data 2002.

[17] NIHCM Foundation: "Prescription Drug Expenditures in 2000: The Upward Trend Continues." 2001

[18] IMS Health, Pharmaceutical Pricing Update, September 2000.

[19] IMS Health, IMS Health reports 14.9 percent growth in US prescription sales to $145 billion in 2000. http://www.imshealth.com/public/structure/dispcontent/1,2779,1203-1203-126684,00.html

[20] Merlis M (2000). Explaining the growth in prescription drug spending: a review of recent studies. www.aspe.hhhs.gov/health/reports/drug-papers/merlis/merlis-final.htm

[21] PMPRB Annual Report 2001. Pharma Pricing and Reimbursement. August 2002 Volume 7 Number 8, p228-229.

[22] AdvancePCS, Schneider Institute for Health Policy, 2000.

[23] National Association of Drug Stores, Inc., "Industry Facts," 1999: 1999 Retail Rx Sales Projected to Rise 18%, Surpass $121B on Volume of Nearly 3 Billion Prescriptions. Aug. 29, 1999.

[24] PhRMA Annual Report 2001-2002

[25] Gelijns A C, Rosenberg N, Moskowitz A J. Capturing the unexpected benefits of medical research. NEJM 1998 339(10):693-698, 1998.

[26] Department of Health PPRS joint project 2002.

[27] Association of the British Pharmaceutical Industry. The Cost of Medicines, ABPI Factsheet. [Available at http://www.abpi.org.uk . Accessed *date*]

[28] Tufts CSDD; Based on 183 NCEs approved in the US during 1986-95.

[29] Grabowski & Vernon; J Health Econ 13; 1994

[30] News from CMR International Spring 2002

[31] PhRMA Annual Survey 2001, national trade associations

[32] Tufts Center for the Study of Drug Development, 2001. Tufts Center for the Study of Drug Development Pegs Cost of a New Prescription Medicine at $802 Million [Available via www.tufts.edu/med/csdd. Accessed *date*].

[33] Public Citizen, America's other drug problem: a briefing book on the R_x drug debate, 2002