The pharmaceutical industry as a medicines provider

David Henry, Joel Lexchin

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.

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. 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.

**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 negotiate discounts, but individual patients cannot.10 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.

**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. 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. 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.

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, 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.

Despite these controversies, companies have remained profitable, with better margins than other industries. 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.

**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. SmithKline Beecham (now GlaxoSmithKline) has made a similar commitment with albendazole for helminth infection. Other programmes have not been so well received, mainly because of limitations imposed by sponsors. Pfizer offered to supply flucloxacilone free in South Africa for treatment of cryptococcal meningitis, but not for people with AIDS-related monilial infections. 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.
Sans Frontières has argued that development of generic drugs is a less costly and more sustainable method of supplying necessary drugs than donations. Reliance on drug donations poses additional risks. In the early 1990s, allegations were widespread about donations of inappropriate and out-of-date products. In response, WHO, in collaboration with other agencies, issued a set of guidelines for appropriate donations. 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 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. 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). 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. 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. New Zealand has had some success in control of drug prices by the same level of reimbursement. Drugs can be priced with a tough (but unpopular) system of reference pricing, which assigns a drug to a group of products, which receive the same level of reimbursement. Drugs can be referenced on the basis of clinical performance, sometimes to the cheapest generic product. 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.

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. 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. Major companies have also been openly critical of attempts by European governments to use their buying power to secure price discounts.

**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. The pharmaceutical industry is the most profitable business sector, with an average 16–2% profit, ahead of financial companies (11–6%) and beverages (10%). However, net income growth has declined, and growth in the value of drug stocks has been reversed in the past year.

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. Over 46% of the market value was from sales in North America. 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.

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. 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). 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. Industry is expanding in developing countries—eg, India, China, and...
Table 1: Summary of performance data from the world’s major pharmaceutical manufacturers

<table>
<thead>
<tr>
<th>Company</th>
<th>Drug sales (US$ billion)</th>
<th>Operating profit margin (% revenue)</th>
<th>Net profit or loss (% revenue)</th>
<th>Research and development (% revenue)</th>
<th>Marketing and administration (% revenue)*</th>
<th>Approximate share price movement (%)†</th>
<th>Market capitalisation, November, 2001 (US$ billion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eli Lilly</td>
<td>10·19</td>
<td>N/A</td>
<td>30·0</td>
<td>17·8</td>
<td>27·6</td>
<td>N/A</td>
<td>2000</td>
</tr>
<tr>
<td>Bristol Myers Squibb</td>
<td>15·88</td>
<td>N/A</td>
<td>29·7</td>
<td>9·1*</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Novartis</td>
<td>10·42</td>
<td>N/A</td>
<td>40·9</td>
<td>18·3</td>
<td>N/A</td>
<td>N/A</td>
<td>1000</td>
</tr>
<tr>
<td>Hoffmann-La Roche</td>
<td>10·47</td>
<td>33·2</td>
<td>48·9</td>
<td>18·1</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>American Home Products</td>
<td>10·80</td>
<td>27·1</td>
<td>-21·9</td>
<td>15·0</td>
<td>37·2</td>
<td>1000</td>
<td>78·4</td>
</tr>
<tr>
<td>Pharmacia</td>
<td>12·65</td>
<td>8·7</td>
<td>5·7</td>
<td>17·1</td>
<td>38·6</td>
<td>970</td>
<td>58·7</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>15·70</td>
<td>25·6</td>
<td>16·2</td>
<td>N/A</td>
<td>0%</td>
<td>N/A</td>
<td>450 (since January, 1994)</td>
</tr>
<tr>
<td>Bristol Myers Squibb</td>
<td>15·88</td>
<td>33·2</td>
<td>48·9</td>
<td>18·1</td>
<td>N/A</td>
<td>N/A</td>
<td>400 (since January, 1994)</td>
</tr>
<tr>
<td>Pfizer</td>
<td>22·57</td>
<td>39·3</td>
<td>16·5</td>
<td>17·1*</td>
<td>39·2</td>
<td>5800</td>
<td>274·3</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>23·38</td>
<td>30·7</td>
<td>28·0</td>
<td>N/A</td>
<td>166·4</td>
<td>92·7</td>
<td>6·4</td>
</tr>
<tr>
<td>Merck</td>
<td>20·22</td>
<td>57·2</td>
<td>11·6</td>
<td>3·9</td>
<td>19·5</td>
<td>7200</td>
<td>149·2</td>
</tr>
<tr>
<td>Eli Lilly</td>
<td>10·19</td>
<td>N/A</td>
<td>30·0</td>
<td>17·8</td>
<td>27·6</td>
<td>N/A</td>
<td>2000</td>
</tr>
</tbody>
</table>


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.

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. 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, which would make it the largest direct funder of medical research in the USA, and which would make it the largest direct funder of medical research in the USA. The true importance of generic drugs is seen by their impact 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.

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

<table>
<thead>
<tr>
<th>Country</th>
<th>Value of sales (US$ million)</th>
<th>Generics, percentage of total market</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>6500</td>
<td>11%</td>
</tr>
<tr>
<td>Japan</td>
<td>3500</td>
<td>1%</td>
</tr>
<tr>
<td>Germany</td>
<td>2600</td>
<td>6%</td>
</tr>
<tr>
<td>UK</td>
<td>1100</td>
<td>12%</td>
</tr>
<tr>
<td>Canada</td>
<td>670</td>
<td>15%</td>
</tr>
<tr>
<td>Denmark</td>
<td>269</td>
<td>50%</td>
</tr>
</tbody>
</table>

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

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. 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.

For personal use. Only reproduce with permission from The Lancet Publishing Group.
failures) of between US$115 and $240 million.50

been lower. For instance a private/public sector
governments have been reluctant to exercise such rights
research that is needed to ensure a continuing supply of
international battlefield has been intellectual property

Although the pharmaceutical industry’s high profits and
reasons, compared with 31% for efficacy issues and 21%
safety problems.47

However, during the early 1980s, 43% of terminations
stage at which drugs enter clinical development.

There is a high failure rate in drug development at the
place. In practice, because of the time taken to get a
right to license the drug to other
government has the right to license the drug to other

Patents are also intended to benefit
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
developed with public support are subject to so-called
“march-in rights”, which means that the

government has the right to license the drug to other
countries 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.

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.43 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
developed with public support are subject to so-called
“march-in rights”, which means that the

government has the right to license the drug to other
countries 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 product.53,55 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).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.55 This arrangement can be a rather
one-sided for less-developed countries.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.59

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.58 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-

Table 3: Effect of generic products on drug prices*

<table>
<thead>
<tr>
<th>Generic product (Australian prices)</th>
<th>Branded product†</th>
<th>Price ($US)</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>November, 1998</td>
<td>N/A</td>
<td>43-28</td>
<td></td>
</tr>
<tr>
<td>November, 1999</td>
<td>30-86</td>
<td>31-27</td>
<td></td>
</tr>
<tr>
<td>November, 2000</td>
<td>30-01</td>
<td>30-63</td>
<td></td>
</tr>
<tr>
<td>November, 2001</td>
<td>24-10</td>
<td>24-51</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antiretroviral combination therapy*</th>
<th>Branded product</th>
<th>Price ($US)</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>July, 2000</td>
<td>230-59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>September, 2000</td>
<td>66-67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>February, 2001</td>
<td>29-17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>August, 2001</td>
<td>24-58</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Brand product</th>
<th>Price ($US)</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.

For personal use. Only reproduce with permission from The Lancet Publishing Group.
developed countries was extended from 2006 to 2016. 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. 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. Differential pricing has been applied successfully to some vaccines, contraceptive preparations, and antimarial 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.

References


