Sector profile of the pharmaceutical industry

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Summary

Products and business description

This sector profile covers pharmaceutical end products only. These can be divided into three categories:

- **Prescription drugs**, based on chemical compounds and prescribed or administered by healthcare professionals
- **Over the counter (OTC) drugs**, based on chemical compounds and freely sold
- **Vaccines**, based on bacteria and viruses

The distinction between branded and generic products is also important. A branded product is the original version, produced by the innovative company that developed the product. A generic product is a copy of the original by another company. Many innovative companies have divisions that produce generics as well.

R&D for new drugs requires high investments. After the discovery of new chemical compounds with a therapeutic effect, a patent is filed. This protects the potential new drug against generic competition, usually for 20 years. The drug then still has to be tested in several phases of clinical trials. The total development process costs several hundred million dollars and takes over 10 years. If the new drug is finally proven safe and effective, it is approved by a regulatory authority. As long as a branded product is protected by a patent, companies charge high prices to recover R&D investments and make high profits. After patent expiry, competition from cheap generics usually causes a large drop in prices.

R&D investments for vaccines are comparable to those for drugs. However, the production process of vaccines is more complicated and their delivery requires an advanced infrastructure ('cold chain'). Furthermore, the new vaccines currently used in high income countries are of a different type than those recommended for poor countries. They are much more expensive, but are preferred due to the lower risk of adverse reactions.

The largest pharmaceutical markets are the US, Europe and Japan. Together, these account for 84% of the $460 billion of global drug and vaccine sales in 2003. Cardiovascular and central nervous system (CNS) medicines are the largest selling therapeutic classes.

Companies and business strategies

Over the last years, there have been many large mergers and acquisitions in the sector, while many companies have divested non-core activities. Although R&D investment has strongly increased over the past decade, many large companies do not have promising R&D pipelines and increasingly pursue growth through enhanced marketing. Outsourcing of production and alliances for R&D, distribution or marketing are common business strategies.

Key figures for 2003 of largest companies, ranked by market value (in $ billion)

Company (country)	Market value[1]	Sales	Net profit
Pfizer (US)	262	45.2	3.9
Johnson & Johnson (US)	149	41.9	7.2
Novartis (Switz.)	116	24.9	5.0
GlaxoSmithKline (UK)	116	35.2	7.8
Merck & Co (US)	97	22.5	6.6
Roche (Switz.)	90	25.5	2.5
AstraZeneca (UK)	77	18.8	3.0
Amgen (US)	76	8.4	2.2
Eli Lilly (US)	74	12.6	2.6
Aventis (France)[2]	70	17.8	1.9

Corporate Social Responsibility (CSR)

CSR refers to the responsibility of a company for the social, ecological and economic impacts of its operations. Some sector-

[1] (Number of shares) x (share price at 25-03-04)

[2] Aventis merged with Sanofi-Synthélabo in 2004.

specific critical CSR issues are outlined below.

- **Clinical trials**. This includes adequate protection of volunteers, also in poor countries, and disclosure of test results.
- **Drug safety**. This is heavily regulated and official manufacturing standards apply.
- **Drug promotion**. Drugs are sometimes promoted in irresponsible ways, e.g. misrepresenting drug safety. Related to this, some companies have bribed doctors to prescribe more of their products.
- **Tax payments**. Several companies have recently been charged with underpaying more than $1 billion of taxes.
- **Workplace health, safety and environment**. These are very important because of the processing of chemical compounds.

Access to medicines for poor people is also highly important. **Intellectual property rights**, which protect a drug against generic competition, can be an obstacle to access to medicines. The agreement on Trade-Related aspects of Intellectual Property Rights (TRIPS) of the World Trade Organizations (WTO) forms an international framework for these rights. It specifies minimum standards for intellectual property protection in national legislation, but allows exemptions to ensure access to medicines in the case of a public health crisis. The Pharmaceutical Research and Manufacturers of America (PhRMA), an industry organization to which all major pharmaceutical companies are affiliated, has been pressing governments to offer stronger intellectual property protection than is currently required by the TRIPS agreement. This is against the interests of poor people.

Access to medicines can be enhanced by setting **preferential prices**, far below the retail prices in the US or EU, for supplies to poor countries. In some cases companies set a single reduced price, often at cost, for a group of countries. However, in other cases deals that were unfavourable for poor countries have been negotiated with individual governments.

R&D for drugs and vaccines of special importance to poor countries is also a central issue. Because of the poor target populations, the returns on such research are relatively low. As a consequence, only 10% of R&D investment goes to developing countries' diseases and some companies continue to neglect this area.

Global Public-Private Initiatives (GPPIs)

GPPIs bring together different partners to address health problems in poor countries. They serve to bring together complementary expertise and to bring in additional funding. Different types of GPPIs include partnerships to increase R&D for a specific disease, to deliver drugs at low prices or for free, to strengthen local healthcare systems and to coordinate the efforts of various partners. Depending on the approach, some GPPIs are closely related to the core business of a company (e.g. R&D) while others are mere charity (e.g. donations).

There are a number of concerns about GPPIs and the role of pharmaceutical companies in them. Regarding the governance of GPPIs, transparency can be low, there may be conflicts of interests and recipient countries have sometimes little influence. Furthermore, GPPIs sometimes operate parallel to existing health systems, do not address underlying poverty-related causes of health problems, fail to reach the poorest people or may be unsustainable. Some companies use contributions to GPPIs to create a positive public image, while they do not pay attention to access to medicines or behave responsibly in day-to-day operations. They may be lobbying for stronger patent protection against public health interests, or the high profits enabling donation programmes can be partly based on excessive drug pricing or tax evasion.

Contents

1 Description of the sector

1.1 Definition of the sector

For the definition of the pharmaceutical sector, the NACE code[3] is helpful. The manufacture of pharmaceuticals is broken down into two Classes within NACE:[4]

- The manufacture of basic pharmaceutical products (NACE Class 24.41). These are the supplies and raw materials used in the next class.
- The manufacture of pharmaceutical preparations (NACE Class 24.42). These are the pharmaceutical end products and include medicaments, vaccines, homeopathic preparations, chemical and hormonal contraceptives, dental fillings, as well as medical impregnated bandages and dressings. This covers prescription and non-prescription pharmaceuticals, including homeopathic preparations, for human and veterinary use.

In the first class, DSM stands out as the world's largest supplier of pharmaceutical compounds. Nearly half of the twenty highset selling drugs in the world contain active ingredients from DSM.

When the pharmaceutical industry is mentioned in the press or in reports, this usually refers to the second class only, the manufacture of end products. This sector profile is also confined to that part of the industry.

Within this part of the sector, it important to recognize the distinction between branded and generic producers.

- **Branded companies** are the innovative companies that carry out the Research and Development (R&D) of new drugs (or contract this process). Initially, their products are protected by patents. The clinical test data, used for the approval of the drugs, is usually protected as well.
- **Generic companies** produce drugs that they have not developed themselves. Normally these drugs are not protected by patents anymore.

This report focuses mainly on the branded industry. However, many branded companies have divisions or subsidiaries that produce generics as well.

With regard to the products of these companies, three categories of drugs are commonly distinguished.

- **Prescription drugs**. These have to be prescribed or administered by healthcare professionals.
- **Over the counter (OTC) drugs**, also called self-medication drugs. These can be purchased without a prescription.

[3] NACE: *Nomenclature Generale des Activites Economiques dans l`Union Europeenne* (General Name for Economic Activities in the European Union).
[4] NACE Code, Centraal Bureau voor de Statistiek.

- **Vaccines**. These are usually regarded as a separate category next to pharmaceuticals.[5] In contrast to pharmaceuticals, vaccines are not based on chemical compounds but on live bacteria and viruses. The production process of vaccines is therefore quite different and far more complicated.

1.2 The business of drug development

Branded companies make high investments in R&D to discover new drugs. It is estimated that the development of a major drug costs up to US$ 400 million and requires as long as 10 years to be introduced into the market.

The development of new drugs usually starts with the discovery of new chemical compounds with a therapeutic effect. This is the first research phase. Once the basic compounds have been identified, pharmaceutical companies obtain patent protection for their potential use in new drugs. These patents grant the exclusive right to sell and market a specific drug for a specified time period, usually twenty years. After the discovery of a new compound follows the further development into an effective and safe treatment and the testing of the new drug candidate in subsequent phases of clinical trials. Finally, a new drug has to be approved by a regulatory authority, like the Food and Drug Administration (FDA) in the case of the US. Drug approval may take 1–1.5 year. The estimated duration, cost and rate of success for the various development stages of an average drug are provided in the table below. A short description of the testing phases is given as well.

Overview of different stages of drug development.

Phase	Description	Test group size	Cumulative time (years)	Success rate	Cost ($ mln)
Preclinical	Identify benefits and risks to participants in clinical trials		1-2	1 %	<1
Phase I	Test safety, dosage range and side effects on volunteers	20–80	3-4	10 %	0.5-15
Phase II	Test effectiveness and safety on patients	100–300	5-6	40 %	2-100
Phase III	Confirm effects on patients, compare with other drugs	1,000-3,000	8-9	80 %	} 30-400
Approval			10	95 %	

Source: CoreRatings (May 2003). *Philanthropy or Good Business? Emerging market issues for the global pharmaceutical industry*, p4,12.

[5] In this report the pharmaceutical industry generally refers to pharmaceuticals as well as vaccines. Occasionally the term pharmaceuticals will be used to distinguish prescription and OTC drugs from vaccines, but this should be clear from the context.

Thus, when a pharmaceutical company launches a new drug on the market, it has only a limited period of time of considerably less than twenty years in which it has exclusive marketing rights. During this period companies charge high prices for the drugs to recover their R&D investments and make high profits. The production costs of drugs are never disclosed, but they are only a fraction of the exclusive marketing price of a drug. It is estimated that average manufacturing cost are usually in the order of 5% of this price. Marginal production costs are still considerably lower due to economies of scale.[6]

Apart from patent protection, there is usually a period of data exclusivity that protects the clinical testing data of pharmaceutical companies. This period starts at the moment a product is approved and may have a duration of five years or more. During the data exclusivity period, other companies cannot rely on the data of the company that developed the drug for the approval of a generic version.

After the expiry of patent protection on a pharmaceutical product, other companies may legally copy the drug and sell a generic version. For the approval of a generic, a company has to proof that its drug is a biological equivalent of the original. This allows a company to rely on the clinical testing data of the branded company, provided that these are not protected by data exclusivity anymore. Generic producers therefore do not have to make high R&D investments and generic competition usually causes a large fall in prices. In the US, drugs face fierce competition right after the expiration of a patent. In Europe, generics are generally introduced slowly and at higher prices.[7]

A successful drug can generate enormous revenues for a pharmaceutical company. Some drugs, the so-called blockbusters, have sales of well over US$ 1 billion per year. Yet after the expiration of a patent, revenues can quickly diminish and companies may be forced to lower their profit margins because of generic competition. For example, in 2003 the quarterly sales revenue of its three medicines Glucophage IR, Taxol and Serzone of Bristol-Meyers Squibb dropped by 90% after patent protection expired.[8]

1.3 Market structure and trends

The largest pharmaceutical markets are the USA, Europe and Japan. The total world market for pharmaceuticals (sales of pharmaceutical products) displayed strong growth over the past years and increased by almost 9% in 2003. Due to the ageing populations in the major markets, drug use will probably continue to grow. Market size estimates of regional pharmaceutical markets and of the largest selling therapeutic areas are provided in the tables below.

[6] A. Guilloux (October 2000). Hidden price tags. Disease-specific drug donations: costs and alternatives. MSF.
[7] Financial Times (May 5, 2004). The wrong diagnosis: national champions may not cure the ills of the European drug indsutry.
[8] Bristol-Meyers Squibb Annual Report 2002 & 2003.

World pharmaceutical market by region, year prior to September 30, 2003.

Region	Value (£ bn)	% of total
USA	127	46
Europe	76	27
Japan	31	11
Asia Pacific excl. Japan	19	7
Latin America	12	4
Middle East, Africa	8	3
Canada	6	2
Total	**279**	**100**

Source: GSK Annual Report 2003, p61.

World pharmaceutical market for top five therapeutic classes, year prior to 30 September 2003.

Therapeutic class	Value (£ bn)	% of total
Cardiovascular	47	17
Central nervous system	46	16
Alimentary tract and metabolic	36	13
Anti-infectives (bacterial, viral and fungal), excl. vaccines	31	11
Respiratory	20	7
Total top five	**180**	**64**

Source: GSK Annual Report 2003, p61.

In the USA, some 50% of all prescribed drugs are generics, representing almost 20% of sales value. In Europe, market shares of generics range from a low 6% of sales value in France to 60% in Denmark. Competition from generics is increasing, and the market shares of generics are growing due to the attempts of governments to reduce healthcare spending.[9] Budget pressures are becoming larger because of the ageing populations in developed countries. Governments increasingly criticize the pharmaceutical industry for charging excessive drug prices.[10]

1.4 The vaccines market

The market for vaccines is somewhat different from that of other therapeutic classes. Like pharmaceuticals, the development of new vaccine products usually takes 7-12 years and

[9] Drug store news (February 17, 2003). *Getting poised for a steeper growth curve*. (special report: Generic drugs), see http://www.findarticles.com/p/articles/mi_m3374/is_2_25/ai_97998966; CoreRatings (May 2003). *Philanthropy or Good Business? Emergins market issues for the global pharmaceutical industry*, p6; Financial Times Global 500, 27 May 2004.

[10] Financial Times (October 22, 2003). Debate is raging over whether Nexium, a widely used ulcer drug, is really a worthwhile improvement for most patients over an earlier treatment - especially with healthcare budgets under growing pressure, writes Geoff Dyer.

costs several hundred million dollars. The development of new vaccines also requires the construction of new facilities. The strict government regulations that are imposed have profound implications for the vaccine industry, and vaccine producers have to continue to invest in production facilities in order to meet production standards. In addition, vaccines have to be kept at the right temperature during distribution and therefore the delivery of vaccines requires an advanced infrastructure ('cold chain') and active support of the producer.

A large majority of vaccines is procured at the national level by public health sector organizations. Large market segments may be served by a single company. Merck is the sole supplier of measles-mumps-rubella vaccines in the US, for example. Yet the demand for vaccines is difficult to forecast and may change during the actual production cycle, which is considerably longer than for pharmaceuticals. Demand for vaccines changes according to for example the severity of diseases, production lead times, regulations, and actions of competitors.[11]

The vaccines currently used in the US and other high income countries are often of a different type than those used in developing countries. For example, the US use the acelullar pertussis type and Measles-mumps-rubella (MMR) combination, whereas developing countries use wholecell pertussis vaccines and measles alone instead of MMR. The Netherlands has recently decided to start administrating the wholecell pertussis vaccine instead of the acellular type. This is because of the higher risk of adverse reactions associated with the older vaccine types.

Furthermore, high income countries use Inactivated Polio Vaccine (IPV) for routine immunization programmes, whereas developing countries use Oral Polio Vaccine (OPV).[12] OPV is easier to administrate and much cheaper. It is also the preferred vaccine when a polio outbreak needs to be contained, because it causes higher immunity in the intestinal tract and is therefore more effective to interrupt the circulation of the polio virus. However, in extremely rare cases (less than 1 in a million doses), the live attenuated virus in OPV can cause vaccine-associated polio. For this reason high income countries prefer IPV for regular immunization.

The newer vaccines, used in high income countries, are much more expensive. In some cases they cost over a hundred times more. A diphteria-tetanus-wholecell pertussis (DTwP) vaccine, for example, costs US$ 0.07 only. By contrast, the diphteria-tetanus-acellular pertussis (DTaP) vaccine that is used in high income countries, in combination with for example IPV or hepatitis B, costs over $10. Similarly, a single measles vaccine costs $0.14

[11] Communication with S. Gilchrist, Aventis, June 21, 2004.
[12] http://www.polioeradication.org/vaccines.asp.

only, whereas the MMR combination costs over $15. The prices of polio vaccines are $0.10 or less for OPV and $8.25 for IPV. [13]

Some vaccine producers based in industrialized countries, like Merck & Co., produce vaccine types used in high income countries only.

[13] A. Roberfroid (November 2000). A. presentation to the GAVI Partners' Meeting, Noordwijk, the Netherlands. See http://smain.synergynewmedia.co.uk/gavi/vaccinealliance/reference/ppt/roberfroid.ppt; S. McKinney & S. Jarrett (14 June 2002). Update on vaccine security. See http://www.who.int/vaccines-access/supply/Vaccine_security_Jarrett_McKinney.ppt.

2 Industry structure

2.1 Major pharmaceutical companies

The table below lists the 20 largest pharmaceutical companies in the world, ranked by market value.

Pharmaceutical companies ranked by market value.[14]

	Company	Country	Market value on 25-03-04 (US$ bln)	Turnover in 2003 (US$ bln)	Net profit in 2003 (US$ mln)	Employees at year-end 2003	GPPI part.*
1	Pfizer	USA	261.6	45.2	3,910	122,000	4
2	Johnson & Johnson	USA	149.0	41.9	7,197	109,500	2
3	Novartis	Switzerl.	115.8	24.9	5,016	78,500	4
4	GlaxoSmithKline	UK	115.5	35.2	7,816	101,000	9
5	Merck & Co	USA	97.2	22.5	6,590	62,300	7
6	Roche	Switzerl.	89.6	25.5	2,506	65,400	-
7	AstraZeneca	UK	76.9	18.8	3,036	60,000	-
8	Amgen	USA	75.6	8.4	2,260	12,800	-
9	Lilly (Eli)	USA	73.6	12.6	2,560	46,000	1
10	Aventis	France	69.8	17.8	1,901	75,600	5
11	Abbott Laboraties	USA	62.2	19.7	2,753	55,000	2
12	Genentech	USA	55.5	3.3	635	5,600	-
13	Sanofi-Synthélabo	France	48.6	9.9	2,570	33,000	-
14	Wyeth	USA	49.4	15.9	2,051	52,000	-
15	Bristols-Myers Squibb	USA	46.7	20.9	3,106	44,000	3
16	Takeda Chemical Ind.	Japan	39.3	10.3	2,699	15,000	-
17	Forest Laboratories	USA	25.8	2.2	622	4,000	-
18	Schering-Plough	USA	23.6	8.3	-92	31,000	-
19	Teva Pharmaceuticals	Israel	18.9	3.3	618	13,000	-
20	Bayer	Germany	17.7	35.4	-1,673	115,000	2

*** = participation in Global Public-Private Initiatives for health in developing countries.**[15]
Source: Financial Times Global 500 (27 May 2004), company websites and annual reports.

[14] Market value is also called market capitalization. The market value is the multiplication of the number of all the issued shares with the exchange rate at a specific time. The fiscal year of Takeda ended on March 31, 2004. Turnover and profits have been converted from Euro in the case of Sanofi-Synthélabo and Bayer and from CHF in the case of Orche at exchange rates of 8 July 2004 (US$ 1.238 per Euro, US$ 0.8164 per CHF).

[15] This selection of GPPIs excludes the Single Nucleotide Polymorphisms Consortium (SNP) and Pharmaceutical Security Institute (PSI), for example. Figures are mainly based on data from http://www.ippph.org, but it is known that these are not always accurate. A participation of a company in a GPPI may occasionally have been overlooked.

Apart from main financial characteristics and the number of employees, the table also mentions the numer of Global Public-Private Initiatives (GPPI), specifically aimed at healthcare in developing countries, in which each company participates.

Regarding the classification of the above companies as pharmaceutical producers, a the following should be noted.

- In the Financial Times Global 500, Abott Laboratories is be classified as a health sector company rather than a pharmaceutical manufacturer.
- Sanofi-Synthélabo and Aventis are listed separately, but agreed on a merger in which Aventis would be absorbed into Sanofi-Synthélabo. The acquisition took effect on 31 July 2004.[16]
- Amgen and Genentech are biotechnology companies.
- Teva is a major producer of generic drugs, but also manufactures innovative drugs in niche markets.[17]
- Bayer is actually a chemical company, but has an important pharmaceutical division that generates 35% of its sales.

The table shows that the pharmaceutical sector is dominated by US-based companies, yet Europe has some very large pharmaceutical companies too. Switzerland, the UK, France and Denmark each have two pharmaceutical companies ranking among their ten largest enterprises.

Analysts expect that biotechnology companies will gain a larger share of the pharmaceutical market. These companies apply new technologies for the discovery and development of new drugs. In 2002, eight out of the ten fastest growing pharmaceutical companies were biotechnology companies and in ten years, some of them may have surpassed many of the present pharmaceutical giants in market value. Investors already attribute very high market values to Amgen and Genentech, which indicates that they have high expectations of these companies.[18] Other main biotech companies are Novo Nordisk and UCB.

Vaccine producers in developing countries, supplying the type of vaccines used in developing countries, have recently experienced considerable growth. Historically they produced for the domestic market only, but more recently they have started to export to other developing countries too. The largest of these companies is the Serum Institue of India, that supplies 65% of all measles vaccines used in developing countries.[19]

[16] http://www.amf-france.org/inetbdif/viewdoc/affiche.aspx?id=12525&txtsch=.
[17] http://www.tevapharm.com/about.
[18] Financial Times Global 500 (May 27, 2004).
[19] http://www.vaccinealliance.org/site_repository/resources/ny2810.pdf; Communication with Ms. E. Esber, June 29, 2004.

2.2 R&D pipelines

In principle, the quality and the marketing potential of the products in the R&D pipeline of a company determine its potential for future growth. At present, the largest 20 pharmaceutical companies have almost 700 new drugs in development.[20] Over the past decade, R&D investments of the pharmaceutical industry have grown faster in the US than in Europe. In Europe, 2002 investments were Euro 20 billion, compared to 8 billion in 1990, whereas R&D investments in the US were at 28 billion in 2002, down from 5 billion in 1990. As companies are investing more heavily in the US, analysts perceive that the European pharmaceutical industry is in not in a favourable competitive position.[21]

Yet the increase in investment has not been matched by a comparable increase in new drug approvals, hence the R&D results of most companies are declining.[22] The complexity of the investigated treatments has increased and it has become more difficult to obtain approval for new drugs due to the stricter application of existing regulations in the US by the FDA. The most common reasons for not approving a drug are negative by-effects of the drug that were identified in clinical trials and the limited added value over existing drugs.[23] Worldwide drug approvals hit an all time low in 2003.[24]

The largest pharmaceutical companies, which have grown fastly during the 1990s, do not have promising R&D pipelines while patents on successful drugs are expiring. For the period 2002-2007, the drugs on which patent protection expires in these years generate combined sales of about US$ 40 billion.[25]

2.3 Protection against generic competition and growth through marketing

Pharmaceutical companies have several strategies to reduce or prevent competition form generic producers, which often greatly reduces the renevues from a drug. One strategy is to obtain additional patents to extend the period of patent protection, if possible. Another strategy is to fight the approval of generic drugs and charge generic producers of infringing patents or data exclusivity.

For example, in 2003 Mylan, Watson and Ranbaxy Laborories, two generic producers from the US and one India, resectively, sought FDA approval to produce generic versions of Actos. Actos is a blockbuster diabetes drug of Takeda, Japan's largest pharmaceuticals

[20] Financial Times Global 500 (May 27, 2004).
[21] Financial Times (May 5, 2004). The wrong diagnosis: national champions may not cure the ills of the European drug indsutry.
[22] CoreRatings (May 2003). *Philanthropy or Good Business? Emergins market issues for the global pharmaceutical industry*.
23 Het Financieele Dagblad/FD-Research (2003). *FD 300 Handboek Internationale Bedrijven & Sectoren*, p157.
24 Financial Times Global 500 (May 27, 2004).
25 Het Financieele Dagblad/FD-Research (2003). *FD 300 Handboek Internationale Bedrijven & Sectoren*, p157.

group. Takeda then took legal action against those three companies to prevent cheaper versions of its patented drugs from penetrating one of its most profitable markets.[26]

Yet generic producers are also becoming more aggressive and regularly try to bring generic drugs into the market before a patent is expired, usually arguing that a patent is invalid or not infringed. As a consequence, pharmaceutical companies are continuously involved in many lawsuits over intellectual property, either filed by themselves or by generic competitors.

Another strategy to protect a drug from competition is to launch a slightly improved version or more convenient formulation of the same drug. A new patent can be obtained for this improved drug. The company then tries to persuade doctors and patients to use this improved version. The effectiveness of this strategy depends to a large extent on the marketing of the new drug. Examples of attempts to curb generic competition in this way include AstraZeneca's marketing of Nexium, a slightly improved version of its out-of-patent ulcer drug Prilosec,[27] and the release of Wellbutrin XR by GlaxoSmithKline, a sustained release version of its antidepressant Welbutrin that now faces generic competition.[28] In the US, the growth of the industry over the last ten years has been partly based on such slightly improved new drugs, backed by massive sales and marketing operations and TV advertisement. [29]

Because of the disappointing results of their R&D pipelines, pharmaceutical companies increasingly pursue growth through enhanced marketing of their drugs. Especially the large pharmaceutical companies have developed into marketing specialists that are very good at putting products into the market. The focus on growth through marketing is reflected by the high marketing expenses compared to R&D investment. The Swiss company Roche, for instance, spends 31% of its turnover on marketing against 16% for R&D.[30] Corporate philanthropy and corporate responsibility programmes help to enhance a company's identity and hence such initiatives might support marketing efforts.

Marketing is also a stategy to reduce generic competition in itself. By promoting the propietary brand names of patented drugs, pharmaceutical companies may be able to sustain drug sales even if these are no longer protected by patents.

2.4 Restructuring and outsourcing

26 Financial Times (October 23, 2003) *Takeda files suits against US drug groups.*

27 Financial Times (October 24, 2003). *Twists and turns along the Crestor run.*

28 Financial Times (June 27, 2003). *GSK wins case against generic drugs.*

29 Financial Times (May 5, 2004). The wrong diagnosis: national champions may not cure the ills of the European drug indsutry.

30 Het Financieele Dagblad/FD-Research (2003). *FD 300 Handboek Internationale Bedrijven & Sectoren*, p157.

Several companies are restructuring their businesses to cut costs. Among these are Merck, which eliminated 4,400 jobs worldwide, and Organon, the human health division of Akzo Nobel, which cut 800 jobs in the US.

The contracting of drug manufacturing to low cost producers is a common business practice in the pharmaceutical industry. These are usually located in lower cost countries, such as India, China or South Africa. It is not unusual that the production is contracted to a company that produces generics too. Hence, although the development of the generic drug industry in low cost countries may lead to increased competition for branded pharmaceutical companies, it also creates opportunities for cost-saving through outsourcing of production.

There is a trend towards the outsourcing of R&D towards countries with lower wages too. For example, Novartis established its new R&D facility, the Novartis Institute on Tropical Diseases (NITD), in Singapore. GlaxoSmithKline linked up with the Ranbaxy, an Indian producer of competing generic drugs, for early-stage research of new drugs.[31] GlaxoSmithKline is also carrying out trials for its Rotavirus vaccine in Latin America, among other reasons because trials are considerably cheaper there, whereas reasonable infrastructure is readily available.

2.5 Consolidation and specialization

Over the last years, many pharmaceutical companies have been involved in large-scale margers and acquisitions and there is a trend towards further consolidation and concentration in the sector. Recent large mergers and acquisitions include the following:

- In 2004, UCB is to take over Celltech for US$ 2.7 billion, creating the fifth largest biotechnology company in the world
- In 2004, Sanofi-Synthélabo has taken over Aventis for Euro 55 billion
- In 2003, Pfizer acquired Pharmacia for US$ 56 billion[32]
- In 2002, Amgen acquired Immunex for US$ 16 billion
- In 2001, Johnson & Johnson acquired Alza for US$ 12 billion
- In 2001, Broistol-Myers Squibb acquired DuPont Pharmaceuticals for US$ 8 billion
- In 2000, Glaxo Wellcome and SmithKline Beecham merged to from GlaxoSmithKline[33]
- In 2000, Pfizer and Warner-Lambert merged to form the new Pfizer
- In 1999, Rhône-Poulenc and Hoechst merged to form Aventis[34]

At the same time, there is a trend towards concentration on pharmaceutical core-business and the divestment of non-core activities. Recent major divestments include the following.

[31] Financial Times (October 23, 2003).

32 http://www.pfizer.com/are/investors_reports/annual_2003/financial/p2003fr29_30_31_32.htm.

[33] http://www.gsk.com/about/background.htm.

[34] http://www.aventis.com; http://www.aventispasteur.com.

- In 2003, Merck divested Medco Health, a provider healthcare services
- In 2002, Aventis sold its agrochemical business to Bayer and its animal health division to CVC Capital Partners
- In 2002, Novartis divested its agrochemical business to form Syngenta

The consolidation leads to increased concentration of drug portfolios. For example, when Rhône-Poulenc and Hoechst merged in 1999, their combined portfolio included three fo the four medicines against sleeping sickness. The present merger between Sanofi-Synthélabo and Aventis could also lead to serious competition concerns, and in an effort to head these off Sanofi-Synthélabo has already agreed to sell two heart disease drugs and a manufacturing plant to GlaxoSmithKline.[35]

Because of the far more complicated production process and a series of litigation lawsuits in the 1980s, the number of industrialized country vaccine manufacturers has decreased over the past decades and they have consolidated into five major corporations. These are Merck & Co, GlaxoSmithKline, Aventis, Wyeth and Chiron. For some vaccines the number of producers is even lower. Yellow fever vaccines, for example, are produced exclusively by Aventis, GlaxoSmithKline and UCB (formerly Celltech).[36]

2.6 Strategic alliances

Strategic alliances are also common in the industry, mainly for combining the strengths of companies in different areas such as distriubution and marketing, manufacturing and R&D. For example, distribution or marketing agreements provide smaller companies, especially biotechnology companies, with access to large sales infrastructures. However, the number of alliances between biotechnology companies themselves has also been increasing, suggesting that they are becoming less dependent on large pharmaceutical companies for the marketing of their products.[37] On the other hand, biotechnology companies continue to offer interesting opportunities for large companeis to improve their R&D pipelines. Pfizer recently announced a new strategy to buy biotech companies, for example.[38]

2.7 Expansion towards generic drugs

In the first section of this report it was already mentioned that many branded companies have divisions or subsidiaries that produce generics as well. Of the twenty largest pharmaceutical companies listed in this report, only Teva Pharmaceuticals has the production of generic drugs as its main activity. However, some of the other companies are important generic producers too.

35 Financial Times (May 6, 2004). p 23, Sanofi expects a June close.

36 http://www.vaccinealliance.org/home/General_Information/Immunization_informa, 'underused vaccines'.

37 CoreRatings (May 2003). *Philanthropy or Good Business? Emergins market issues for the global pharmaceutical industry*, p6; Financial Times Global 500, May 27, 2004.

38 Financial Times (May 3, 2004). New Pfizer strategy to buy biotech companies.

Novartis some 15 generic companies, which were united under the single name Sandoz in 2003. Novartis has the goal to become the largest generics manufacturer in the world through takeovers. As part of this strategy, the company acquired the Canadian generics company Sabex in June 2004 for US$ 565 million. Sabex is has a leading position in generic injectables in Canada.[39] Similarly, Schering-Plough has 14 subsidiaries that manufacture generics, of which Warrick is the largest, and Abbott laboratories has a large generics division as well. The generics producer Greenstone was a daughter of Pharmacia and now belongs to Pfizer. The generics producers Bedford and Roxane Laboraties are both subsidiaries of Boehringer Ingelheim, a large innovative pharmaceutical company.

39 http://dominoext.novartis.com/NC/NCPRRE01.nsf.

3 CSR issues on access to medicines for developing countries

3.1 Recent developments on TRIPS

The protection of intellectual property is an important aspect of access to medicines. As decribed above, patents and other forms of intellectual property rights protect a innovative drugs against generic competition. The pharmaceutical industry itself stresses that access to medicines depends on many more factors than patents, including the infrastucture for the distribution of medicines.

The potential effects of generic competition on drug prices in developing countries will be illustrated with a common example of anti-retroviral (ARV) therapy. Before 2001, ARV treatment would cost more or less the same in Africa as in the US and Europe, about $10,000 a year. Only a relatively small number of countries had negotiated prices in the range of $1,000 a year, after lengthy negotiations with the patent holders, who sometimes required them to keep the lower prices a secret. In february 2001, prices suddenly dropped when the Indian generics manufacturer Cipla offered ARV therapy for US$ 350 a year. India recognizes patents on drug-making processes, not on products, so Cipla can legally produce generics as long as it uses a slightly different process.[40] In August 2003 Aspen Pharmacare launched the first domestically produced generic in South Africa, a copy of Bristol-Myers Squibb's Zerit. [41]

An important international framework for the protection of intellectual property is the World Trade Organization (WTO) agreement on Trade-Related aspects of Intellectual Property Rights (TRIPS). This agreement was concluded in the Uruguay round of WTO negotiations that ended in 1994. The TRIPS agreement requires all WTO members (currently 147 countries) to pass legislation that protects intellectual property, such as patent protection. It also states that signatories must protect patent holders' data from '*unfair commercial use*', but it does explicitly not oblige data exclusivity periods. Least developed countries were given until 2006 to comply with these requirements.

The articles 6, 30 and 31 of the agreement are of special relevance for access to medicines in developing countries.

- Article 6 specifies that countries can decide whether or not to allow international exhaustion of patents. This is also called parallel importing and means that patented products may be imported from foreign markets at a lower price.
- Article 30 allows countries to provide exceptions to the exclusive rights conferred by a patent, provided that they do not unreasonably conflict with a normal exploitation of the patent.

[40] New York Times (March 21, 2002). *New list of safe AIDS drugs, despite industry lobby.*
[41] World Market Analysis (April 8, 2004). *Merck licenses efavirenz to Adcock Inrgam/Ranbaxy JV.*

- Article 31 allows countries to issue a temporary compulsory license for the generic production of a medicine in order to address acute or severe public health problems. However, Article 31(f) prohibits the exportation of drugs made under compulsory license from 2005. In practice, this would limit the use of a compulsory license to countries that have the capacity to produce generic drugs. Most developing countrie do not have this capacity.[42]

At the 2001 Ministerial Meeting in Doha, Qatar, the WTO adopted the Doha Declaration on TRIPS and Public Health.[43] This declaration extends the deadline for the implementation of patent protection by least developed countries to 2016, after which they may apply for individual deferment. Paragraph 6 of the Doha Declaration instructed the TRIPS Council to find an '*expeditious solution*' so that countries without drug production capacity could make use of compulsory licenses to import generics when necessary, and report back to the WTO before the end of 2002. On 16 December 2002 an agreement was almost reached in the form of the so-called Motta-text on TRIPS. However, the US blocked the proposal because the text would be too much against the interests of the pharmaceutical industry. NGOs also opposed the text because the strict conditions to use compulsory licensing would be unworkable. The proposal excluded vaccines as technically not being pharmaceuticals.[44]

At the fifth WTO ministerial conference, which took place in September 2003 in Cancún, a temporary agreement was reached to allow the exportation of generic drugs made under compulsory license. Strict conditions apply. These include disclosure of the names and expected quantities of the products, the special marking of the products and the postage of the supplied quantities on a website before shipment. Development organizations stress that the temporary solution does nothing to ensure access to cheap medicines on regular terms in the future. In addition, they are concerned that the strict conditions will be heavy obstacles to use the provision. The arrangement will last until the WTO amends Article 31(f) of the TRIPS agreement.[45]

In 1997 South Africa passed legislation to enable compulsory licensing and parallel importing. In 1998 a group of 39 pharmaceutical companies sued the government to overturn the law. However, the companies withdrew the lawsuit in April 2001 after a large amount of negative publicity. Similarly, in June 2001 the US withdrew a complaint it had filed with the WTO against a Brazilian law allowing generic drug production.[46]

Up to present no compulsory licenses have been actually issued. However, even if a government does not use a compulsory license, the possibility to do so may considerably

[42] Oxfam briefing paper 56 (November 2003). *Robbing the poor to pay the rich?*
[43] See http://www.wto.org/english/thewto_e/minist_e/min01_e/mindecl_trips_e.htm.
[44] Stijn Oosterlynck (September 2003). *Akkoord toegang tot medicijnen in WTO: beter geen oplossing!* In: WTO-Zip 28.
[45] Managing intellectual property (October 1, 2003). *A test of resolve.*
[46] See e.g. http://www.sfaf.org/treatment/beta/b48/b48drug_access.html.

strengthen its negotiating position to obtain lower medicine prices or a voluntary license. Some believe that pharmaceutical companies are doing everything to prevent the use of compulsory licensing, which could create a precedent for further compulsory licenses. Companies might therefore prefer to grant voluntary licenses instead.

3.2 Industry lobbying for intellectual property protection

Pharmaceutical companies have been accused of agressively lobbying against the weakening of international patent protection during TRIPS negotiations.[47] A large part of the industry lobby is carried out by the Pharmaceutical Research and Manufacturers of America (PhRMA). It is therefore difficult to determine the lobby positions of individual pharmaceutical companies. The PhRMA is a US-based organization that represents the country's leading research-based pharmaceutical and biotechnology companies.[48] Its members include all major pharmaceutical companies in the world, not just those based in the US.

The PhRMA pursues a TRIPS-plus agenda, that is, provisions on intellectual property protection that go beyond the requirements of TRIPS agreement. The main issues of this agenda are the following. [49]

- Limitations to compulsory licensing.
- The protection of test data by data exclusivity periods.
- No approval of generic drugs until the patent on a drug has expired, also called linkage of regulatory approval with patent status. This delays the launch of generic drugs beyond patent expiry, as generic producers typically obtain approval well in advance to prepare the launch of the generic product.
- No exhaustion of patent rights and no export of generics. This means that patented or generic products cannot be purchased in foreign markets at lower prices.

Recently the focus of the industry lobby has shifted towards the establishment and extension of data exclusivity periods. As explained before, this effectively prevents generic competition by not allowing other producers to rely on the clinical test data of the patent holder for approval of the drug. This may delay the launch of generic medicines beyond patent expiry. In line with these industry interests, the European Commission proposed in 2003 an extension of the data exclusivity period, which could threaten access to cheap generic medicines in accession countries.[50]

[47] Core Ratings (2003). Philanthropy or good business? Emerging Market issues for the global pharmaceutical industry. London: Core Ratings.
[48] See http://www.phrma.org.
[49] Oxfam briefing paper 56 (November 2003). *Robbing the poor to pay the rich?*
[50] G. Perry (2003). *Affordable medicines threatened in Europe*, see http://www.epha.org/a/703; Oxfam briefing paper 56 (November 2003). *Robbing the poor to pay the rich?*

The industry has a strong influence through the US Trade Representative (USTR), currently Mr. R. Zoelick. The USTR has taken positions similar to those of the innovative pharmaceutical industry, including on a deal on the paragraph 6 issue of the Doha Declaration. The Industry Functional Advisory Committee 3 (IFAC 3) to the USTR is the most immportant US advisory committee on intellectual property issues and consists of industry representatives. It includes a vice president of PhRMA, director of Public Policy for Merck, and Pfizer vice president. Not surprisingly, the IFAC 3 is advocating a TRIPS-plus agenda.[51]

Furthermore, PhRMA has 625 lobbyists based in Washinton DC and spent US$ 7.5 million on lobbying in 2000.[52] Total branded industry expenses on lobbying for this year amounted to $90 million. In the 2002 US election cycyle, the industry gave a total of US$ 29 million in contributions to political parties, and PhRMA alone spent $3.2 million. 74% of the total donations went to the Republican Party, which is most likely to defend the interests of the branded drug industry.[53]

Apart from multilateral trade negotiations, the US has several ways of enhancing intellectual property protection beyond the TRIPS provisions. [54]

- The US provides biased technical assistance to developing countries for the design and implementation of intellectual property regimes. This assistance is provided through USAID, other US agencies and the World Intellectual Property Organization (WIPO). Uganda's TRIPS-plus Industriual Property Bill of 2002 is an example of the outcomes of biased assistance. Advocacy of development organizations helped to prevent this bill from being passed.
- TRIPS-plus provisions are negotiated in regional or bilateral trade agreements. The US-Singapore Free Trade Agreement is example of this. PhRMA and the USTR regard this agreement as a basis for other Free Trade Agreements.[55] PhRMA also would like to see the US-South African Customs Union (SACU) Free Trade Agreement, currently being negotiated, to come into closer alignment with US standards.[56]
- The US threatens developing countries with trade sanctions. Under Section 301 of the Trade Act of 1974, the USTR issues a yearly report threatening foreign countries with trade sanctions for not adequately protecting intellectual property of US companies. These threats consist of the withdrawal of consessions under the US general system of preferences (GSP).

In contrast to the TRIPS-plus agenda of the PhRMA, some individual pharmaceutical companies have adopted a more flexible approach towards patent protection and granted voluntary licenses for the production of generic ARV drugs in Africa.

[51] Oxfam briefing paper 56 (November 2003). *Robbing the poor to pay the rich?*
[52] The Center for Responsive Politics.
[53] See http://www.opensecrets.org.
[54] Oxfam briefing paper 56 (November 2003). *Robbing the poor to pay the rich?*
[55] IFAC 3 report on US-Singapore FTA (2003); USTR special 301 report (2003).
[56] PhRMA special 301 submission.

3.3 Pricing of medicines[57]

Pricing is one of the areas where pharmaceutical companies can make a major contribution to enhance access to medicines in developing countries. Lower medicine prices can considerably increase their availability to poor populations, regardless from other problems such as the weak infrastructure for the delivery of medicines in developing countries. Sales in poor countries, especially least developed countries, typically generate a very small proportion of the total sales of a pharmaceutical company. Companies could therefore supply medicines too these countries at differential, strongly reduced prices, without a substantial loss of profits.

This brings two potential risks for pharmaceutical companies. Firstly, the supply of cheaper medicines in developing countries can result in parallel imports of these medicines into high income markets, where they can be sold by others for a much higher price. Such product diversion means that the medicines will not reach the target population and that the company will suffer reduced sales in high income countries. Most industrialized countries prohibit parallel imports without the permission of the patent holder. Some companies have taken additional steps to prevent preferentially priced medicines from being illegally re-sold at higher prices. Preferentially priced products from GlaxoSmithKline, for example, have different colours and come in different packages, so they can be easily recognized.[58]

Secondly, the preferential prices may be used as a reference by healthcare providers in high income countries for negotiating lower prices. This is called reference pricing. Companies sometimes set preferential drug prices for least developed countries at production cost, which is normally kept secret because it is higly sensitive commercial information. The prevention of reference pricing requires political commitment from developed countries. The Accelerating Access Initiative (AAI), a partnership that searches to enhance access to ARVs, has demonstrated that this problem can be overcome.

From a public health point of view, there are several concerns about the preferential pricing offers of pharmaceutical companies. In the past most pharmaceutical companies used to negotiate preferential prices on a case-by-case basis with individual countries. Such negotiations are a lengthy process often yield sub-optimal outcomes for developing countries. Individual negotiations also limit the transparency and reliability of preferential prices. Furthermore, governments may be required to offer advantages to the company in exchange, such as refraining from resorting to generic drugs, or to keep medicine prices secret.[59] This type of negotiations for ARV prices under the AAI have caused the

[57] This section is based on Oxfam, VSO & Save the Children (2002). *Beyond Philanthropy: the pharmaceutical industry, corporate social responsibility and the developing world, p12-14.*
[58] GlaxoSmithKline annual report 2003, p29.
[59] Act Up Paris (15 May 2002). *"Accelerating Access"serves pharmaceutical companies while corrupting health organizations.* Press release.

partnership to be heavily criticized. Furthermore, price reduction have often been limited to small numbers of products. Development organizations therefore stress the need of a generalized global system of differential prices, which covers a broad range of a company's medicines and bases eligibility on objective indicators.[60] Several companies have recently adopted preferential pricing schemes for ARVs that meet the criteria of fixed prices for groups of countries, objectve eligibility criteria and transparent offers. Yet in some cases negotiations still take place on a country basis, especially with middle-income countries.

3.4 R&D for developing countries' diseases

The majority of R&D expenditures is aimed at treatments for diseases that are mainly prevalent in high income countries. It is estimated that only 10% of R&D investment goes to diseases of developing countries, whereas these diseases account for 90% of the global disease death burden. Many poor people suffer or die from diseases that are treatable or curable, but for which little research is being performed. These include sleeping sickness (African Trypanosomiasis), diarrhoeal diseases, schistosomiasis, chagas disease and leprosy. Compared to for example HIV/AIDS research, R&D investment for leishmaniasis, tuberculosis (TB) and malaria is also relatively low.[61]

The reason for this discrepancy is that there are only 'small markets' for these medicines, which means there is little profit to be made, except for HIV/AIDS treatments. They will therefore not yield an adequate return on R&D investments. This contrasts with treatments against diseases and disorders such as hypertension, elevated cholesterol levels, depression, arthritis, allergy and schizophrenia. These treatments fall in the therapeutic areas that generate the largest sales worldwide, as indicated earlier in this report.

3.5 Drugs donations

Many pharmaceutical companies make drug donations to developing countries. Although these may help to improve access to medicines, there are some important concerns about drug donations. [62]

- Donations may have an undue influence on the choice of medicines that are used in a recipient country. If one drug is available for free and other drugs are not, the first drug might be used even though it is not the prefered treatment.
- Various types of restrictions may apply, such as geographic, quantitative, indication and time restrictions.

[60] Oxfam, VSO & Save the Children (2002). *Beyond Philanthropy: the pharmaceutical industry, corporate social responsibility and the developing world.*

[61] http://www.globalhealthforum.org; CoreRatings (May 2003). *Philanthropy or Good Business? Emergins market issues for the global pharmaceutical industry*, p7.

[62] See A. Guilloux (October 2000). Hidden price tags. Disease-specific drug donations: costs and alternatives. MSF; Health Action International (15 July 2003). *Health Action International to the Global Fund: say no to medicine donations.*

- Sometimes donations require the implementation of a separate donations programme and are accompanied by high administrative costs for the recipient country.
- Recipient countries may become dependent om medicine donations.
- Donations may be more costly for donor governments than the procurement of preferentially priced or generic drugs, because of tax breaks that are under certain conditions granted to the donating companies, especially in the US. Not all donation programmes qualify for tax breaks, though.
- Donations may have a negative impact on the development of the generic drugs industry and therefore cause unfair competition.
- Assuming that tax breaks are not a substantial compensation for donating companies, it is generally considered that offering preferentially priced medicines at production cost is more sustainable than medicine donations, because it enables companies to recover their expenses. In addition, the decision to donate a certain medicine involves setting priorities for the use of resources available to enhance healthcare in developing countries. If companies offer preferential prices for a wide range of drugs instead, this would allow developing countries more autonomy to set their own priorities.
- In the past there have been several cases of medicine donations that were inappropriate and sometimes even useless for the recipients. For example, donated medicines were not requested and could not be used, they could not be identified due to inappropriate labelling, or they had a remaining shelf-life too short to be used in time. [63]
- Donations may be a disguised form of medicine promotion. In one case, for example, the Swiss company Novartis announced free supplies of its cancer drug Glivec to people around the world that could not afford its costs of US$ 27,000 per year. Some estimated that this number of patients would be as high as 600,000. However, in the end only 1,500 patients outside the US benefited from these donations, of which just 11 in least developed countries. It became clear that Novartis had used Glivec as part of a marketing strategy, and even encouraged patients benefiting from the donations to press public health systems to pay high prices for the drug.[64]

In 1999 the WHO adopted a set of guidelines for drug donations. These guidelines deal mainly with the last issue, inappropriate donations due to the quality of donations. The guidelines include the following standards.[65]

- No donations should be made without consent of the recipient.
- There should be no double standards in quality. For instance, the donation of drugs that were returned to pharmacies are not allowed.

[63] WHO (Revised 1999). *Guidelines for Drug Donations.*
[64] A. Zammitt (2003). *Development at risk: Rethinking US-business partnerships,* p64. South Centre/UNRISD.
[65] WHO (Revised 1999). *Guidelines for Drug Donations.*

- After delivery, the donated drugs should have a remaining shelf-life of at least half a year.
- The declared value of a drug should be based upon the wholesale price of its generic equivalent, to decrease the burden of customs clearance and import duties.

High standards of medical donations are promoted by the Partnership for Quality Medical Donations (PQMD). This is an alliance of private voluntary organizations that develops and promotes sound donation practices, represents the interests of its members and encourages the study of health and socioeconomic impacts of donations. It identified 7 key components in the comprehensive management of drug donations, including needs assessment, appropriateness of the donation, quality standards, and impact evaluation. These are consistent with the WHO guidelines, but address a broader range of issues.[66]

Some pharmaceutical companies have been addressing various types of concerns about medicine donations on an individual basis. For example, companies commit themselves to donate a drug for as long as it is needed and seek to integrate drug donation programmes into existing healthcare infrastructures.

3.6 Global Public-Private Initiatives

Global Public-Private Initiatives (GPPIs) for health are partnerships of public and private actors that work together to achieve health outcomes. Although this type of collaborations is not new, they are increasingly regarded as one of the most appropriate ways to improve access to medicines in developing countries. In the past 10 years, many new GPPIs have been established. There are at present some 80 GPPIs for health. The Initiative on Public-Private Partnerships for Health (IPPPH) registers some (but not all) of these partnerships and maintains a public database with information about the registered partnerships.[67] The nature of the partnerships is diverse. Often GPPIs have one or more of the following goals:

- Support or accellerate R&D for major diseases in developing countries
- Deliver medicines to developing countries for free or at preferential prices
- Strengthen the health care infrastructure in developing countries
- Coordinate the efforts of various individual partners or other partnerships

GPPIs serve to bring together the expertise of different partners and to bring in additional funds to improve health in developing countries. However, there are a number of concerns about GPPIs.[68] The inventory below applies mainly to partnerships that seek to improve access to medicines. Some concerns are related to the governance of GPPIs.

[66] http://www.merck.com/about/cr/policies_performance/social/medical_outreach.html; see for more information http://www.pqmd.org.

[67] See http://www.ippph.org. The TB Free programme, a collaboration between Aventis and the South African government, is an example of a partnership that is not registered at the IPPPH.

[68] See Health Action International Europe (2001). *Public-Private 'Partnerships: Addressing public helath needs or corporate agenda's? Seminar report*; K. Buse (2004). *Governing Public-Private Infectuous disease*

- The recipient countries and populations have sometimes very little influence on the goals and strategy of a partnership. They are often underrepresented in GPPI boards.
- There may be conflicts of interest and undue influence of private sector partners on public health policies. For example, the participation of pharmaceutical companies in the management of GPPIs may enable them to influence public health priorities and technical standards according to their commercial interests.
- Transparency about the governance of partnerships and the commitments and responsibilities of various partners is often low.
- It may not be clear to whom the management of a GPPI is accountable.
- The role and responsibilities of the various partners to a GPPI may not be clear. In addition, it may not be able to hold them accountable for their commitments to the partnership.
- The impacts of GPPIs are not always well monitored and evaluated.

In 2000 the WHO secretariat adopted internal *Guidelines on interaction with commercial enterprises to achieve health outcomes* to deal with potential conflicts of interests. They recommend that the WHO *'should always consider whether a proposed relationship might involve a real or perceived conflict of interests' and call for a 'step-by-step evaluation of the commercial enterprise'*.[69] However, these guidelines were not always followed when new GPPIs were initiated.[70]

Other concerns are related to the strategies and impact of GPPIs.

- GPPIs may create parallel structures in developing countries that are an additional burden on the health sector in developing countries, instead of integrating with local healthcare infrastructures. Coordination between different GPPIs is often lacking too.
- GPPIs may not deliver sustainable results, because they do not strengthen the local health sector and commitments from commercial partners are usually for a maximum period of five years.
- GPPIs may not be linked to sector-wide approaches and national poverty reduction strategies.
- GPPIs may have a narrow focus and medicalize health problems. An integrated approach, including prevention of a disease, may be lacking. Furthermore, many GPPIs are focused at the enhanced delivery of medicines but do not address the underlying causes of health problems, such as unsafe drinking water, malnutrition and inadequate sanitation.

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partnerships. In: The Brown Journal of World Affairs, 10(2), p225-42; G. Yamey (23 Novermber 2002). Faltering steps towards partnerships. In: MBJ, 325, p1236-40.

[69] WHO (30 Novermber 2000). *Guidelines on working with the private sector to achieve health outcomes,* annex.

[70] WHO (19 April 2001). *Management and financial matters: Report of the internal auditor*. Provisional agenda item 15.1 of the 54th World Helath Assembly, p9.

- Some GPPIs aim at quick results that are relatively easy to reach and generate high public recognition. They therefore fail to reach the poorest people and least developed countries and regions.

Finally, GPPIs do not always form part of a broader company policy for access to medicines in developing countries that addresses the company's approach to patent protection, pricing and R&D as well. [71] A pharmaceutical company that makes a positive contribution to health in developing countries through its involvement in GPPIs may at the same time neglect the interests of developing countries in its core-business. Similarly, companies that support GPPIs do not always have general CSR policies. A company may be able to sustain large contributions to GPPIs through irresponsible practices in its core-business such as bribery, anti-competitive behaviour, tax evasion and excessive drugs prices. This might enable a company to obtain a positive corporate image thanks to its support to GPPIs while its CSR performance is not particularly good.

[71] This section is based on Oxfam, VSO & Save the Children (2002). *Beyond Philanthropy: the pharmaceutical industry, corporate social responsibility and the developing world, p12-14.*

4 Other CSR issues

4.1 Clinical trials[72]

The clinical test phases of drug development were shortly described in the first chapter. Good clinical practices require pharmaceutical companies to provide adequate protection for the volunteers participating in clinical trials, to adhere to standards of care, provide compensation and obtain their informed consent. The standards for clinical trials are laid down in the WHO guidelines for Good Clinical Practice (GCP)[73] and in industry standards.

Clinical trials are increasingly carried out in developing countries because of the lower costs. Observing the same standards in these countries is often more difficult. For exmample, lower education and inadequate local healthcare facilities may be obstacles to obtain informed consent and provide sufficient care and support to the participants. The Declaration of Helsinki, adopted by the World Medical Association (WMA) in 1964 and revised for the last time in 2002, is the most recent and clearest set of guidelines for clinical trials in developing countries.[74] The WMA is a organization of physicians that searches to promote standards for ethical behaviour.[75]

4.2 Drug safety

The safety of drugs is heavily regulated and companies have the responsibility to ensure that healthcare workers understand how their drugs can be safely used. Furthermore, companies have to ensure drug quality and traceability of drugs during manufacturing and distribution. In the case of production errors or contamination, unsafe production batches have to be withdrawn from the market. [76] For products that are sold in the US market, the FDA requires companies to observe current Good Manufacturing Practices (cGMP), a process standard for drug manufacturing. Sometimes companies have failed to comply with such standards, which has resulted in fines, litigation claims, lost contracts and the suspension of production.

Until recently, there was no authority that regulated the safe manufacturing of drugs at the international level for supply to developing countries. In March 2002 the WHO addressed this problem by releasing a first list of prequalified manufacturers for 11 ARVs

[72] This section is based on CoreRatings (May 2003). *Philanthropy or Good Business? Emergins market issues for the global pharmaceutical industry*, p12-3.
[73] WHO (1995). *Guidelines for Good Clinical Practice for Trials on Pharmaceutical Products*. Available at http://www.who.int/medicines/library/par/ggcp/GGCP.shtml.
[74] WMA (2002). Ethical Principles for Medical Research Involving Human Subjects. Available at http://www.wma.net/e/policy/b3.htm.
[75] http://www.wma.net/e/about/index.htm.
[76] CoreRatings (May 2003). *Philanthropy or Good Business? Emergins market issues for the global pharmaceutical industry*, p13.

and 30 other medicines that produce safe drugs according to international standards. The prequalifed suppliers include many generic drugs producers and are eligible for UN procurement. The WHO list would encourage competition in developing countries by clarifying which of hundreds of generic manufacturers produce safe drugs. The PhRMA continued to question the quality standards of the approved generic drug suppliers.[77]

4.3 Drug promotion and advertising

In some cases pharmaceutical companies have promoted their drugs in irresponsible ways, for example misrepresenting the safety of medicines. In June 2004 GlaxoSmithKline was accused of hiding research data suggesting that its anti-depressant drug Paxil was ineffective and unsafe for children and adolescents, increasing the risk of suicide.[78] There have also been cases of celebrities that were paid large fees to mention the benefits of specific brand-name drugs in TV programmes, without disclosing they received a financial reward for these stories. Novartis, for instance, used this type of unethical advertisement for its drug Visudyne In March 2002.[79]

In a few countries, notably the US, direct-to-consumer advertising for prescription drugs is allowed. This form of advertising has been heavily criticized for its unapproprioate and unethical nature.[80]

In 1988 the WHO published a set of *Ethical criteria for medicinal drug promotion*.[81] These criteria are intended to provide a strong ethical framework for drug promotion. However, many pharmaceutical companies favour another code on drug promotion instead, the *Code of pharmaceutical marketing practices* of the International Federation of Pharmaceutical Manufacturers Associations (IFPMA). [82] This code was revised in 1994 and has a complaints procedure. It sets lower standards because it gives precedance to national legislation, and may therefore be insufficient in developing countries where legislation is weak.[83]

4.4 Bribery, corruption, fraud and tax evasion

Many pharmaceutical companies have been involved in large bribery or corruption affairs. Often these are related to the promotion of medicines. For example, doctors were offered large gifts to prescribe more products of a certain company or healthcare officials were

[77] New York Times (March 21, 2002). New list of safe AIDS drugs, despite industry lobby.
[78] Financial Times (June 3, 2004). GSK faces Spitzer suit over Paxil data.
[79] A. Zammitt (2003). *Development at risk: Rethinking US-business partnerships*, p64-5. South Centre/UNRISD.
[80] Health Action International (May 2003). *HAI briefing paper, 56th World Health Assembly, May 2003*.
[81] WHO (1988). Ethical criteria for medicinal drug promotion. Available at http://www.who.int/medicines/library/dap/ethical-criteria/ethicalen.shtml.
[82] IFPMA (1994). *Code of pharmaceutical marketing practices*. Available at http://www.ifpma.org/News/news_market.aspx.
[83] Oxfam, VSO & Save the Children (2002). *Beyond Philanthropy: the pharmaceutical industry, corporate social responsibility and the developing world*.

bribed. In countries where corruption is endemic, pharmaceutical companies may be under great pressure to make illegal payments to speed up the regulatory approval of medicines. The main international standard against bribery is the *Convention on combating bribery of foreign public officials in international business transactions*, adopted by the OECD in 1997. Several pharmaceutical companies have also been guilty of underpaying US$ billions of taxes, and of manipulating medicine prices to overcharge public healthcare services.

4.5 Free competition

On several occasions, large pharmaceutical companies have been found guilty of illegal business practices restricting free competition, such as cartel formation and price fixing. [84] Collaboration to restrict competition may occur between companies that produce the same intermediate materials or different medicines with similar therapeutic functions. Some branded drug producers have also entered into illegal agreements with generic producers to set minimum prices for generic copies in exchange for payments.

4.6 Indigenous knowledge[85]

Traditional medicines are often subject to so-called 'bio-piracy'. This means that pharmaceutical companies acquire treatment methods and plants and animal species that yield effective drug ingredients without the consent of the indigenous community that provided the knowledge of these treatments. These treatments are then adapted and patented. In the case of bio-piracy, the indigenous community does not receive a compensation and the use of traditional medicines may even be prohibited because a pharmaceutical company has obtained a patent exclusivity for the treatment. The legal protection of traditional knowledge is complex because it may be oral and held collectively, for instance.

The Intellectual property rights of local knowledge and plants, as well as the sovereignty of communities and states over their genetic resources, is protected by the Convention on Biological Diversity (CBD).[86] The CBD was adopted at the Earth Summit in 1992 and took effect in 1993. It has been ratified by almost all countries, but not by the US. The TRIPS agreement does not recognize these rights and the CBD can therefore be undermined by WTO rules.

4.7 Workplace health, safety and environment

[84] See e.g. AOF (7 April 2003). *Entente sur le prix de la methionine. Aventis verse 178 M$;* Les Echos (27 November 2002). *Aventis condamné à une amande de 2,85 mE pour entente.*

[85] This section is based on CoreRatings (May 2003). *Philanthropy or Good Business? Emergins market issues for the global pharmaceutical industry*, p14.

[86] Convention on Biological Diversity. Available at http://www.biodiv.org/convention/articles.asp.

Health, safety and environment issues are very important for pharmaceutical companies. Drugs are based on chemical compounds and pharmaceutical production processes are therefore potentially hazardous. However, vehicle accidents seem to be a major source of fatal accidents for pharmaceutical companies too.[87]

Environmental issues in the pharmaceutical industry include the following:

- The disposal of hazardous waste
- The treatment of waste water
- The control of volatile organic compounds (VOC) emissions
- The control of energy use and CFC (greenhouse gasses) emissions
- The transport of chemical ingredients

Issues related to workplace health, safety and environment are usually implemented throughout the supply chain. It is common practice for pharmaceutical companies to audit their suppliers on compliance with global corporate standards.

Chemical industry associations have adopted a voluntary international health, safety and environmental standard called Responsible Care. This standard addresses the manufacture, distribution and use of chemicals and includes performance indicators and verification procedures. The Responsible Care system is implemented by some pharmaceutical companies as well.[88]

4.8 Employment conditions

In contrast to many other sectors, employment conditions are not a main CSR issue in the pharmaceutical industry. Fundamental labour standards set forth in International Labour Organization (ILO) conventions are a ban on child labour, forced labour and discrimination and the right to collective bargaining. However, these are usually no major concerns in the pharmaceutical sector due to the concentration of R&D, manufacturing and marketing in industrialized countries and the relatively high-skilled labour force that is required for the production of medicines. The focus of companies' policies is often on issues like workforce diversity and employee development.

Although employment conditions may be a source of more concern at supplier companies, especially in low cost countries, little information is available yet on the subject. Audits of suppliers in the areas of environment and safety are an established practice and audits on manufacturing practices (production process standards) are often required by regulatory authorities. However, pharmaceutical companies are only just beginning to deal with general employment conditions in their supply chains. Some companies have recently initiated supplier audits of core labour standards.[89]

[87] See e.g. Aventis Sustainability Report 2002; GlaxoSmithKline Corporate Responsibility Report 2003.
[88] http://www.icca-chem.org/section02a.html.
[89] See e.g. GSK Corporate Responsibility Report 2003, p24.

5 Standards and initiatives for CSR in the pharmaceutical sector

There have recently been several studies of large investors and rating companies on the response of pharmaceutical companies to health issues in developing countries.

A study in 2003 by CoreRatings assesses company performance on a selection of CSR issues of special importance to the pharmaceutical sector. Many of these issues are related to health in developing countries, including the following: [90]

- R&D for high burden diseases in developing countries
- Access to essential medicines (patent flexibility, differential pricing, drug donations, participation in GPPIs)
- Safety and testing of medicines (clinical trials, product safety)
- Lobbying with impact on access to medicines

A study in 2004 by the Pharmaceutical Shareowners Group (PSG), a group of large institutional investors, makes proposals for a '*good practice strategy*' for addressing the public health crisis in developing countries.[91] Recommendations include:

- A flexible and broad approach to access to medicines (voluntary licensing, differential pricing, drug donations)
- Responsible use of influence in public policy

Written from an investors perspective, these studies argue that there exists a strong business case for a pro-active approach from pharmaceutical companies. Arguments for this business case include protecting company reputation and the 'license to operate', building political goodwill, attracting and motivating employees, and ultimately the maintenance of competitive advantage.

Despite this kind of attempts to provide a broader framework for responsible business behaviour, there does not exist a comprehensive standard or initiative, originating from the pharmaceutical industry itself, that addresses CSR at large or CSR issues related to access to medicines in developing countries. Instead, there exist various WHO and industry standards that address some of the individual CSR issues described in this report. These are usually explicitly endorsed by the companies that adhere to them. In addition, there is a wide range of general CSR initiatives that is not specifically aimed at the pharmaceutical sector, but may nonetheless be relevant and is explicitly supported by one or more large pharmaceutical companies. A (non-exhaustive) selection of these various types of standards is provided below.

Drug donations

[90] CoreRatings (May 2003). Philanthropy or Good Business? Emerging market issues for the global pharmaceutical industry.

[91] PSG (September 2004). The Public Health Crisis in Emerging Markets: An institutional Investor Perspective on the Implications for the Pharmaceutical Industry.

- WHO. *Guidelines for drug donations*. Revised in 1999.[92]
- Partnership for Quality Medical Donations (PQMD). *PQMD guide*. Probably released in 2002.[93]

Clinical trials

- WHO. *Guidelines for Good Clinical Practice (GCP) for Trials on Pharmaceutical Products*. Adopted in 1995.[94]
- Council for International Organizations of Medical Sciences (CIOMS), an academic organization. *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Revised in 2002. [95] Together with the WHO guidelines, this is considered the most appropriate standard for clinical trials in developing countries.[96]
- World Medical Association (WMA). *Ethical Principles for Medical Research Involving Human Subjects (Declaration of Helsinki)*. Industry standard, revised in 2002.[97]
- International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). *Guideline for Good Clinical Practice*. Industry standard, adopted in 1996. Contains technical guidelines to meet regulatory standards in high-income countries.[98]

Drug promotion and advertising

- WHO. *Ethical criteria for medicinal drug promotion*. Adopted in 1988.[99]
- International Federation of Pharmaceutical Manufacturers Associations (IFPMA). *Code of pharmaceutical marketing practices*. Industry standard, revised in 1994.[100] It has a complaints procedure, but is considered weaker than the WHO standard.[101]

Workplace heath, safety and environment

- International Council of Chemical Associations (ICCA). *Responsible Care*. Established in 1985.[102] It applies to chemical and related industries, throughout the supply chain. National chemical industry associations that support the initiative are responsible for its implementation.

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[92] WHO/EDM/PAR/99.4. Available at http://www.who.int/medicines/library/par/who-edm-par-1999-4/who-edm-par-99-4.doc.
[93] See for more information http://www.pqmd.org.
[94] Available at http://www.who.int/medicines/library/par/ggcp/GGCP.shtml.
[95] Available at http://www.cioms.ch/frame_guidelines_nov_2002.htm.
[96] CoreRatings (May 2003). *Philanthropy or Good Business? Emerging market issues for the global pharmaceutical industry*.
[97] Available at http://www.wma.net/e/policy/b3.htm.
[98] See for more information http://www.ich.org.
[99] Available at http://www.who.int/medicines/library/dap/ethical-criteria/ethicalen.shtml.
[100] Available at http://www.ifpma.org/News/news_market.aspx.
[101] Oxfam, VSO & Save the Children (2002). *Beyond Philanthropy: the pharmaceutical industry, corporate social responsibility and the developing world.*
[102] See for more information http://www.icca-chem.org/section02a.html.

Indigenous knowledge

- United Nations (UN). *Convention on Biological Diversity (CBD)*. Adopted in 1992 and ratified by most countries.[103]

Standards that are not sector-specific

- Organization for Economic Cooperation and Development (OECD). *Convention on combating bribery of foreign public officials in international business transactions*. Adopted in 1997. Supported by national legislation of OECD member countries.[104]
- OECD. *OECD Guidelines for Multinational Enterprises*. Revised in 2000. Voluntary guidelines addressing a broad range of CSR issues, with a complaints mechanism.
- International Organization for Standardization (ISO). *ISO 14000 series*. Widely used industry standard for environmental management, started in 1996.[105]
- UN. *Global Reporting Initiative (GRI)*. CSR reporting standard, initiated in 1997.
- UN. *Global Compact*. CSR forum, initiated in 1999.

[103] Available at http://www.biodiv.org/convention/articles.asp.
[104] http://www.oecd.org/document/21/0%2C2340%2Cen_2649_34855_2017813_1_1_1_1%2C00.html.
[105] http://www.iso.org/iso/en/iso9000-14000/iso14000/iso14000index.html.

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