Medicines, society, and industry III

The pharmaceutical industry as a medicines provider

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Rising prices of medicines are putting them beyond the reach of many people, even in rich countries. In less-developed countries, millions of individuals do not have access to essential drugs. Drug development is failing to address the major health needs of these countries. The prices of patented medicines usually far exceed the marginal costs of their production; the industry maintains that high prices and patent protection are necessary to compensate for high development costs of innovative products. There is controversy over these claims. Concerns about the harmful effects of the international system of intellectual property rights have led the World Trade Organization to relax the demands placed on least developed countries, and to advocate differential pricing of essential drugs. How these actions will help countries that lack domestic production capacity is unclear. Better access to essential drugs may be achieved through voluntary licensing arrangements between international pharmaceutical companies and manufacturers in developing countries.

Products of the modern pharmaceutical industry have improved the outlook for patients with many disorders. Drug manufacturers have been highly successful in translation of discoveries into successful products. Despite these successes, pharmaceutical companies have come under increasingly critical public scrutiny,[1,2] for example, the unsuccessful legal campaign against the South African government, their tardiness in lowering of prices for antiretroviral drugs in the face of the pandemic of AIDS, and the high price of many drugs in the USA compared with other countries.[3–6]

Despite these controversies, companies have remained profitable, with better margins than other industries.[6] International companies now face increasingly demanding customers, constrained expenditure on drugs, an expanding generics business, and imminent expiry of patents for several very profitable products. The combination of these factors is creating uncertainty about the continued growth of the industry.

Access to drugs

WHO has maintained a list of essential drugs since 1977; the 12th version of the list contains 325 drugs, many of which are available in bulk generic forms from low-cost suppliers.[7] Despite the relatively low prices that can be obtained on the international market, availability of essential drugs remains deficient, and over half the poorest people in Africa and Asia still do not have access to these drugs.[8] High prices (in part attributable to inappropriately high taxes, mark-ups, and dispensing fees), poor purchasing and distribution programmes, uncertain product quality (including counterfeit drugs), and inappropriate prescribing practices continue to undermine availability.[5,9]

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Inadequate access to essential drugs is not confined to less developed countries. In the USA, many elderly and uninsured people cannot afford the drugs they need. Large buyers—such as health maintenance organisations—can negotiate discounts, but individual patients cannot.[10] The absence of pharmaceutical benefits has left a third of Medicare recipients in the USA (over 13 million elderly people) without insurance cover, and they are asked to pay the highest prices in the world.[10]

Market failure and the pharmaceutical industry

Markets work well for society when there is price competition, comprehensive and accurate information, an adequate supply of drugs, where consumers are able to make informed unpressured choices between competing products, and when there are few barriers for entry to the market. However, substantial evidence shows that markets have failed to work. Timely, independent, comprehensive, and accurate information on new drugs is hard to find.[11] Diseases that affect a large proportion of the world's population have been neglected in drug development.[5] Where treatments are available for disorders, drugs are unaffordable for those who need them most.[5] Price competition between patented products is weak and pharmaceutical companies have featured prominently in antitrust court actions.[12,13]

Corporate philanthropy

The pharmaceutical industry has responded to the poor availability of its products in the developing world by donations. Some companies have maintained excellent programmes. Since 1987, Merck has given away well over 100 million treatments with ivermectin for onchocerciasis.[14] SmithKline Beecham (now GlaxoSmithKline) has made a similar commitment with albendazole for helminth infection.[14] Other programmes have not been so well received, mainly because of limitations imposed by sponsors. Pfizer offered to supply fluconazole free in South Africa for treatment of cryptococcal meningitis, but not for people with AIDS-related monilial infections.[15] However, the company did not extend its offer to other sub-Saharan countries where the need is as great as in South Africa.

A concern about philanthropic programmes is that they are a mechanism for keeping world prices high while being seen to assist the most disadvantaged groups. Médecins

Sans Frontières has argued that development of generic drugs is a less costly and more sustainable method of supplying necessary drugs than donations.[16] Reliance on drug donations poses additional risks. In the early 1990s, allegations were widespread about donations of inappropriate and out-of-date products.[17,18] In response, WHO, in collaboration with other agencies, issued a set of guidelines for appropriate donations.[19] These guidelines have a core set of principles, including maximum benefit and respect for the wishes and authority of recipients, support for existing government policies, and avoidance of double standards in quality. Drugs should be on the recipient country's essential drug list and should have a shelf life of at least a year after they arrive in the country. Reich and colleagues[20] assessed 16 566 drug donations shipped from the USA to 129 countries between 1994 and 1997. Although most of the donations fulfilled the criteria for relevance and time-to-expiry, 10–40% were listed on neither the national essential drugs lists nor the WHO model list of essential drugs, nor were they permissible therapeutic alternatives. In three countries that were surveyed, around 30% of items had a shelf life of a year or less.

Subsidisation of drugs

Because of market failure, government intervention is widespread. Most governments in rich countries subsidise use of drugs in their communities. A survey done by the Organisation for Economic Cooperation and Development reported that member countries spent an average of 15·4% of their health budgets on drugs in 1996.[21] Although this figure was unchanged from 1990, the variation between countries (7·6–28·9%) was substantial, and proportions were higher in low-income countries. Total per capita expenditure on drugs ranged from US$129 in Ireland to over US$300 in Japan and the USA. The amount of government subsidisation of costs (generally through insurance programmes) varied by country, being lowest in the USA (15%), and highest in Norway, Turkey, and the Czech Republic (80% or more).[21] Recent data suggest that drug expenditure is increasing rapidly and creating financial pressures in several countries. Between 2000 and 2001, the costs of drugs rose by 16% in the USA and Canada, 14% in Australia, and 12% in Italy.[22] These rises can be attributable to aggressive promotion and rapid uptake of several drug classes, including cyclo-oxygenase-2 inhibitors, new antidepressants, and neuroleptics.

Price controls

In countries in which governments are large buyers of drugs, dialectic with industry over prices will inevitably take place. Companies want prices to be as high as possible, but they recognise that governments will only tolerate these high prices to a certain point. Governments generally want prices at levels that will not break their drug budget, but recognise that if they demand too low a price, companies might decide not to market a product, and could reduce local investment.

Many governments in developed countries use their purchasing powers to enforce price controls. Several, including the UK and Turkey, use profit controls.[21] New Zealand has had some success in control of drug prices by a tough (but unpopular) system of reference pricing, tendering, and therapeutic substitution.[23] Reference pricing assigns a drug to a group of products, which receive the same level of reimbursement.[21] Drugs can be referenced on the basis of clinical performance, sometimes to the cheapest generic product.[21] Findings of a programme in Canada have so far shown substantial savings in drug expenditure, but the overall effects of this policy on patients' health and associated health care and administrative costs remain unclear.[24]

Several countries, including Australia, Canada, and the UK, use cost-effectiveness analysis as a basis for subsidisation decisions. Findings of an international analysis concluded that this policy had provided Australia with low prices for me-too drugs, whereas innovative products were priced somewhat closer to the average of the price in comparison countries, suggesting that this approach to pricing can reward advances in treatment.[25] The effects of these policies have been controversial. In Australia (under the control of the Pharmaceutical Benefits Advisory Committee) and the UK (National Institute for Clinical Excellence), advisory bodies have been subjected to repeated criticisms by industry, and legal and political challenges.[26,27] Major companies have also been openly critical of attempts by European governments to use their buying power to secure price discounts.[28]

The international pharmaceutical industry as a business

Pharmaceutical companies are not especially big in terms of revenues, but they are very profitable. For instance, in 2001, Pfizer was ranked 127th in the world on total revenue (US$32·2 billion) but 7th in terms of profit.[29] The pharmaceutical industry is the most profitable business sector, with an average 16·2% profit, ahead of financial companies (11·6%) and beverages (10%).[30] However, net income growth has declined, and growth in the value of drug stocks has been reversed in the past year.[31]

In 2000, the global market value of prescription drugs sold by leading companies exceeded US$320 billion, a rise of 11% over the previous year.[32] Over 46% of the market value was from sales in North America.[32] Until recently drug company shares consistently outperformed market indices (table 1). By February, 2001, Pfizer, had become the 18th largest market entity, bigger than the listed domestic equity markets of many countries, including South Africa and South Korea.[33]

Mergers of pharmaceutical companies have been common, and the number of major international manufacturers is predicted to fall from over 30 to around 12 in the next 10 years.[34] The main point of mergers seems to be to replenish depleted product pipelines, cut costs (including research and promotion), and maintain growth and profitability, rather than to reduce prices to customers (see also article by Abraham, published in *The Lancet* on Nov 9, p 1498).

The net profits of the industry generally exceed the amounts that are spent on research and development (table 1). Average claimed expenditure on research and development by major companies was 16% of their revenue in 2000 (table 1). According to the Pharmaceutical Research and Manufacturers Association of America, this is substantially higher than for other industry sectors, which spend on average 4% (9% in the case of the software industry).[35] However, most controversy surrounds the very high company outlays on promotion and marketing (see article by Collier and Iheanacho, published in *The Lancet* on Nov 2, p 1405).

The generic drugs industry

In developed countries, generic drug manufacturers provide many patients with non-patented drugs; some of these companies have consolidated to produce internationally important businesses.[36] Industry is expanding in developing countries—eg, India, China, and

	Drug sales (US$ billion)	Operating profit margin (% revenue)	Net profit or loss (% revenue)	Research and development (% revenue)	Marketing and administration (% revenue)*	Approximate share price movement (%)†	Market capitalisation, November, 2001 ($US billion)
Company							
GlaxoSmithKline	23·38	30·7	28·0	N/A	N/A	890	166·4
Pfizer	22·57	39·3	16·5	17·1*	39·2	5800	274·3
Merck	20·22	57·2	29·2	11·6	15·9	7200	149·2
Bristol Myers Squibb	15·88	N/A	29·7	9·1*	22·6	4700	108·0
AstraZeneca	15·70	25·6	16·2	N/A	N/A	450 (since January, 1994)	81·5
Aventis	14·90	19·4	–0·91	16·8	N/A	230 (since January, 1994)	55·0
Pharmacia	12·65	8·7	5·7	17·1	38·6	970	58·7
Johnson and Johnson	11·95	34·9	40·2	15·9	38·2	17 000	185·8
American Home Products	10·80	27·1	–21·9	15·0	37·2	1000	78·4
Hoffmann-La Roche	10·47	33·2	48·9	18·1	N/A	N/A	N/A
Novartis	10·42	N/A	40·9	18·3	N/A	100 (since May, 2000)	95·4
Eli Lilly	10·19	N/A	30·0	17·8	27·6	2000	92·7

Data refer to 2000 unless otherwise specified. N/A=data not available. *1999 data. Sources: http://www.finance.yahoo.com; http://www.fortune.com; http://www.pjbpubs.co.uk. †Between January, 1990, and November, 2001, unless otherwise stated. By comparison, the S&P 500 index rose by about 650% during this period (approximate values read off graphical displays).

Table 1: **Summary of performance data from the world's major pharmaceutical manufacturers**

Brazil—with companies legally selling drugs that are patent-protected in high-income countries.

In 1997, the top ten generic drugs companies had sales of around US$6 billion.[35,36] These companies have considerably grown in size in recent years. Despite revenues that are much smaller than those of the major international companies, they have a substantial effect on health-care delivery. Generic drug companies provided treatments to more than half the patients in some countries in 1997 (table 2), and this figure is rising.[37]

The true importance of generic drugs is seen by their effect on prices (table 3). Introduction of a generic form of omeprazole in Australia led to a 43% reduction in the price of Losec over a 2-year period. More important has been the 97% reduction in price of combination antiretroviral drugs after marketing by Indian generic-drug manufacturing companies.

Privatisation of research

The pharmaceutical industry claims to have invested US$30·5 billion in research and development in 2001, which would make it the largest direct funder of medical research in the USA.[35,38] The nature of this research is changing. Increasing numbers of studies seem to be concerned with marketing issues—eg, establishing equivalence with existing products rather than trying to develop superior drugs. In the USA, studies are done increasingly by for-profit contract research organisations, rather than by academic medical centres (60% in 1998 *vs* 20% in 1991).[39] Concerns relate mainly to loss of independence in the implementation and reporting of research. Studies have shown that industry-sponsored research is more likely than independent research to have results favourable to the study drug[40–42] (see article by Collier and Iheanacho, published in *The Lancet* on Nov 2, p 1405).

	Value of sales (US$ million)	Generics, percentage of total market	
		Value	Volume
Country			
USA	6500	11	49
Japan	3500	6	N/A
Germany	2600	16	40
UK	1100	12	49*
Canada	670	15	40
Denmark	269	30	60

N/A=not available. *Recent data suggest that this figure may have risen to over 70%.[37]

Table 2: **Summary of sales and market share for generic products in selected countries in 1997[36]**

Identification of development targets

Pharmaceutical companies may choose diseases that offer the largest return on investment, such as chronic disorders with a high prevalence in developed countries. The enormous earnings from drugs for raised cholesterol concentration, depression, and musculoskeletal disorders confirm the success of this strategy. Widening the indications for existing drugs is a useful means for pharmaceutical companies to enhance revenue further, but can distort benefit-to-harm ratios when increasing numbers of individuals with mild disorders take the products.

Low-income countries do not benefit from this largesse. According to a report from Médecins Sans Frontières, of 1223 new chemical entities commercialised from 1975 to 1997, only 13 (1%) were specifically for tropical diseases, and just four could be deemed products resulting directly from research activities of the pharmaceutical industry.[5,43]

In some rich countries, companies have incentives to develop drugs for rare diseases. The Orphan Drug Act was introduced in the USA in 1983, and similar legislation has since been introduced in Japan and Australia.[44] Rare diseases have been defined as those with a prevalence of 0·1–0·75 in 1000. The benefits offered to the pharmaceutical industry vary between countries, but include tax credits, relief from registration fees, and marketing exclusivity for periods of 5–10 years. Up to 1999, 92 companies or institutions submitted applications for orphan status for 890 drugs, of which 173 were licensed for the treatment of disorders such as Gaucher's disease and cystic fibrosis.[44] Some of these orphans have grown into lusty adolescents—for instance erythropoietin and interferon alpha. These factors have contributed to the generally low tax liability of pharmaceutical companies. Between 1993 and 1996, the average tax rate was only 60% of that levied on other manufacturing industries in the USA.[6]

Costs of drug development

The pharmaceutical industry justifies its research decisions and the high cost of its products by pointing to the time, risk, and cost associated with new drug development: drugs take about 12 years to develop, companies have a low success rate, and each product is claimed to cost US$500–600 million to develop.[45] Development time is shorter for some classes of drugs, for example, the first 14 antiretroviral drugs took an average of 4·4 years from the date of filing of key patents to approval by the US Food and Drugs Administration.[46]

Omeprazole (Australian prices)				Antiretroviral combination therapy*			
Generic product		Branded product†		Generic product		Branded product	
Date	Price (US$)	Date	Price (US$)	Date	Price (US$)	Date	Price (US$)
November, 1998	N/A	November, 1998	43·28	July, 2000	230·59	September, 2000	869·92
November, 1999	30·86	November, 1999	31·27	September, 2000	66·67	October, 2000	77·58
November, 2000	30·01	November, 2000	30·63	February, 2001	29·17	March, 2001	59·33
November, 2001‡	24·10	November, 2001	24·51	August, 2001	24·58	August, 2001	59·33

N/A=not available. *Monthly cost of combination treatment with stavudine and lamivudine and nevirapine. †Dispensed prices for 30×20 mg capsules of Losec brand on the Australian Schedule of Pharmaceutical Benefits (converted to US$ using exchange rate on Nov 30, 2001). ‡Further price drop after withdrawal of prescribing restriction.

Table 3: **Effect of generic products on drug prices**[38]

There is a high failure rate in drug development at the stage at which drugs enter clinical development. However, during the early 1980s, 43% of terminations that arose at least 4 years after submission of an investigational new drug application were for economic reasons, compared with 31% for efficacy issues and 21% for safety problems.[47]

The most widely quoted estimate of the cost of bringing a new drug to market is that of DiMasi and colleagues of US$500 million.[48] This figure was recently updated to US$800 million. A substantial proportion of the cost was the lost income that might have been earned had companies invested their assets rather than making drugs (the opportunity cost of the capital). There was no consideration of tax credits from doing research and development, which can reduce totals costs by between 16% and 39%, or savings made by licensing in drugs from other organisations.[38] The balance sheet did not reflect the contribution made by public institutions, especially in the USA. A study of 21 drugs introduced between 1965 and 1992, and considered to have had the highest therapeutic effect on society, found that public funding of research was instrumental in the development of 15.[49] Other estimates of drug development costs have been lower. For instance a private/public sector partnership, using a business plan that involved the outsourcing the different stages of drug development, estimated a total drug development cost (adjusted for failures) of between US$115 and $240 million.[50]

Use and abuse of patents

Although the pharmaceutical industry's high profits and promotional costs have been criticised, the major international battlefield has been intellectual property rights. The industry argues that extensive protection of these rights is essential to generate income to reinvest in research that is needed to ensure a continuing supply of new drugs.[45] Only a small proportion of the price of a drug is accounted for by manufacturing costs. The value that is attributed to intellectual property is large and controversial. Governments protect intellectual property through patents. These grant exclusive manufacturing rights for a period of 20 years from the date of filing for the patent. In practice, because of the time taken to get a drug to market, the monopoly selling power is usually around 12–14 years. Patents are also intended to benefit the community, by encouraging innovation and ensuring an affordable supply of the drug. Governments have great authority over the granting and use of patents. For instance, in the USA, patents covering drugs that have been developed with public support are subject to so-called march-in rights,[51] which means that the government has the right to license the drug to other companies if the patentee does not make it available to the public on reasonable terms (a fair price). In practice, governments have been reluctant to exercise such rights on behalf of their communities.

Pharmaceutical companies rely heavily on patents and go to great lengths to maintain and extend them. The techniques they use are known as "evergreening",[52] and include: introduction of new formulations (including fixed combinations), which are marketed heavily before the generic version of the drug is released; second-medical-use patents for drugs nearing the end of their basic patent life; repeated patent infringement suits, which trigger an automatic 24–30 month delay in processing of the generic product claims in Canada and the USA; and collusion with generic manufacturers to keep products off the market.[52,53] Also, a company can manufacture and patent a near-identical product that has no real therapeutic advantage over the original agent—for example, esomeprazole, an enantiomer of the top-selling proton-pump inhibitor omeprazole.

Trade-related intellectual property rights

Internationally, exclusivity of production is protected through World Trade Organization (WTO) agreements on trade-related intellectual property (TRIPS).[5,54–56] Countries that join the WTO benefit from a reduction in tariffs when selling their goods. In return, they must guarantee protection of products and processes by granting patents. TRIPS agreements set the minimum standards of protection that must be implemented by member governments.[56] This arrangement can be a rather one-sided for less-developed countries.[5,57] A promised reduction in tariffs imposed on their exports (which may not happen) seems a poor exchange for large rises in the prices of important drugs that would otherwise be sourced from low-cost generic suppliers. The recent report by the Commission on Intellectual Property Rights provides a clear view that intellectual property rights are instruments of public policy and that "there are no circumstances in which the most fundamental human rights should be subordinated to the requirements of [intellectual property] protection".[58] TRIPS agreements include safeguards, including the granting of compulsory licences, which enable local production of drugs by non-patent-holders in the case of public-health emergencies or abuse of patent rights. An early-working provision allows product development, test manufacture, and registration of generic versions of the drugs before patent expiry.[55]

In practice, many developing countries need extensive assistance to implement the provisions in TRIPS agreements. Progress has not been helped by the tactics of governments in developed countries, aimed at protection of the interests of their large domestic industries.[57] At a ministerial meeting in Doha, Qatar, the WTO reaffirmed that the TRIPS agreement should be interpreted and implemented so as to protect the public health and promote access to drugs for all.[59] If countries declare an emergency, they can issue compulsory licences without previous negotiation with the patent owner. The deadline for adherence with WTO conditions for least-

developed countries was extended from 2006 to 2016.[60] Because compulsory licences are issued for domestic markets, countries with limited manufacturing capacity have difficulty taking advantage of this provision. Effectively, they can only import drugs under compulsory licence from countries where the products are not patented.[59]

The WTO has also recognised the need for differential pricing of essential drugs, whereby prices vary in accordance with national wealth, with safeguards to prevent parallel importation of these cheap products to high-income countries.[61] Differential pricing has been applied successfully to some vaccines, contraceptive preparations, and antimalarial drugs.

Conclusions

The international pharmaceutical industry manufactures and distributes many drugs, displays generosity in its philanthropic activities, and has an important role in maintenance of manufacturing standards. However, evidence shows that companies have shifted their core activities from discovery and development of innovative drugs to marketing of products that keep profit to a maximum in high-income countries.

Access to important drugs by low-income countries is generally agreed to remain grossly inadequate. Some international manufacturers have responded to this crisis by sharp reductions in prices of some products. These moves largely seem to have been in response to external pressures, especially bad publicity and generic competition, rather than initiatives of the companies themselves.

Improved access to patented drugs could be enhanced by widespread voluntary licensing arrangements with the growing number of pharmaceutical companies in developing countries and freer trade between countries with varying amounts of manufacturing capacity. The knowledge and technical expertise of international companies could help to guarantee the quality and appropriate use of these drugs.

Conflict of interest statement

None declared.

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