MID-PHARMA: HOW BIG IS IT AND WHERE IS IT GOING?

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1. Introduction

The transformation of large, global pharmaceutical companies - due to a number of challenges facing contemporary drug development such as low productivity, high attrition rates of compounds in phase 2 development, patent expirations on blockbuster drugs and increasingly stringent regulatory hurdles - is now well-known and much commented upon.[1] Large companies are struggling to develop sufficient novel therapies and deliver them to market for sustainable long-term growth. While much has been written about the changing fortunes of the large, multinational drug developers, as well as the emerging small and medium biotechnology companies that are increasingly a rich source of knowledge and innovation, the growth of medium sized pharmaceutical companies has been under explored. The purpose of this paper is to examine a select group of medium-sized pharmaceutical firms; that is companies that are global players with significant internally driven R&D and broad product portfolios (excluding those exclusively in the generics market) but are not in the "first league" of global industry players. We will explore how these companies are situated within the broader competitive environment and how they are managing the opportunities and challenges arising from changes in the underlying science and technology (e.g., the shift from conventional chemical compounds to the life sciences and biologics).

Our analysis will be presented in three sections. The first section will describe the structure of the medium-sized pharmaceutical sector. We will develop definitional criteria and justify the sample of companies studied. We will also provide an overview of key statistics regarding the development of the companies since 2000. The second section will focus on the innovation processes of the respective companies; particularly their organisational structure, key R&D strategies and how they have sought to balance in-house R&D with externally sourced knowledge and expertise (through equity relationships, licensing, and R&D collaborations). The third section will examine the innovation trajectories and strategies underlying the innovation processes explored in section two. Here, we will describe how the companies have exploited new technologies, selected therapeutic foci and shaped their pipeline. In the concluding section, we will summarise the key findings and discuss the broader implications of the study for pharmaceutical innovation and strategic innovation management.

2. Towards an Understanding of the Structure of the Mid-Pharma Sector

In this section, we will discuss the general structure of the Mid-Pharma sector from a number of perspectives and range of criteria. First, we will present evidence relating to our hypothesis that there is indeed a size-based continuum of pharmaceutical companies. Taking this as a starting point, we will define what we consider to be the main characteristics of a medium-sized firm in this sector. On the basis of this definition, we will select a sample of companies to be studied and justify their inclusion. It will be demonstrated that medium-sized pharmaceutical firms can be usefully ranked and graded into two main groups; upper and lower mid-pharma. This gradation will be used as the central unit of analysis in the rest of the paper. It is important to note that much of the quantitative and qualitative data are derived from publicly accessible information posted on company websites and within annual reports.

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1 The Economist, 'From Bench to Bedside', November 2nd, 2006 http://www.economist.com/research/articlesBySubject/displaystory.cfm?subjectid=531766&story_id=8116707

Mittra, J. (2008) 'Impact of the Life Sciences on Organisation and Management of R&D in Large Pharmaceutical Firms', Int. J. Biotechnology, 10 (5), pp. 416-440

Mittra, J. (2007) 'Life Science Innovation and the Re-structuring of the Pharmaceutical Sector: Mergers, Acquisitions and Strategic Alliances', Technology Analysis and Strategic Management, 19 (3), pp. 279-301

2.1 The Starting Point – Key Sources for Data

The pharmaceutical industry has always been one of the most innovation-driven and profitable sectors. As such, various consulting firms prepare annual reports ranking these pharmaceutical companies for comparative analysis (e.g. IMS Health, Wood Mackenzie, Bain&Company, Boston Consulting Group, Ernst &Young etc.). However, few of these reports are available free of charge. One source that has provided a comprehensive list of the top 50 pharmaceutical and biotech companies in 2006 is MedAdNews[2]. Their table has also been published on Wikipedia (for the complete list, see appendix Tables A.1.1 and A.1.2).[3,4] Nevertheless, this list provides insufficient data for our purposes. It is based on the companies' total revenues, including those accruing from non-pharmaceutical activities. Since our aim is to compare firms based on pure pharmaceutical R&D, such a list is inadequate. Another online magazine is *Pharmaceutical Executive*,[5] which publishes special annual reports of the world's top 50 pharmaceutical companies (see Tables A.1.3.1, A1.3.2 and A.1.3.3 in the appendix). Their ranking is based only on the human prescription drugs sales of the companies (we also provide rankings based on year-on-year sales growth year and R&D spending in the appendix). Since it is published annually, it covers a long time period (2001-2006), which allows us to observe changes in a particular company's ranking over the years as well as trends in its growth and/or decline.

A third online list of pharmaceutical companies in 2005 and 2006 is provided by Wood Mackenzie. The table in the appendix (see Table A.1.4) provides market shares and sales growth compared to the pervious year as well. It appears from this report that the market share of the mid-pharma companies is below 2%.

We have taken these lists as a starting point for our own sampling of mid-pharma companies, focusing predominantly on companies with pharmaceutical sales below $10bn. The reason for this cut off point is explained below.

2.2 Definition of a Medium-Sized Pharmaceutical Company

In the MedAdNewslist of pharmaceutical companies, there is an important introductory note on "Big Pharma". It explains that "the phrase *Big Pharma* is often used to refer to companies with revenue in excess of $3 billion, and/or R&D expenditure in excess of $500 million".[6] This classification leaves us with only two sizes of firm in the pharmaceutical industry, eliminating an important group of medium-sized companies. The most comprehensive report on the Mid-Pharma sector available online comes from Datamonitor,[7] which defines 'mid pharma' as those companies within the PharmaVitae company universe with less than $10 billion in ethical revenues in 2005, excluding Japanese and biotechnology companies.[8] The report segments this PharmaVitae Mid Pharma peer set of 22 companies into 5 clusters as the **'Big 6'** (Boehringer Ingelheim, Schering Plough, Novo Nordisk, Bayer, Schering AG and Merck

[2] MedAdNews is a magazine of the Pharmalive website:
http://www.pharmalive.com/magazines/medad/view.cfm?articleID=5496
[3] http://en.wikipedia.org/wiki/List_of_pharmaceutical_companies
[4] An additional list of companies with general explanations about the companies, also provided by the same website, is re-structured according to the size of the companies and included in the appendix. There are a vast number of small-sized pharmaceutical firms around the world, mostly focusing on generic drug manufacturing. In addition, we provide information regarding some companies' mergers and acquisitions with Big Pharma or Mid-Pharma companies.
[5] http://pharmexec.findpharma.com/pharmexec
[6] http://en.wikipedia.org/wiki/List_of_pharmaceutical_companies
[7] Datamonitor, "Mid Pharma Sector: In-licensing and other externalization strategies", Information regarding this report is downloaded from the website of Bharat Book Bureau, One-stop-shop for business information, http://www.bharatbook.com/bookdetail.asp?bookid=3712&publisher
[8] "Mid pharma looks outside itself to drive revenue", 28 Sep 06
http://www.hospitalpharma.com/Features/feature.asp?ROW_ID=911

KGaA), **Central Nervous System (CNS) focused** (Lundbeck, Forest and Shire), **Cardiovascular (CV) focused** (Servier, King, Menarini and Schwarz), **'Small Domestic'** and **'Multi-Business Unit'** clusters. The report also reveals that the firms are arrayed along a CNS-CV axis, with CNS- and CV-focused mid-pharma companies at either end of the spectrum and the 'Big 6' players located in the middle range, addressing a much broader range of therapy areas. In this report, we have defined medium-sized pharmaceutical firms according to the most common indicator of firm size in almost every industry, namely net product sales. 'Big Pharma' is generally defined as companies with annual revenues or net product sales exceeding $10 billion. This corresponds to the top 10-15 companies in the pharmaceutical company rankings, which display features of an oligopolistic industrial structure. Hence, the medium-sized pharmaceutical firm sector (from now on referred to as Mid-Pharma) consists of companies whose net product sales range from $1-10 billion (i.e. $1bn< pharmaceutical sales <$10billion).

Of course, it is also important to distinguish mid pharma from the small and medium sized enterprise (SME) sector. We suggest that a key difference between large/mid-size firms and small firms in the pharmaceutical industry lies in their capability to innovate. Small pharmaceutical firms create a large part of the industry in the world by product volume (e.g., the Indian pharmaceutical industry ranks fourth in the world by volume, but only 13th by value)[9]; yet most often they rely on the production of cheap generic versions of drugs invented by Big Pharma. The evolution of these industries is adversely affected by government policies that discourage innovation. India provides a good example with its patent laws, which prior to 2005 did not protect newly discovered compounds, only the process of making them, leaving the producer un-rewarded.[10] However, medium-sized pharmaceutical firms follow a different route and often display a mixture of firms that are balancing generic with innovative drugs production, although some are not involved in generics. For the purposes of his report, we are interested mainly in Mid Pharma companies that – like big Pharma – possess full in-house drug discovery and development capabilities.

2.3 The Sample of Pharmaceutical Companies to be Analysed in this Report

The sample of pharmaceutical companies researched in this report was selected on the basis of pharmaceutical sales that allow us to make a meaningful gradation or grouping of companies for comparison. For this reason, we have also included Bausch & Lomb, a company that does not appear in any of the top 50 lists, to augment our picture of the industry by the addition of a firm that, although large, has only small-scale pharma operations.[11] (see Table A.2.2 in the appendix)

Some of the companies in our sample also operate in sectors related and/or unrelated to pharmaceuticals (Table 1; see also Tables A.2.2 and A.2.3 in the appendix for general information about the sample of the companies in this report). Although we focus only on the (bio)pharmaceutical operations of the firms (including biotech drugs, as shown with italics in Table 1), some company statistics were declared only for the Group as a whole (without any segmentation of the business branches) in their annual reports. When pharmaceutical data

[9] Economist November 10th 2007; A special report on technology in India and China, p.6.
[10] "Thanks to India's WTO obligations, its law now respects patents on products invented after 1995. (Precisely how much respect it bestows is still being worked out in the courts—in August, for example, the Chennai High Court ruled that Novartis's drug Gleevec was not new enough to deserve protection.) But despite the new law, imitation still crowds out invention, if only because of the 'cultural mindset' it has bequeathed, says Ms Mazumdar-Shaw of Biocon. Few companies are prepared to take the deep risks that new drug research entails" (Economist November 10th 2007; A special report on technology in India and China, p.6).
[11] Biggest portion of Bausch & Lomb's sales consist of ophthalmic surgery devices and vision care products (all together $1634 million in 2006) (Bausch & Lomb, Annual Report 2006, p.43). The company signals an interesting strategic option: focusing on a narrow area in pharmaceuticals and developing a range of diagnostic and therapeutic applications. It is not a small-scale operation in itself; nevertheless it is so when compared with pharmaceutical operations of other companies.

were not available, we indicate this in the tables. For example, Boehringer Ingelheim, Abbott Laboratories (indicated as big Pharma), Schering Plough, Baxter, Solvay, Merck KGaA[12] and Allergan have business segments unrelated to pharmaceutical innovation. We attempt to handle their statistics with care in order to be able to make meaningful comparisons with companies that have operations exclusively in pharmaceuticals. Furthermore, Eisai, Alcon and Bausch & Lomb have segmented their operations within pharmaceuticals. However, this report focuses predominantly on ethical pharmaceuticals (as opposed to off-patent/generics) and excludes any diagnostics, over-the-counter products, animal health divisions, and medical or surgical devices, as well as consumer products. Table 1 below reveals the mid-pharma companies by scope of business.

Table 1. Mid-Pharma by scope of business, 2006

Company	Country	Scope of business
Boehringer Ingelheim	Germany	*Prescription Medicines, Biopharmaceuticals, Pharma chemicals and phamaceuticals production,* Consumer Health Care, and Animal Health.
Abbott Laboratories	USA	Medical products, Nutritional products, *Pharmaceuticals*
Schering-Plough	USA	*Human prescription pharmaceuticals,* Consumer health and Animal health
Baxter International	USA	*Bioscience* , Medical devices and *Renal*
Astellas Pharma	Japan	*Pharmaceuticals*
Novo Nordisk	Denmark	*Diabetes care and Biopharmaceuticals*
Eisai	Japan	*Pharmaceutical drugs,* Over-the-counter drugs and Pharmaceuticals Production Systems and Equipment.
Merck KGaA	Germany	*Pharmaceuticals* and Chemicals
Alcon	Switzerland	Surgical, *pharmaceutical eye care* and consumer eye care health
Solvay Pharmaceuticals	Belgium	*Pharmaceuticals* , and Chemicals, Plastics and Processing
Forest Laboratories	USA	*Pharmaceuticals*
UCB Biopharma	Belgium	*Biopharmaceuticals*
Allergan	USA	*Pharmaceuticals and biologics* , and Obesity intervention and Medical aesthetics
Gilead Sciences	USA	*Biopharmaceuticals*
Bausch & Lomb	USA	*Ophthalmic pharmaceuticals* , Ophthalmic surgery devices and vision care
H. Lundbeck A/S	Denmark	*Pharmaceuticals*
Shire plc	UK	*Specialty pharmaceuticals; Biopharmaceuticals*
Source: Web sites of the companies		

2.4 Gradation of Medium--Sized Pharmaceutical Companies

We have been able to derive a workable gradation of medium-sized pharmaceutical companies from the 17 firms analysed. Table 2 displays the companies' total sales, net income, and number of employees for all the firms' business segments as of 2006, the year we took as a reference for this research.[13] Product sales exclusively in the pharmaceutical segment of the firms are deliberately highlighted and taken as the principal indicator for company ranking. Ranking companies according to their dedicated pharmaceutical product sales allows us both to display a size-based continuum of pharmaceutical companies (Figures 1 and 2) and distinguish two peer sets of companies in the Mid-Pharma sector, which we will refer to as upper and lower Mid-Pharma companies (Table 2).

[12] Merck KGaA acquired Serono and became Merck Serono in 2006. In this paper, we will continue to refer to two companies separately as Merck KGaA and Serono for operations before 2006.
[13] The five-year period (2002-2006) statistics of each company are available in the appendix.

Table 2 also includes two Big Pharma companies. They are at the lower end of Big Pharma (on our definitional criteria) and are included here because they are useful for highlighting the boundary between Big and Mid-Pharma. Finally, one company in the sample (Bausch & Lomb) is categorised as a small pharmaceutical firm due to its level of sales in ethical pharmaceuticals, despite the fact that it achieves higher net sales compared to some of the other Mid-Pharma companies in the sample.14

Table 2. Mid-Pharma by total sales, sales only in pharmaceuticals, net income, R&D expenditure, number of employees, and ratio of R&D spending to sales, 2006 (USD million); sales growth in 2006 compared to 2002 (%); sales rank according to sales in pharma segment only

Gradation of Pharma companies	Sales Rank 2006	Company	Country	Total Sales	Sales in pharma segment only	Net Income	R&D expenditure	Employees	Ratio of R&D spending to sales	Growth 2002-2006
Big Pharma	1	Abbott Laboratories*	USA	22,476	**12,395**	1,717	2,255	66,663	10.0%	33.7%
	2	Boehringer Ingelheim^	Germany	13,270	**10,200**	2,170	1,527	38,428	15.0%	28.8%
Upper Mid-Pharma	3	Schering-Plough*	USA	10,594	**8,561**	1,143	2188**	50,000	20.7%	-2.6%
	4	Astellas Pharma^	Japan	7,802	**7,802**	1,118	1,430	13,900	18.3%	85.1%
	5	Novo Nordisk^	Denmark	6,518	**6,518**	1,086	1,088	23,613	16.7%	85.5%
	6	Baxter International*	USA	10,378	**6,461**	1,397	614	48,000	5.9%	108.4%
	7	Eisai^	Japan	5,738	**5,738**	678	793	9,081	13.8%	77.1%
	8	Merck KGaA^	Germany	6,259	**5,169**	1,256	772	29,999	14.9%	56.1%
Lower Mid-Pharma	9	Solvay^	Belgium	11,796	**3,264**	1,025	532	10,088	16.3%	66.9%
	10	Forest Laboratories	USA	2,794	**2,794**	709	410	5,000	14.7%	78.3%
	11	UCB^	Belgium	2,746	**2,746**	461	772	8,477	28.1%	4.0%
	12	Allergan	USA	3,010	**2,639**	-127	476	5,200	18.0%	90.5%
	13	Gilead Sciences	USA	2,590	**2,590**	-1,190	384	more than 2900	14.8%	43.2%***
	14	Alcon*	Switzerland	4,897	**2,007**	1,348	512	13,500	10.5%	84.1%
	15	H. Lundbeck A/S^	Denmark	1,551	**1,551**	186	329	5,171	21.2%	28.9%
	16	Shire plc	UK	1,536	**1,536**	278	387	2,868	25.2%	78.7%
Small Pharma	17	Bausch & Lomb*	USA	2,292	**658**	15	197	approx 13,700	8.6%	66.3%

*R&D expenditures are for the Group of Abbott Labs, Schering-Plough, Baxter Intl, Alcon and Bausch & Lomb; and the last column displays the ratio of their R&D expenditure to net sales. The other companies' R&D expenditures are only for pharmaceutical segments and therefore the last column displays the ratio of their R&D expenditure in pharmaceutical sector to sales in pharmaceutical sector.

** Schering Plough has more R&D expenditures than Boehringer Ingelheim because only R&D spending in the human pharmaceutical segment is taken for the latter, whereas for the former it represents total R&D spending, including consumer and animal health segments of its business.

^ These firms have presented their financial figures in their national currencies, so they are converted into US dollar by using http://www.oanda.com/convert/fxhistory (interbank rate and annual average) for Yen/USD and DKK/USD, and UCB Annual Reports for Euro/USD.

Source: Company Annual Reports and websites (see appendix for a list of company website addresses).

Table 2 reveals a clear division of medium-sized pharma companies based on product sales in 2006,[15] and Figure 1 below displays the rankings of the companies according to their pharmaceutical product sales in the five-year period 2002-2006 (see also Table A.4.1 and A.4.2 and also Table A.1.3.1 of Pharmaceutical Executive List of companies). In 2002, the sales value of all the companies in the sample were below $10 billion, with two clear breaks at sales below $7.9 billion and $2.6 billion. Over the years, Abbott Laboratories, in particular, distinguished itself as a Big Pharma company. In 2003, apart than Boehringer-Ingelheim and Schering-Plough, the companies in our sample all displayed sales values below $5 billion, again with two clear breaks at sales below $5 billion and $3 billion. 2004 appeared to be a year of growth for all the companies except Schering-Plough, which fell back to the mid-pharma category with decreasing sales in 2003, and Abbott Laboratories, which did not

[14] See footnote 11.

[15] Not surprisingly, companies with higher sales levels appear to have higher R&D expenditures also (Table 2). R&D expenditures can also be used as an indicator for the classification of pharma companies (see Figure A.1 in the appendix).

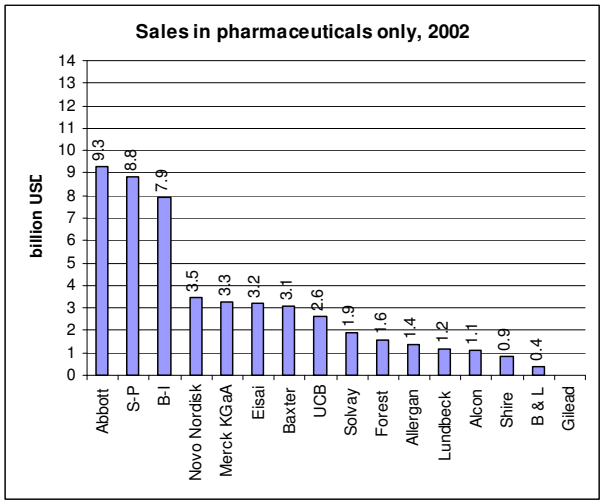
seem to be affected in total sales. Also, Boehringer-Ingelheim continued to grow in 2004, but not fast enough to catch up with the sales level of Abbott Laboratories. In 2004, a break between companies is found at sales below $4 billion. 2005 figures also display two breaks, one at sales below $5 billion and another below $4 billion, reducing the gap to $1 billion between the first group of mid-pharma companies while increasing their distance from the smaller mid-size companies. In 2006, the contraction in sales of Abbott, coupled with increases in sales of Boehringer-Ingelheim and Schering-Plough, levelled up the size continuum of the companies studied. The data in Figure 1 suggest that some companies that were clearly mid-pharma companies in 2002 are now approaching Big Pharma; thus creating what we refer to as an upper tier of mid-pharma companies. Indeed, the break between this group of mid-pharma companies and Big Pharma is less clear-cut than that between upper-tier mid-pharma companies and those firms with sales below $5 billion, which constitute a lower tier of mid-pharma. Therefore, referring to this progression of the companies over the five-year period, two peer groups of Mid-Pharma companies appear:

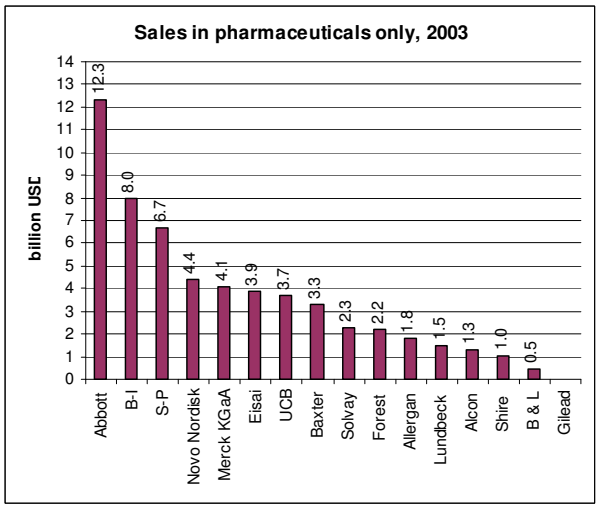
Upper Mid Pharma companies with sales ranging between $5bn and $10bn in pharmaceuticals (consisting of Schering-Plough, Baxter International, Astellas Pharma[16], Eisai, Novo Nordisk and Merck KGaA

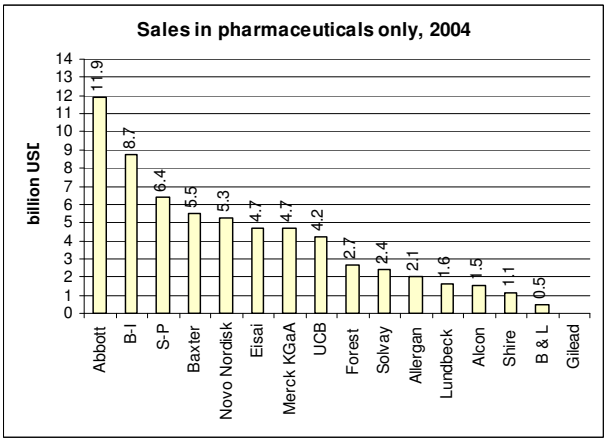
Lower Mid-Pharma companies with sales well below $5bn and approaching the definition of small pharma (less than $1bn in pharmaceutical sales). Firms in this category include Solvay Pharmaceuticals, UCB Biopharma, Forest Laboratories, Allergan, Gilead Sciences, Alcon, Lundbeck and Shire.

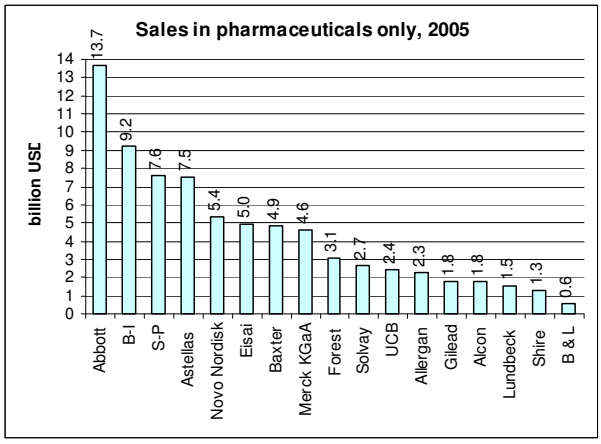
[16] Astellas Pharma (Japan) was created in April 2005 through the merger of two Japanese pharmaceutical companies, namely Yamanouchi Pharmaceutical Co., Ltd. and Fujisawa Pharmaceutical Co., Ltd.

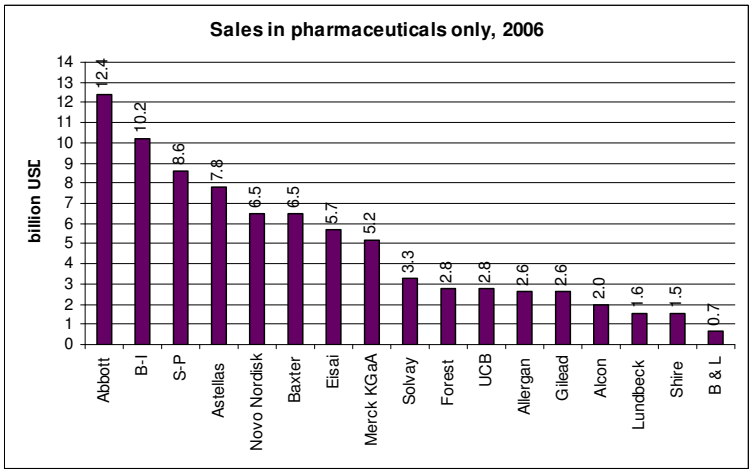
Figure 1 Size-based Continuum of Mid-Pharma Companies, by sales only in pharmaceuticals (USD billion), 2002-2006











We have also attempted to rank the companies according to the number of drugs they have taken to market since the early 1990s (Table 3). The figures for the two Big Pharma companies were available directly from their websites, whereas for the mid-pharma companies we have had to derive information indirectly from their websites and various annual reports. For Gilead Sciences, Allergan and Solvay Pharmaceuticals, the US FDA approvals and clearances are included in the calculations. In addition, the number of

launches of new formulations of existing drugs is shown separately. Lundbeck's estimated product launches in 2008 are also indicated.

Table 3. Number of drugs companies have taken to market, in different time periods (as available)

Company	Country	Time period	Number of products	Source
Shire plc	UK	1998-2007	17 (2 new formulations of new drugs)	Annual Reports 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, and 2006
Allergan	USA	1993-2007	15 (3 new formulations of exisitng drugs)	http://www.allergan.com/about/history.htm and Annual Reports 1999-2006
Schering-Plough	USA	1998-2006	13 (1 new formulation of existing drugs)	Annual Reports 2000, 2001, 2002, 2003, 2004, 2005, and 2006
Boehringer Ingelheim	Germany	1996-2007	13	http://www.boehringer-ingelheim.com/corporate/corp_hist1_4_oprod.htm
Merck KGaA	Germany	2000-2007	12 (2 new formulations of existing drugs and 9 generic products)	http://www.merck.de/servlet/PB/menu/1328710/index.html
Baxter International	USA	1998-2007	12	http://www.baxter.com/about_baxter/company_profile/sub/history.html
Bausch & Lomb	USA	2000-2007	10 (2 new formulations of existing drugs)	Annual Reports 2000, 2001, 2002, 2003, 2004, 2005, and 2006
Alcon	Switzerland	2001-2006	10	Annual Reports 2002, 2003, 2004, 2005, and 2006
Gilead Sciences	USA	1990-2007	10	http://www.gilead.com/corporate_history
UCB Biopharma	Belgium	1998-2007	8 (3 new formulation of existing drugs)	Annual Reports 2001, 2002, 2003, 2004, 2005, 2006, and Half Report 2007
Abbott Laboratories	USA	1990-2007	8	http://www.abbott.com/global/url/content/en_US/10.30:30/general_content/General_Content_00069.htm#6
Novo Nordisk	Denmark	1996-2004	8	http://www.novonordisk.com/about_us/history/milestones_in_nn_history.asp
Astellas Pharma	Japan	2005*-2007	7 (2 new formulations of existing drugs) (1 in 2002)	http://www.astellas.com/global/about/history/index.html and Annual Reports 2005,2006,2007 *The year Astellas is founded as a result of merger between Yamanouchi and Fujisawa Pharmacueticals
Solvay Pharmaceuticals	Belgium	2000-2004	7 (1 new formulation of existing drugs)	http://www.solvay.com/about/history/timeline/0,28490-2-0,00.htm
Forest Laboratories	USA	1998-2007	6 (Licenses promising new products from innovative companies worldwide at virtually every stage of development)	http://www.frx.com/products/index.aspx
Eisai	Japan	1994-2007	6	http://www.eisai.co.jp/ecompany/eprofile/etimeline.html
H. Lundbeck A/S	Denmark	2002-2007 (2008)	4 (1)	http://www.lundbeck.com/aboutus/history/company_history/1990/default.asp

2.5 Overview of medium-sized pharmaceutical companies

This section provides an overview of the researched companies with respect to various indicators for the five-year period of 2002-2006 (see relevant tables in the appendix).

2.5.1 Mid-Pharma by therapeutic foci

With regard to the therapeutic foci of the mid-pharma companies, there appears to be a concentration in immunology and inflammation (for 7 companies); central nervous system (CNS), cardiovascular and metabolic diseases (CV), neuroscience, and oncology (5 companies in each category); and to a lesser extent in endocrinology, gastroenterology and reproductive health (4 companies in each category). See Table 4 for full listing.

Among the therapeutic foci of Mid-Pharma companies, oncology appears to be largely monopolised by the Upper Mid-Pharma firms. One might speculate that this is due to its need for higher levels of R&D expenditure, particularly when shifting research from small molecules to biologicals, and the competitive nature of the area. Similarly, ophthalmology is a therapeutic area generally preferred by the Lower Mid-Pharma companies (including the small Bausch & Lomb pharma operation). Immunology and inflammation has also attracted greater attention amongst the Upper Mid-Pharma companies. However, neuroscience, CV and metabolics and gastroenterology have become the foci of Lower Mid-Pharma companies far more than the Upper Mid-Pharma companies (Table 5).

Table 4. Mid-Pharma by therapeutic foci (in comparison with Big Pharma in the sample)

	Pharma companies focusing on therapeutic area	
therapeutic areas	**Big-Pharma companies**	**Mid-Pharma companies**
Biosurgery and cellular therapies (technologies used in adult stem-cell therapies)		Baxter
Cardiovascular and Metabolic diseases	Boehringer and Abbott	Schering Plough, Forest Labs, Gilead Sciences, Merck KGaA, Solvay
Endocrinology (inc. Diabetes)		Novo Nordisk, Solvay, Forest Labs, Merck KGaA, Astellas
Gastroenterology		Eisai, Solvay, Allergan, Shire
Haemotology		Baxter, Novo Nordisk
Human genetic therapies	Boehringer and Abbott	Shire
Immunology and inflammation	Boehringer and Abbott	Schering Plough, Baxter, Astellas, Novo Nordisk, Merck KGaA, Solvay, UCB
Infectious diseases		Schering Plough, Baxter, Astellas
Neuroscience (inc. CNS)	Boehringer and Abbott	Eisai, Merck KGaA, Solvay, Allergan, Shire, Schering Plough, Astellas, Forest Labs, UCB, Lundbeck
Pain management	Abbott	Forest Labs
Plasma-based therapies (plasma proteins and vaccines)		Baxter, Novo Nordisk
Oncology	Boehringer	Schering Plough, Astellas, Novo Nordisk, Eisai, Merck KGaA
Ophthalmology		Alcon, Allergan, *Bausch & Lomb*
Regenerative medicine		Baxter
Renal	Abbott	Baxter, Shire
Reproductive health (inc. women's health)		Schering Plough, Merck KGaA, Solvay, Forest Labs
Respiratory		Schering Plough, Forest Labs, Gilead Sciences
Urology		Astellas, Allergan
Virology	Boehringer and Abbott	Astellas, Gilead Sciences

Source: Company Annual Reports and websites (see appendix for a list of company website addresses).

Table 5. Distribution of most important therapeutic foci by the gradation of Mid-Pharma

	Number of Companies	
Therapeutic foci	**Upper Mid-Pharma**	**Lower Mid-Pharma**
Immunology and inflammation	5	2
CV	2	3
Neuroscience (inc.CNS)	4	6
Oncology	5	0
Endocrinology	2	2
Gastroenterology	1	3
Opthalmology	0	2 + (1)*
Reproductive health	2	2

* Bausch&Lomb

Source: Table 3

2.5.2 Mid-Pharma by net pharmaceutical sales

Over the past five years, most of the Mid-Pharma companies have had sustainable growth (see Tables A.4.1 and 4.1.2 in the appendix), although in one of its reports on the pharmaceutical industry, Wood Mackenzie states that "the negative factors influencing the growth of the industry continue to dominate and further forecasts that the growth of the global market will continue to slow from the double digit rates of the early 1990s to around 7% by the end of this decade (Source: Wood Mackenzie's Productview. March 2006)".[17] The report refers mainly to Big Pharma; the implication being that mid-pharma companies may not perhaps be negatively affected by this perceived downturn, although Schering Plough is a counterexample (see also Table A.1.3.1 in the appendix), as its ranking has declined over the past five years. Schering Plough was in a downward performance spiral just before its current CEO, Fred Hassan, arrived in 2003.[18] He attempted to account for this in terms of the patent expiration of one of the company's best selling drugs and the general lack of innovative capability to replace it with a new product. In other words, Schering Plough had experienced what might be awaiting many Big Pharma companies in 2010 (see also the net income of Schering Plough in Table A.7 in the appendix). In our sample of companies, the performance of Astellas Pharma requires some explanation. Since the annual fiscal year for Japanese companies is from March 31, 2004 to March 31, 2005 (i.e. the time period that is covered in the 2005 Annual Report), the 2005 annual report incorporates the company's acquisition of Yamanouchi and Fujisawa (which created Astellas Pharma on April 1st, 2005) and the 2004 figures therefore appear inflated in all of the tables.

Upper Mid-Pharma's net pharmaceutical sales show a general upward trend over the years (see Table A.4.1 in the appendix), but some companies have experienced difficulties from time to time (See Table A.4.1.2 in the appendix). This growth is not purely endogenous, but largely a result of mergers and acquisitions, R&D collaborations and licensing strategies (as will be discussed below in section 3.2). The 2002 figures of the Upper Mid-Pharma companies (all below $5bn) show a significant difference from the 2002 figure of Schering Plough, which was then clearly a Big Pharma company. Over the five-year period, the relatively small pharmaceutical companies of 2002 have grown into the Upper Mid-Pharma companies of 2006 and narrowed the gap between Big Pharma.

In Lower Mid-Pharma, the 2005 net sales of UCB halved in comparison to 2004. This is likely a result of a strategic decision to specialize in biopharmaceuticals, and divest its other major business segment; namely Surface Specialties (see Table A.9 in the appendix). In general, the lower Mid-Pharma companies have also grown steadily over the five-year period, yet it seems that the upper mid-pharma sector has grown more dynamically (see also Figure 1 to see how the gap between upper mid-pharma companies and Big Pharma has narrowed over the five-year period, and Table A.1.3.1 in the appendix).

2.5.3. Mid-Pharma by R&D expenditures

All the companies in our sample have increased their R&D spending over the last five years (Table A.5.1 in the appendix). All experienced strong growth in R&D spending, except Boehringer Ingelheim in 2003 and Shire in 2004 (Table A.1.5.2 in the appendix). In fact, all

[17] **"**Increasing cost of product deals requires change of strategy, says Wood Mackenzie", Edinburgh and Boston, 13th March 2006, http://www.woodmacresearch.com/cgi-bin/corp/portal/corp/corpPressDetail.jsp?searchStr=pharmaceuticals&oid=726367&BV_SessionID=@@@@1348335154.1197300811@@@@&BV_EngineID=ccceaddmkefjihjcflgcegjdffjdgih.0

[18] "The company had lost exclusivity on its single most important growth driver, CLARITIN, with nothing substantial to replace it. On top of that, we found that market share and sales were falling in the other key businesses of hepatitis C and in other areas of respiratory disease. And we learned that we would also soon lose an important stream of royalty revenues on another important product in Europe." (Fred Hassan, CEO of Schering Plough, 2005, http://www.schering-plough.com/schering_plough/about/hassanspeech9232005.jsp)

the companies officially state in their most recent Annual Reports that they will continue increasing their R&D expenditures in the coming years as part of a long-term strategy. A major means for increasing R&D expenditure is mergers and acquisitions. Companies that pursue M&As tend to have higher increases in their R&D expenditures in following years. The most distinctive examples are Astellas, UCB, Shire, and Merck KGaA. The increase in the R&D expenditure of Novo Nordisk has roots in the increase of its R&D partnerships in the areas of oncology and inflammation from one to four in just one year (2006). These resulted in two compounds progressing to clinical trials. Also, in 2006, the company's R&D expenditures increased more than its net sales (Novo Nordisk Annual Report 2006, p.93). Another company with a significant increase in R&D expenditure in 2006 was Forest Laboratories[19], which is highly committed to in-licensing and therefore includes licensing fees and the upfront and milestone payments made in conjunction with the license agreements in its R&D expenditures (Forest Laboratories, Annual Report 2006, p.41-42).

The ranking of the companies according to their R&D expenditures is also in line with their ranking according to their net pharmaceutical sales. An exception is UCB BioPharma. The company, which is ranked 11th in the 2006 sales ranking and located in the Lower Mid-Pharma grouping, has moved up to 8th position in the 2006 R&D expenditure ranking. The other two companies that have shown a significant jump in their ranking in 2006 R&D expenditure with respect to 2006 sales ranking are Alcon and Shire (from 14th to 11th and from 16th to 14th respectively). However, the R&D expenditures in absolute figures do not tell us very much. Using ratio of R&D expenditure to pharmaceutical sales provides us with far more insight into the sector.

2.5.4. Mid-Pharma by R&D expenditure as % of product sales

Over the last five years, most of the pharmaceutical companies have increased their ratio of R&D expenditures to sales (Table A.6 in the appendix). If we compare the figures for sales growth in Table A.4.2 and for R&D expenditure growth in Table A.5.2 in the appendix, we can observe that almost without exception, the rise in the ratio of R&D spending to sales is due to the fact that that these companies have increased their investment in R&D faster than their sales have grown (although we do see one or two cases of significant growth in a single year, but these are due largely to mergers and/or acquisitions). In fact, for one firm in Table A.6 (Forest), we see a fall in the ratio between 2002 and 2004 in spite of the fact that R&D spending increased at a respectable two-digit rate, because of an even higher rate of growth in sales. In only two cases do we see an increase in ratio due to a fall in sales. One of these is UCB, whose ratio rose from 11.2% to 26.3% in 2005. But we must note that the growth in R&D spending was extremely strong for UCB throughout the analysed period. The other case is that of Schering-Plough, whose ratio rose from 14% in 2002 to 19.4% in 2004 due to declines in sales in 2003 and 2004. Here again, however, we note healthy growth in R&D spending in 2004-2006 (see also Table A5.2).

By 2006, more companies show an increase rather than a decrease in the ratio. Of particular interest is that the three companies currently performing best in this area are drawn from the lower reaches of lower Mid-Pharma with respect to sales, although we can not speak of a general inverse relationship here. Some companies seem to allocate a stable percentage of their annual sales to R&D each year, such as Solvay, Baxter, Alcon, Eisai; and Bausch & Lomb. Others show slight increases each year compared to previous years, followed by a sudden jump, such as Merck KGaA, Novo Nordisk, Allergan and Lundbeck. The first two grew 2 - 3 percentage points between 2004-2005 and the latter two grew 1.5 - 2 percentage

[19] Lundbeck describes Forest Laboratories in its website as a company that "does not engage in research itself, focussing instead on the development and sales of other companies products within the U.S." (http://www.lundbeck.com/aboutus/history/company_history/1990/default.asp)

points between 2005-2006. In general, the R&D intensity of mid-pharma companies R&D is either growing or stable. None displays any significant decline.

Table 6 below reveals the R&D intensity for the industry as a whole from 1997 to 2005. If we compare these figures with developments in the companies studied in this report, two important findings emerge. First, only three of the companies studied (for which we have 2002 information) were above the industry average for that year. Second, in the years for which we can compare (2002-2004), our group of companies is mostly stable, whereas the industry trend has been a declinine.

Table 6. R&D intensity of Pharmaceutical Industry, 1997-2005

Pharmaceutical Industry, R&D Intensity, 1997-2005	
	R&D intensity*
2005**	15.8
2004	15.3
2003	15.7
2002	16.1
2001	16.7
2000	16.2
1999	15.5
1998	16.8
1997	17.1

** estimated

* calculated as total R&D a percentage of total sales

Original Source: Pharmaceutical Research and Manufacturers of America, PhRMA Annual Membership Survey, 2006.

Source: Pharmaceutical Research and Manufacturers of America, Pharmaceutical Industry Profile 2006 (Washington, DC: PhRMA, March 2006), p.45.

Unfortunately, we are unable to say anything concrete about R&D productivity, as it is not possible to find a basis for comparison between the incomplete information we have about the number of pipeline projects (see Table 12 below) and the figures for R&D spending. We also have no detailed information about what firms are actually spending R&D money on, as only a few provide such detail in their reports. We are therefore unable at this stage to provide a basis for comparison across firms.

Based on our sample of firms, we can speculate that research intensity might be determined largely by the firm's size and its number/range of therapeutic foci. It seems that the smaller pharmaceutical firms concentrate on a narrower range of therapeutic areas. Therefore, despite their location at the bottom of the list of lower Mid-Pharma list of companies (due to their low levels of product sales and R&D expenditure); UCB, Shire and Lundbeck might be ranked as top three mid-pharma companies in terms of research intensity. This is perhaps because they focus only on one or two therapeutic areas, compared to many of their peers that have a more diversified therapeutic foci (see Table A.2.3 and Table 3 therapeutic foci). Being significantly smaller than Big Pharma and with 50% of the research intensity of the top company (i.e. UCB) in our sample, Forest Laboratories is a case in point. " … our more modest size has been a virtue because our energies are more concentrated. Our size limits the number of projects we can undertake, but not at all the quality of what we can accomplish. Our size encourages the entrepreneurship that pervades Forest" (Forest Laboratories, Annual Report, 2003 p.3). However, there are also contradictory examples, as some mid-pharma companies that are focused strictly on one therapeutic area (such as Alcon and Bausch & Lomb, whose only therapeutic area is ophthalmology) still have the lowest research intensity. This can only be explained by the potential of the therapeutic areas to R&D and innovation.[20] In order to draw some more concrete conclusions, more research is required on this topic.

[20] Bausch & Lomb declares that the company holds approximately 2,200 patents and has approximately 1,900 pending patent applications in 2006 (Bausch & Lomb, Annual Report, 2006, p.30) As we have found on the US Patent Office website, Alcon has also a relatively strong history of patents (see Table A.14 in the appendix).

The smaller, lower mid-pharma companies might be benefiting from scale advantages by avoiding sales, marketing and distribution costs, as opposed to the larger upper mid-pharma firms, and allocating their resources effectively to R&D. Some, in fact, have pursued a strategy of organic growth by developing co-marketing and co-promotion partnerships with Big Pharma companies, from which they are able to acquire some marketing capabilities. (see Mittra, 2007) [21]

Finally, among the Big Pharma companies, Boehringer seems to be less intensively engaged in R&D compared to Abbott, but this might be a result of the specific nature of the data reported. For Abbott, the R&D expenses for the Group are divided by the net sales for the Group, whereas for Boehringer both the denominator and the nominator are for pharmaceuticals only (Table A.6 research intensity). In fact, it is not possible to say a great deal about Boehringer Ingelheim, but it looks like in the last two years it has had a relatively stable R&D intensity. Abbott Laboratories has shown a sudden growth of almost 5 percentage points in 2006 R&D intensity. Contrary to expectations, the Big Pharma companies do not appear to be in the higher ranking of the R&D intensity table. One reason for this might be the shift of Big Pharma companies from a core strategy of in-house R&D (which also includes external sourcing such as M&A and in-licensing that become an integral part of internal R&D efforts) to contract-based R&D collaborations.

2.5.5. Mid Pharma by products on the market

In the late 1990s/early 2000s, Mid-Pharma companies began to introduce key products that could be compared with the blockbuster drugs of Big Pharma (see Table 3 for the number of drugs each mid-pharma company has launched on the market). Their initial expectations with of these products at the time of launch were not proved wrong in 2006. For example, **Lundbeck** in-licensed memantine, for the treatment of moderate to severe Alzheimer's disease, from Merz Pharmaceuticals GmbH in 2000 with an expectation that sales would reach a considerable level within a few years, and launched it in 2002 under the name Ebixa (Lundbeck, Annual Report 2000). The share of the sales of memantine in total sales in 2006 was 15%. The other best-selling products of Lundbeck are Cipralex (escitalopram), one of the world's leading drugs for the treatment of depression and anxiety, and Azilect (rasagiline), for the treatment of Parkinson's disease. Cipralex was invented by Lundbeck in 1988, launched in 2002, and is currently marketed globally by Lundbeck and its partner Forest Laboratories, Inc. in the USA. The sales of Cipralex accounted for 59% of total sales in 2006. Azilect was developed in collaboration with Teva Pharmaceutical Industries Ltd. and launched in the first market in Europe in 2005 (Lundbeck, Annual Report 2006, p.6).

Eisai launched Aricept, a drug for a treatment for mild-to-moderate Alzheimer's disease, and Aciphex/Pariet, a proton pump inhibitor used for treatment of ulcers and gastroesophageal reflux disease, in 1997. Both were results of in-house R&D. The growing sales potential of Aricept and Pariet required Eisai to give special emphasis to the products. The share of the sales of these products in total sales in 2006 was 37.5% and 25.9% respectively, indicating the company's dependency and over reliance upon their continued success. In recent years, Eisai has focused its sales efforts on other therapeutic areas of the company, with cancer research becoming an important domain.[22]

This may sound like a paradox, but as mentioned before in the footnote 5, these companies have most of their profit from other segments of eye healthcare sector rather than pharmaceuticals segment.

[21] Regarding marketing, distribution and co-promotion relations in the mid-pharma industry, there is vast amount of information on the internet. Some have been gathered. However, they will not be presented in this report as they are not the main concern.

[22] http://www.eisai.co.jp/ (Product Pipeline)

Schering-Plough's most successful drug is Remicade, which was produced in-house and became the first anti-TNF biologic therapy approved by the U.S. Food and Drug Administration (FDA) for the treatment of moderate to severe Crohn's disease in 1998. The indication for Crohn's disease was quickly followed by additional indications, such as rheumatoid arthritis, early rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis, and ulcerative colitis, as a drug for the treatment of immune-mediated inflammatory disorders. International net sales of Remicade are growing every year, e.g. 32% to $1.2 billion in 2006 as compared to 2005; and 26% in 2005 to $942 million as compared to 2004, due to greater demand, expanded indications and continued market growth. The share of the sales of Remicade in 2006 total sales is 11.7% (Schering-Plough, Annual Report 2006, p.14).

Merck KGaA developed cetuximab in 2002: the first monoclonal antibody on the market to specifically target and block the epidermal growth factor receptor and inhibit tumor growth. It was the first product to emerge from Merck's oncology pipeline and received the first marketing authorisation for colorectal cancer in combination with chemotherapy in Switzerland in December 2003 (Merck KGaA, Annual Report 2003, p.25). The marketing authorization was granted in mid-2004 for all member states of the EU (Merck KGaA, Annual Report 2004, p.33). Erbitux (cetuximab) sales reached EUR 77 million in the product's first year on the market, significantly exceeding the company's expectations (Merck KGaA, Annual Report 2004, p.13). In 2006, the share of Erbitux sales in Merck's total ethical pharmaceuticals sales was 17.7%.

UCB enjoys world leadership in allergy treatments, with Zyrtec and Xyzal, and the top position in epilepsy in the US with its flagship anti-epileptic drug, Keppra® (29% market share in the USA) and with a 26% market share of epilepsy treatment in value in 2006 in Europe.[23] For its product Keppra, the company uses a small molecule therapy with a unique mechanism in epilepsy treatment. This has enabled the drug to retain its market leadership in the US, where its share in total sales was 35% in 2006 (UCB, Annual Report 2006, p.57). Zyrtec, despite significant generic and over-the-counter pressure since it was launched eleven years ago, has managed to extend its US market share to 45% by value (UCB, Annual Report 2006, p.4). In 2006, eleven large and small molecules progressed successfully through clinical development, including Cimzia; UCB's first biologic therapy, which was filed in the US and Europe for the treatment of Crohn's disease. The company inherited Cimzia, which has substantial potential in Crohn's disease and rheumatoid arthritis, from Celltech (UCB, Annual Report 2006, p.5).

Shire's focused strategy on developing and marketing products for specialty physicians and a pipeline of innovative products with strong patent protection have resulted in a strong position for responding strategically to a changing market. "Shire's ADDERALL and ADDERALL XR (mixed amphetamine salts) constitute the market-leading franchise for prescriptions in attention deficit hyperactivity disorder (ADHD). ADDERALL, launched in the US in 1996 and stayed Shire's ADHD brand leader until the end of 2001. Applying Shire's patented MICROTROL® extended release technology, Shire developed and launched ADDERALL XR in 2001, a novel formulation of ADDERALL, to provide an all-day treatment, with one morning dose. ADDERALL XR has a rapid onset of action, controlling symptoms throughout the day. ADDERALL XR has since become one of the most widely prescribed ADHD treatments in the US with approximately 11 million prescriptions and a 23% share of the US prescription ADHD" (Shire plc., Annual Report, 2003, p.11). In 2006, 85% (2005: 83%) of total revenues were derived from product sales, of which 48% was from ADDERALL XR (2005: 46%). Moreover, with the acquisition of Transkaryotic Therapies, Inc. in 2005, Shire gained two advantages. First it "acquired ELAPRASE (global rights), REPLAGAL

[23] UCB, Annual Report 2006, p.4 and http://www.ucb-pharma.com/about_ucb/management/track_record/index.asp

(which is presently sold only outside the US) and DYNEPO (to which the Group has exclusive marketing rights outside the US), and second it substantially increased its presence in Europe and thereby diversified the risk associated with being reliant on one geographic market, i.e. US" (Shire plc., Annual Report, 2003, p.6). ELAPRASE is the first human enzyme replacement therapy for the treatment of Hunter syndrome, and received FDA approval in 2006 with a highly successful launch in the US. The drug was granted market authorization in Europe in January 2007. Sales of REPLAGAL, an enzyme replacement therapy for the treatment of Fabry disease, rose substantially in Europe principally due to improved patient diagnosis (Shire Annual Report 2006, p.5).

Allergan displays a distinction within mid-pharma companies with a drug that achieved a true *blockbuster status*: namely Botox (a drug with applications in neurosciences, medical dermatology, medical aesthetics and urology). The drug has joined the exclusive ranks of pharmaceutical products to achieve greater than $1 billion in sales (both sales by Allergan, which were $982 million, and by out-licensee GlaxoSmithKline's (GSK) sales of Botox in Japan and China). The company attributes this faster sales growth to the creation of two separately focused sales and marketing organizations over the course of the last two years, as well as doubling the sales forces in the USA at the beginning of 2006 (Allergan, Annual Report 2006, p.6).

As the company cases above show, Mid-Pharma companies seem to rely heavily on individual products. A large portion of their total product sales depends on these individual products, which may make them more greatly exposed to the threat of generic competition. On the other hand, the focus on niche markets could also be regarded as a key strength of these companies, as they exploit gaps in the strategic priorities of the big pharma companies. The small biotechnology company sector emerged and expanded successfully by developing highly novel treatments for areas of unmet medical need, so it is possible that smaller pharmaceutical companies might also benefit from a similar strategy.

3. R&D Models of Mid-Pharma Companies

In order to understand the organisation of R&D and strategic management of Mid-Pharma firms, and how they might compare to Big Pharma, one has to consider two key factors:

The organisational capacity of Mid-Pharma companies to conduct and to internationalise in-house R&D, and
The ability to exploit external opportunities in international contexts; in other words, the ability to outsource R&D and establish strategic alliances and licensing agreements in a way that is harmonious with internal capabilities.

The development of a wide range of life science technologies to improve the R&D process, and exploitation of a more rational approach to drug design, has engendered a broader restructuring of the pharmaceutical industry (Drews, 2000; Mittra, 2007). In particular; large, vertically integrated pharmaceutical firms increasingly depend on the knowledge, expertise and products of external innovators; such as the new dedicated biotechnology firms and academic research institutions (Mittra & Williams, 2007). New technologies have engendered significant organisational restructuring and subsequent changes in the innovation value chain (Quéré, 2003). Pharmaceutical R&D has become characterised as a distributed or networked innovation system (Cambrosio et al, 2004; Chiesa & Toletti, 2004), in which the incumbent firms exploit merger and acquisition activity, strategic alliances, outsourcing and licensing models, in international contexts, to sustain innovation (Crossley & Kordel, 2002; Langley et al, 2005; Mittra, 2007; Tait & Mittra, 2004). Coombs & Metcalfe (2002) suggest that large pharmaceutical firms now had to create, coordinate and combine a diverse range of research and development 'capabilities', alongside the normal processes of internal, organic growth, to remain competitive and profitable.

Therefore, from the point of view of Big Pharma, the organisation of internal R&D is strongly linked to the internationalisation of R&D. The literature on internationalisation of R&D brings several issues to the forefront (Patel & Vega 1999; Gassmann & von Zedtwitz 1999). One important set of issues relevant to our research is the degree of internationalisation measured by the geographic dispersion of R&D activities (i.e. choice of location) and the activities of the research subsidiaries (which can be centres, units, divisions, laboratories etc.); including the intensity of their contribution to the knowledge pool of the company (which could be measured by the assignees in the patent applications of the company) and the degree of autonomy of the research subsidiary (i.e. centralised versus decentralised). First, we will consider the extent of such developments (i.e. internationalisation) in in-house R&D as they apply to Mid-Pharma companies and address some of these issues. Second, we will try to understand the role of externalisation of R&D activities on the growth (M&A), scientific endowment (licensing and patents), and innovative capabilities (R&D collaboration) of the Mid-Pharma companies investigated in this report. We will then be able to demonstrate the (im)balance between the internal and external R&D activities of these companies.

3.1 In-house R&D activities of Mid-Pharma companies

Mid-Pharma companies are little different to Big Pharma in terms of their strategy to pursue and exploit R&D at a global level. Table 7 below displays the degree of internationalisation of the Mid-Pharma companies' R&D activities. As mentioned earlier, their locational preference is taken as an indicator for their internationalisation. All but one of the companies in our sample appeared to start their R&D activities in their home country, although there is no information on the German R&D centre of Merck KGaA. Forest Laboratories and Bausch & Lomb seem to have retained their R&D activities only in their home country (the USA). We make this assumption on the basis that there is no information about any other R&D centres. For Gilead Sciences, no information regarding its R&D activities and their location is available. However, since the company is a start-up founded in 1987 in Foster City, California, which has expanded to three continents in 20 years, we assume that its main R&D facility is in the USA.

The European and American companies seem to have expanded their R&D activities as far as China (see Novo Nordisk in Table 7) and Japan, while having an R&D link with the USA seems to be a must for Japanese and European companies. Gilead Sciences is the only company in our sample that has established strong links in India, with eleven generic companies in 2006.[24] The company has signed non-exclusive license agreements that grant these companies the rights to produce and distribute generic versions of tenofovir disoproxil fumarate (tenofovir DF), which is sold by Gilead under the brand name Viread to 95 low-income countries around the world, including India.

[24] These companies are: Alkem Laboratories Ltd., Aurobindo Pharma Ltd., FDC Ltd., J.B. Chemicals & Pharmaceuticals Ltd., Matrix Laboratories Ltd., Medchem International, Ranbaxy Laboratories, Shasun Chemicals & Drugs Ltd., Emcure Pharmaceuticals Ltd., Hetero Drugs Ltd. and Strides Arcolab Ltd

Table 7.Geographic dispersion of the R&D centres of Mid-Pharma companies

Locations of the companies' R&D centers around the world and their number																		
	company	Boehringer-Ingelheim	Abbott	Schering Plough	Baxter Intl	Astellas	Novo Nordisk	Eisai Co.	Merck Serono (together with Serono's)	Alcon Inc.	Solvay	Forest Laboratories	UCB Biopharma	Allergan	Gilead Sciences	Bausch & Lomb	Lundbeck	Shire
	home country	D	US	US	US	JP	DK	JP	D	CH	BE	US	BE	US	US	US	DK	UK
North America	USA	2	3*	5*	1*	1	2	1	3	1	1	2*		1*	1*	1*	1	4
	Canada																	1
Europe	UK							1	1				2	1				1*
	Germany	1*	1			1					1							
	France				1				1		1			1				
	Austria	1			1													
	the Netherlands					1					1							
	Belgium				1						1*		1*					
	Switzerland			1					1	1*								
	Spain								1	1								
	Italy			1					1									
	Denmark						3*										2*	
East Asia	Japan				1	3*		2*		1	1			1				
	China						1											

* home country

Source: Company websites and Annual Reports

The activities of the research sites, their contribution to the knowledge pool of the whole Group; and their degree of autonomy varies between Mid-Pharma companies. Some are more focused in certain therapeutic areas than others, and while some are tightly controlled (i.e. centralised), others appear far more decentralised. Some companies provided the total number of R&D staff (provided in the company profiles below), while others did not disclose this information (see Table A.8 in the appendix for a comparison of the companies that do declare the number of R&D staff). The employee count in R&D centres located in the home country compared to abroad is not possible to provide through publicly available data.

In our sample, the Upper Mid-Pharma companies appear to organise their R&D activities specific to the technology (i.e. small molecule vs biologics), just like Big Pharma. Below are a few illustrative examples.

Boehringer Ingelheim[25] produces therapeutically active proteins from micro-organisms and yeasts, microbial vaccines, plasmid DNA for gene therapy, protein scaffolds and antibody fragments in its relatively new biology research centre based in Vienna, Austria. Its new centre (started in 2006) for pharmaceutical research and development in Biberach, Germany; develops and manufactures therapeutic proteins from mammalian cell cultures. The company allows its R&D sites to maintain strong responsibility and accountability for their therapeutic areas locally. This allows for flexible and decentralised management of R&D; a trend that has been common amongst large pharmaceutical firms. Worldwide, the company employs more than 3,300 scientists, technicians and support personnel in preclinical R&D, and about 2,300 clinical monitors, statisticians and data managers in clinical development and medical departments. In order to strengthen its R&D organisation, Boehringer has created international skill centres to improve efficiency and to secure equal access to state-of-the-art technologies and informatics platforms for all R&D sites. Through its own in-house

[25] Boehringer Ingelheim, 'From Mind to Market, Value through Innovation', 2007, p.11, downloadable from the company's website http://www.boehringer-ingelheim.com

R&D, Boehringer Ingelheim has so far delivered nine DNA-derived biopharmaceutical products to the market.

Schering-Plough[26], as part of its transformation process, has created a new Biopharma unit in order to integrate biotech capabilities within a "bigger pharma" R&D structure. It organises its biopharma R&D sites according to specialisation in small molecules and biologics. The Schering-Plough Biopharma laboratories in Palo Alto, California, are concentrated on biologics research (i.e. monoclonal antibodies and therapeutic proteins), while research on small molecule drug discovery takes place at its laboratories in Kenilworth, N.J., Cambridge, Massachusetts; and in the research facility in Milan, Italy (though with a special expertise in neurobiological indications). The research site in Lucerne, Switzerland; focuses on the full spectrum of R&D activities. Schering-Plough scientists in these R&D sites collaborate throughout the discovery process to understand underlying disease mechanisms, elucidate novel targets and discover potential new therapies to treat specific diseases within each of therapeutic areas (i.e. internal knowledge sharing and creation).

Astellas[27] organises its research activities as "group companies" in North America and Europe. It operates a matrix form, with responsibility allocated both to regional headquarters and by function (R&D, manufacturing, marketing, etc.) in order to ensure efficient operation of the group.
The Biopharmaceuticals Research Unit of **Novo Nordisk**[28] in Denmark discovers and develops new, innovative biopharmaceuticals and creates the foundations for future marketing. It operates two research centres outside of Denmark: Novo Nordisk Research in New Brunswick, New Jersey, which is the first haemostasis research facility in the United States dedicated to investigate new therapies treat life-threatening bleeding, including exploration of treatments for intracerebral haemorrhage, other bleeding disorders and trauma, and the Novo Nordisk R&D centre in Beijing, China, which was the first R&D centre established in China by an international pharmaceutical company. It is evolving into a centre of excellence in molecular biology, protein chemistry and cell biology. Chemistry, Manufacturing and Control Supply develops and produces all new proteins and peptides for clinical trials. Clinical development centres are located in Zurich, Switzerland; Beijing, China; Princeton, New Jersey, US; and Tokyo, Japan. Globally, 4,105 people work together on R&D activities at Novo Nordisk. Novo Nordisk has also been one of the first conventional pharmaceutical companies to take an active interest in the development of stem cell therapies for diabetes; funding the Hagedorn Research Institute for this purpose.

Eisai has a multi-polar R&D organization with clinical research bases in three continents with their own areas of expertise. Eisai R&D Management Co., Ltd. was established in order to administer them centrally, to supervise the international project teams organized by research themes and to provide support to them. The nucleus R&D site of Eisai's new drug development activities is the Tsukuba Research Laboratories in Japan, which conducts basic research at four laboratories.[29] Eisai Research Institute of Boston, Inc. undertakes immunology and oncology research using sophisticated organic synthesis techniques to develop novel high-polymer organic compound materials that form the basis of new drugs. Eisai London Research Laboratories specializes in molecular and cytological research related particularly to the central nervous system (i.e. neuro-degenerative diseases, such as Alzheimer's disease, Parkinson's disease and multiple sclerosis and regenerative medicine).

[26] http://www.schering-plough.com/schering_plough/research/spri/index.jsp
[27] http://www.astellas.com/global/
[28] http://www.novonordisk.com/
[29] These laboratories have such names as: "the Laboratory of Seeds Finding Technology", "Discovery Research Laboratories", "Analytical Research Laboratories", "Drug Safety Research Laboratories". Eisai has an agro-chemical production and sales company in Japan within its Group that may link its operations with the first basic research laboratory and, through this laboratory, also with the pharmaceuticals operations within the Group http://www.eisai.co.jp/ (R&D system Grounded on Global Perspective).

KAN Research Institute in Kobe, Japan, is undertaking life science research using cutting-edge gene research technologies. Most importantly, Eisai's Tsukuba Research Laboratories coordinates collaborative research with Eisai's other labs in Europe and the U.S., allowing knowledge sharing and creation within the company. Clinical research also involves collaboration between the Clinical Research Center in Japan, the U.S. clinical research company Eisai Medical Research Inc. (which has recently been consolidated with Eisai Research Institute of Boston), and the clinical research division of Eisai Ltd. in the U.K. In addition, Eisai Clinical Research Singapore Pte. Inc. was established in October 2006 to facilitate the strategic execution of clinical studies in Asia. In contrast to other companies, Eisai has created a Knowledge Creation Department in order to promote innovations throughout the company and to convert employee knowledge into company assets. The department has two main tasks: "to cultivate human resources that can create innovations and then apply them," and "to emphasize the proper approach to promoting the creation of knowledge."[30]

Merck Serono S.A. has an integrated R&D capability in-house, which employs over 1,300 R&D personnel. The three research sites of Serono, which were acquired by Merck KGaA and became Merck Serono in 2006, are organised to focus on different therapeutic areas. Serono Pharmaceutical Institute in Geneva focuses on its research strengths in autoimmune, inflammatory, and neurological disease. With over 200 top-level scientists and staff, it is a global centre of excellence in understanding the biology of disease, as well as in progressing the concept into small molecule and protein drug molecules. The Serono Research Institute in Boston focuses on the fields of oncology and reproductive health. SRI was started in 1999 as a centre of excellence in Reproductive Biology and has evolved into a major cancer research centre. 90 researchers work in cancer biology in order to develop innovative new therapies for oncology and infertility. The pharmacological research centre in Italy focuses on the progression of drug candidate molecules for Phase I studies. It has a very close interaction and knowledge sharing with the above two centres.

UCB Pharma[31] has created Centres of Excellence that focus on specific therapeutic areas. This way, the R&D organisation is free from bureaucracy and other constraints often associated with large organisations. The centre in Slough, UK, focuses on immunology and oncology; the centre in Cambridge, UK, focuses on inflammation; and the centre in Braine l'Alleud, Belgium, focuses on CNS disorders. The company works on improvements of its in-house R&D organisation by introducing novel electronic tools to connect individuals' knowledge and expertise, as well as to create greater internal transparency. Since 2006, through an innovative intranet tool, called UCB-People, they aim at providing personalised profiles of employees, including insights into their knowledge, skills and objectives, for employees to identify colleagues around the globe with complementary expertise for particular projects. The R&D teams in UCB also establish virtual collaboration platforms, based on the active knowledge sharing principles of Wikipedia.

Alcon[32] claims to have the largest eye-care related R&D operation of its kind, consisting of 1,350 dedicated researchers, scientists, engineers and support staff and state-of-the-art facilities located in the United States, Spain, Japan and Switzerland. Alcon's Research and Development laboratories are responsible for the discovery, development and clinical evaluation of surgical, pharmaceutical and consumer vision care products. The Alcon Research Institute (ARI) is recognized as one of the premier programs in ophthalmic discovery, and supports scientific exploration and advance by awarding nearly $20 million in unrestricted grants to the understanding and treatment of eye disease. Alcon's R&D organization includes more than 300 individuals who are either M.D.s, doctors of optometry

[30] http://www.eisai.co.jp/ (Promotion system)
[31] UCB Pharma, Annual Report 2006, p.21
[32] http://www.alcon.com/ and Annual Report 2006, p.15

or Ph.D.s and has extensive experience in the fields of ophthalmologic and optometric science.

Lundbeck[33] is a well recognised Mid-Pharma company with innovative pharmaceuticals in psychiatry and neurology. While it is not as internationalised as upper mid-pharma companies, it has an international R&D organisation, with R&D site located in New Jersey, US, as well as in its home country. Development headquarters is also kept in Copenhagen, Denmark with clinical research and regulatory personnel spread worldwide. Lundbeck employs over 750 R&D staff with multi-disciplinary, empowered project teams in in-house expertise areas. They developed and marketed four new pharmaceuticals over the past five years and also expanded the number of late-stage projects and their early development portfolio with candidates from in-house research. 70% of Lundbeck's drug development is based on its own research, while 30% is composed of in-licensing (Lundbeck, Annual Report 2006, p.13)

Shire[34] is a Mid-Pharma company with an R&D strategy targeting later-stage and lower risk projects. For instance, Shire's acquisition of Transkaryotic Therapies Inc. (with strong R&D in protein therapeutics) in 2005 was driven, in part, by the comparatively low risk of developing protein replacement therapies for genetic disease compared to other drug discovery approaches. Over the last three years, Shire has significantly refocused its R&D efforts on products in its core therapeutic areas, which meet the needs of the specialist physician. The Group has also concentrated its resources on obtaining regulatory approval of its later-stage pipeline products within its core therapeutic areas.

Allergan[35] opened its first R&D facility in Irvine, California in1994. Then it expanded its R&D centres to France and Japan. In 2005, significant changes led to restructuring of the company's European commercial and R&D operations, out-licensing of Botox in Japan and China to GlaxoSmithKline (GSK), and co-promotion of GSK's Imitrex StatDose System and Amerge, which are indicated for migraine treatment in the United States. As a result, the company decided to close its R&D centers in France and Japan. The company has concentrated all its clinical development for Europe in the United Kingdom and increasingly benefits from effects scale in its Irvine, California facility - transition from a 4-center to a 2-center R&D network. In addition, at the end of 2005, a new R&D facility, called the Herbert Research Center, was opened at Allergan's headquarters in Irvine. The company has focused on discovery research and customer relations, with more than 50 percent of its current workforce engaged either in R&D or field sales.

3.2 External sourcing

All the mid-pharma companies give a great deal of importance to the development of partnerships with other pharmaceutical companies, academic institutions and research laboratories. Merck Serono S.A. has an integrated R&D capability in-house and employs over 1,300 R&D personnel, but it also has a network of biotech alliances with smaller biotech companies and academic groups. Alcon fosters strong relationships with academic institutions, governments, ophthalmic clinicians and corporate partners around the world. Scientists at Novo Nordisk (particularly Novo Nordisk Research US) collaborate with academic institutions, clinical research centres, technology providers and biotech companies in many areas of diabetes and protein-based therapies to further advance medical innovation, ensure the competitiveness of its research programmes, and expand its international network. Schering-Plough scientists also collaborate with research partners from other pharmaceutical companies to build the product pipeline and drive innovation.

[33] http://www.lundbeck.com/products/R_and_D/R_and_D_at_lundbeck/default.asp
[34] Shire plc., Annual Report 2006, p.7
[35] Allergan, Annual Report 2005, p.5.

Similarly, Gilead prides itself on its many long-term collaborations with leading academic institutions and biotechnology and pharmaceutical companies to develop innovative new therapeutics and advance the care of patients confronting life-threatening diseases.

It is well known that the business model of Big Pharma relies heavily on in-house R&D, complemented with external sourcing tools that allows integration of proprietary rights such as M&As and in-licensing. A study conducted by Wood Mackenzie in 2005 on the licensing activity of the largest 25 companies by drug sales over the last 10 years (1995-2005) found that almost 70% of the product licensing deals are with biotechnology companies, reflecting the increasing maturity of that sector and its importance as a source of innovation for the larger companies. The study defined the partner of choice as the company with the greatest success of bringing mid-stage products to market. According to Dr Siân Renfrey, the Principal Consultant at Wood Mackenzie, licensing is going to play an increasing role in the evolving strategies of Big Pharma. Dr James Featherstone, Head of Life Sciences Consulting, talks of the recognition of the trend of companies that have traditionally shunned external business development in favour of organic growth now pursuing a partnership model. He cites the example of Merck & Co., which has signed nine major product licensing deals during 2003-2005, compared to just one in the period 1995-1999.[36]

As mentioned in section 2.2, the Datamonitor report on Mid-Pharma sector on the internet[37] also focuses on the in-licensing and acquisitions as the main externalisation strategy of Mid-Pharma companies that distinguishes them from those of Big Pharma. The report analyses how dependent each Mid Pharma company is on externalization to support their current portfolios and to examine which types of externalization strategy are most popular in the Mid Pharma peer set and are responsible for the largest influx of product revenues to Mid Pharma. According to the report, Mid-Pharma companies secure their access to promising new drugs and therefore populate their portfolios by using in-licensing and acquisitions as an integral component of their business model. Such a strategy does not seem too different from what we observe in most Big Pharma firms.
Furthermore, after years of focus on in-house R&D and acquisitions in small molecule technologies, Big pharma companies have now turned their focus to biologicals and started acquiring small biotech companies.[38] Schering-Plough's CEO Fred Hassan says "We may also see some acceleration of big pharma companies acquiring biotechs to create … in-house capability. But that will not be the main story. The main story will be an accelerating pace of interactions between big pharma and independent biotech companies. The result of this interaction will be to move promising biotech compounds from the "hot house" of the biotech company into the development and global commercialization organization of the big pharma companies. This interaction will take a variety of forms, including partnerships, alliances and in-licensing actions. We will continue to have an array of global, 'big pharma companies over the next decades and their ranks will swell. Their excellence will center in science innovation."[39] Of course, one could also argue that Big Pharma is currently in a a

[36] Wood Mackenzie, " Licensing is pivotal to Pharmaceutical Industry evolving strategies", Edinburgh and Boston, 8 December 2005. http://www.woodmacresearch.com/cgi-bin/corp/portal/corp/corpPressDetail.jsp?searchStr=pharmaceuticals&oid=721147&BV_SessionID=@@@@1348335154.1197300811@@@@&BV_EngineID=ccceaddmkefjihjcflgcegjdffjdgih.0 (about Wood Mackenzie's proprietary tool for the analysis of product licensing deals, Licensingview)

[37] Datamonitor, "Mid Pharma Sector: In-licensing and other externalization strategies", Information regarding this report is downloaded from the website of Bharat Book Bureau, One-stop-shop for business information, http://www.bharatbook.com/bookdetail.asp?bookid=3712&publisher

[38] There is another report by Datamonitor called "Big Pharma Turns to Biologics for Growth to 2010: Financial and strategic segmentation of the Big Pharma sector by drug technology". The report forecasts 60% of revenue growth to come from biologic products (therapeutic proteins and monoclonal antibodies) by 2010, and annual sales of biologics will have increased by $26bn, compared to a $13bn increase for small molecules. http://www.bharatbook.com/bookdetail.asp?bookid=3712&publisher.

[39] Fred Hassan, Chairman and Chief Executive Officer, Schering-Plough Corporation, "Transforming a Company, Transforming Relationships", Remarks for the 15th Anniversary Pharmaceutical Strategic Alliances Conference, New York, Sept. 26, 2005

form of crisis as it's productivity has wained and it faces various internal and external challenges. A swelling in the ranks of Big pharma, and the continuation of large scale M&A is now generally considered to be an unsustainable strategy. Nevertheless, in the following sections we will examine the question of whether similar trends are taking hold in the Mid-Pharma sector.

Mergers and Acquisitions

Mid-Pharma companies do not seem to undertake M&As as intensively as Big Pharma (Table 8). There are two groups of companies in our sample. The first use mergers and acquisitions strategically to complement their organic growth. Although they are limited in number, these companies are Baxter, Shire, Merck KGaA and Solvay. These companies started to grow through M&A in the late 1990s, at the same time as Big Pharma was also experiencing an M&A boom. Shire attributes the highest importance to acquisitions not only in its growth strategy but also in its approach to external sourcing. As will be seen below, Shire seldom enters into partnerships, in contrast to other Mid-Pharma companies. The second group can be referred to as 'latecomers', which started M&A strategies in 2002 or later, and with some reservation (this was the time when M&As in the pharma industry as a whole were on the decline.) Examples include Schering-Plough's acquisition of mid-pharma company Organon, Bausch&Lomb's expansion in to China, Allergan's acquisitions to acquire products and expand its therapeutic areas; Astellas and UCB's strategic acquisitions of biotech companies; Gilead's incorporation of a small company, and UCB's acquisition of another mid-Pharma company Schwarz. Short company cases are provided below.

Table 8. M&As by Mid-Pharma companies, 1990-2007

Number of M&As undertaken, 1990-2007

	M&A		*product acquisition*		*JV*	
Companies	*years*	*total number*	*years*	*total number*	*years*	*total number*
Abbott	1999-2006	6		0		0
Alcon	2007	1		0		0
Allergan	2003-2007	3	2003-2004	2		0
Astellas	2005-2007	3	2006	1	2005	1
Bausch & Lomb	2005	1	2006	1		0
Baxter	1998-2003	10	2001-2003	4	2001-2006	2
Boehringer	1997	2		0		0
Eisai	2007	1	2006	3		0
Forest	2007	1		0		0
Gilead Sciences	1999-2006	4	1998	1	2004	1
Lundbeck	2002	1	1999	2		0
Merck KGaA	2000-2006	8	2006	1		0
Novo Nordisk	2004	2	2006	1		0
Schering Plough	2005-2007	2		0	2000	1
Shire	1997-2007	9	2006	1		0
Solvay	1997-2005	5	1998-1999	2		0
UCB	2004-2006	2	2006 (divest)	2		0

Source: Calculated from the information released in the company websites (news releases) and various annual reports

http://www.schering-plough.com/schering_plough/about/hassanspeech9232005.jsp

As in the case of Big Pharma; mergers and acquisitions seem to be one of the main vehicles for Mid-Pharma companies to grow strategically, to extend their key therapeutic areas, and improve their pipeline. (see Tables A.10.1 andA.10.2 in the appendix). For instance, when **Merck KGaA** acquired Serono,[40] one of the leading small biopharmaceutical companies in Europe, it was attracted by new opportunities to further develop specific therapeutic areas, such as in neurology and reproductive health. Such expansion into new therapeutic areas has a significant 'balancing' effect on company strategy, particularly those firms that have more than one business segment and follow "focused diversification" (see Annual report of Merck 2006, p.12). **Baxter**, which was relatively weak compared to other companies in terms of in-house R&D, is aggressively pursuing M&As, JVs, and product acquisition (Table 8), and is likely to enhance its in-house capabilities by acquiring proprietary rights and integrating them into the company.

Gilead has proved successful with the acquisition of a small but highly innovative company. In 2006 it acquired Corus Pharma, bringing its founder, A. Bruce Montgomery, onto its Executive Committee as Senior Vice President and Head of Respiratory Therapeutics. Montgomery founded Corus Pharma in January 2001 and served as the company's CEO and Director for five years. His previous experience included management of the development of inhaled tobramycin for the treatment of cystic fibrosis at PathoGenesis Corporation and work on development of Pulmozyme, another treatment for cystic fibrosis, at Genentech.

Allergan has recently acquired two small pharma companies. The first was Oculex Pharmaceuticals, which was acquired in 2003. The company was a leader in developing treatments for sight-threatening diseases of the eye and already a licensor to, and research collaborator with Allergan in discovery, development and commercialisation of compounds for ophthalmic use, based on Oculex's proprietary biodegradable (BDDTM) and reservoir (RDTTM) drug delivery technologies. With this acquisition, Allergan gained the rights to Posurdex, a bioerodable, extended release implant that Oculex was developing to deliver dexamethasone to the targeted disease site at the back of the eye. In 2007, the company acquired Esprit Pharma, allowing it to create a dedicated urologics division and thereby enter another core specialty market with significant growth potential. Allergan expects to launch SANCTURA XR(TM), which Esprit licenses from Indevus Pharmaceuticals, in the first quarter of 2008 in the United States.

In 2005, **Bausch & Lomb** acquired a controlling interest in the Shandong Chia Tai Freda Pharmaceutical Group (CTF), the leading ophthalmic pharmaceutical company in China, in order to accelerate its expansion into the rapidly growing ophthalmic pharmaceuticals market in China. Freda's focus is the development, manufacturing and marketing of medications used to treat ocular inflammation and infection, glaucoma and dry eye. Company news releases suggest that market-seeking motives were behind this acquisition rather than asset-seeking motives, as Freda provides Bausch & Lomb with a national pharmaceuticals sales and distribution network, a locally compliant manufacturing facility, and expertise in regulatory affairs and product development.

Shire's declared strategic intention is to grow both organically and by acquisition. It has merged with seven companies over a ten-year period, allowing it to grow faster than many companies in the industry (with sales almost doubling between 2002 and 2006). In 1997, Shire acquired the advanced drug delivery company, Pharmavene Inc., and the specialty

[40] **Merck Serono** was established in 2007 following the acquisition of Serono S.A. (now Merck Serono S.A.) by Merck and the integration of the business with the former Merck Ethicals division. The new company is regarded as an important source of innovative prescription pharmaceuticals for the Group.

sales and marketing company, Richwood Pharmaceutical Company, Inc. Then, in 1999 it acquired the German, French and Italian sales and marketing subsidiaries of Fuisz Technologies Ltd. At the end of the same year, Shire merged with Roberts Pharmaceutical Corporation. In 2000 Shire extended its operations to the Pacific Rim countries, registering a Representative Office of Shire Pharmaceuticals Limited in Singapore, and to Spain. In May 2001, Shire merged with Canadian Pharmaceutical company BioChem Pharma. In 2005, it acquired Transkaryotic Therapies Inc. (TKT), a US-based biopharmaceutical company specializing in therapies for the treatment of rare genetic diseases caused by protein deficiencies. In 2007, Shire acquired New River Pharma to gain control of its ADHD product VYVANSE.

With the acquisition of Fournier Pharma in 2005, **Solvay Pharmaceuticals** became the global leader in fenofibrate, a successful cardio-metabolic product for treating aised blood lipids. The integration of Fournier Pharma added a strong product line in dyslipidemia (i.e. control of cholesterol and triglycerides) to Solvay's cardiology business.

As an example of a mid-pharma company acquiring a biotech company, **Astellas** acquired Agensys, Inc., in 2007. This was a company that specialised in therapeutic antibody R&D in cancer. In another example of a takeover of a biotech company, **UCB's** 2004 acquisition of Celltech, a UK-based biotech company brought together important capabilities in antibody technology and chemistry to create a pure biopharma platform for serious and life threatening disease. In 2006, UCB acquired Schwarz Pharma, giving it a rich late-stage pipeline, as Schwarz had two promising late-stage therapies in four important indications, supplementing UCB's existing therapeutic areas and taking it into new growth markets, such as Parkinson's disease. These included a novel transdermal patch for Parkinson's disease (Neupro, the first once-a-day, non-ergolinic dopamine agonist), which had also successfully completed Phase III trials for restless legs syndrome, and lacosamide, an epilepsy drug (responding to the fact that 30% of patients are not served optimally by existing therapies) also useful in treating diabetic neuropathic pain.

Schering-Plough's 2007 acquisition of Organon BioSciences N.V. (OBS), the human and animal health care businesses of Akzo Nobel N.V.built on the company's growing strength in primary care, giving them access to central nervous system (CNS) and women's health care products and filling a gap in their late-stage pipeline by adding five compounds in Phase III development and a number of projects in Phase II development. It also enhanced Schering-Plough's strength in human and animal biologic products, including the potential to develop human vaccines. OBS was comprised mainly of Organon, a human pharmaceutical business, and Intervet, an animal health business, and also included Nobilon, a human vaccine development unit, and Diosynth, the third-party manufacturing unit of Organon.

Joint Ventures

Joint ventures are not common between Mid-Pharma companies. However, Mid-Pharma companies do sometimes enter joint ventures with Big Pharma companies (Table A.11 in the appendix). In 2000, for example, Schering-Plough joined forces with Merck Co. to establish Merck/Schering-Plough Pharmaceuticals to develop and market prescription medicines in cholesterol management in the US and other world markets (excluding Japan). Gilead established a JV with Bristol-Myers Squibb in 2004; the first of its kind in the field of HIV therapy, to develop and commercialise in the US a fixed dose combination of two drugs belonging to each company. Astellas's (then Fujisawa) JV with Sanofi-Aventis K.K - the Japanese subsidiary of Sanofi-Aventis (then Sanofi only) - dates back to 1982, and with some modifications the relationship still continues in 2007. The JV gives the rights to Astellas to manufacture and sell certain products originating from Sanofi-Aventis. Baxter International established a JV with Chinese company, Guangzhou Baiyunshan Pharmaceuticals Co. Ltd., in 2006 to produce and sell parenteral nutrition products of the partner and then gradually

expand the portfolio to include Baxter products in China, aiming at growth in that emerging market. The company has had another JV with Nutricia and Andreas Rudolph since 2001, with the aim of taking advantage of the growing homecare market in Germany.

Unique patterns of external sourcing

Corporate Venture Capital Financing

In the case of Novo Nordisk, we see a good example (indeed, the only examples we have observed in this group of companies) of corporate venture capital financing. In 2004, Novo A/S invested in Arakis Ltd., a UK-based company founded in March 2000 with the objective of building a product based company specialising in low risk, rapid development opportunities. In only four years, Arakis had been able to generate a seven-product pipeline. In the same year, Novo Nordisk also participated with a number of venture funds in a private equity financing of in California-based Metabolex, Inc., a privately held pharmaceutical firm that discovers and develops drugs to treat diabetes and related metabolic diseases.

Financing the development, marketing and distribution of drugs

In Forest, we see a unique example of a company securing revenue streams by making deals to finance the development, marketing and distribution of drugs developed by smaller companies. For example, it has made such deals with Barcelona-based Almirall, Replidyne, the Swiss-based Glenmark Pharmaceuticals SA, the German PAION GmbH, and ChemoCentryx Inc.

A new kind of external sourcing

Product Acquisition

Licensing has been thought to be the norm in the pharmaceuticals industry. However, a different kind of external sourcing than licensing is also apparent; namely product acquisition. Pharmaceutical companies acquire the patent of a product and sometimes continue to collaborate with the ex-owner to develop it further. Some examples are as follows:

- In 2006, Duramed Pharmaceuticals, Inc., a Barr subsidiary, purchased Shire's immediate release ADDERALL product, a smaller product with significant generic competition which no longer fit Shire's ADHD strategy, for US$63 million.
- In 1998, Isis Pharmaceuticals purchased from Gilead Sciences, Inc. the patents and patent applications covering a broad range of antisense chemistry and antisense drug delivery systems.
- In 1999, Lundbeck acquired the rights to two products in phases II and III for the treatment of Parkinson's disease from the Israeli company Teva Pharmaceuticals and entered collaboration agreement with the same company to pursue clinical trials, which were completed successfully in 2003.
- In October 2006, Eisai acquired the exclusive global rights for marketing to four oncology products from US-based Ligand Pharmaceuticals Inc. This acquisition has helped the development of the company's commercial capabilities while it prepares for the introduction of the in-house developed products. Moreover, as a result of this product acquisition, cancer researchers, marketing and sales teams, and other specialists who had worked at Ligand Pharmaceuticals have joined Eisai's team, strengthening the capabilities of the company in conference activities, distribution, and regulatory affairs.
- Such product acquisitions have always been of strategic importance for Forest.

Licensing

In-licensing

In-licensing is one of the commonly used tools of pharmaceutical companies to complement their internal R&D efforts for new drug discovery and development as well as to build strength in their global franchises through not only internal research but also external licensing opportunities. The companies openly declare that they actively pursue new compounds, new therapies and technologies through in-licensing. One such company is Bausch & Lomb. The pharmaceutical companies claim to improve their pipelines with new compound or technology licensing, introduce R&D activities completely new to the firm such as in new therapeutic areas or new technologies (e.g. biologicals), and as a result foster innovative capability development in new scientific areas.

Boehringer Ingleheim is an example from Big Pharma that has tried to expand its discovery and development portfolio into new biological entities through in-licensing and at fostering internal new chemical entities (NCE) R&D capabilities (Annual Report 2006). Between 1997-2006, Boehringer in-licensed 13 compounds, drugs and technologies, by far the highest figure in Table 9. In 2001, Boehringer Ingelheim received exclusive worldwide rights to commercialize ImmunoGen's maytansinoid Tumor-Activated Prodrug (TAP) technology using a Boehringer Ingelheim antibody targeting CD44. The company aimed at developing a new product, and under the terms of the agreement, was responsible for the manufacturing, product development and marketing of products resulting from the license, while ImmunoGen manufactured preclinical and initial clinical materials for manufacturing payments.

Table 9. Licensing by Mid-Pharma, 1991-2007

Number of licensing undertaken 1990-2007

	In-licensing		*Out-licensing*		*Cross-licensing*		*Return of rights*	
Companies	*years*	*total number*	*years*	*total number*	*years*	*total number*	*years*	*total number*
Abbott	2005-2006	5		0		*0*		0
Alcon	1993-2007	3	2007	1		0		0
Allergan	2001-2002	2	2004-2005	4	2001	1		0
Astellas	2005-2006	8		0		0		0
Bausch & Lomb	2005-2006	5		0		0		0
Baxter	2005-2007	4	2006	1		0		0
Boehringer	1997-2006	14	1997-2003	3	2003	1		0
Eisai	2004-2007	10	2006	2		0		0
Forest	1998-2007	5		0		0		0
Gilead Sciences	1991-2007	12	1996-2007	10		0		0
Lundbeck	1999-2007	9	1996-2004	5		0		0
Merck KGaA*	2002-2006	3	2001-2007	6		0	2004	1
Serono*	before 2006	9		0		0		0
Novo Nordisk	2006-2007	3	2000-2007	5		0		0
Schering Plough	2003-2007	11	2007	1		0		0
Shire	1998-2007	9	1990-2007	7		0		0
Solvay	1997-2003	4	2002	1		0		0
UCB	2006	4	2000-2006	2		0	2006	1

** Serono's external sourcing relationships before Merck KGaA's acquisition in 2006.*
Figures for Merck KGaA represent Serono only after 2006.
Source: Calculated from the information released in the company websites (news releases) and various annual reports

Abbott Laboratories has in-licensed 5 patents and technologies in 2005-2006, allowing the company to make its position even stronger in its therapeutic areas. In 2005, the company in-licensed BioCurex's Recaf material and technology. The receptor for alpha-fetoprotein, Recaf has emerged as a potential biomarker that may be useful in the development of new cancer diagnostics tests. Abbott's goal was to further develop this technology, incorporating it into future tests on its Architect system, for use in cancer diagnosis and monitoring.

The approach of Big Pharma firms to in-licensing is more to do with the R&D and drug development side. The Mid-Pharma companies are also interested in in-licensing for enhancing their marketing and distribution around the world.

Schering-Plough in-licensed 11 compounds and drugs between 2003-2007. When the company in-licensed garenoxacin (Toyama's proprietary quinolone antibacterial agent) from Toyama Chemical Co. Ltd. in 2004, it expected the addition of the compound to broaden the anti-infective portfolio it was developing. Another in-licensing example is related to Schering-Plough's interest in biologicals. In 2005, Schering-Plough in-licensed right to develop and commercialize Centocor, Inc.'s golimumab, a new anti-TNF-alpha monoclonal antibody which is developed as a therapy for the treatment of rheumatoid arthritis and other immune-mediated inflammatory diseases. The company shared the development costs with Centocor and was responsible for worldwide marketing and distribution.

Among Mid-Pharma companies in our sample, both Japanese firms, **Eisai** (10 in-licensing) and **Astellas** (8 in-licensing), seem to be among the forerunners in in-licensing in the last few years. Both have in-licensed a variety of compounds, technologies, drugs and patents (Table A.12 in the appendix) between 2004-2007. These in-licensing agreements are

complemented with R&D and commercialisation agreements, which helps them to balance the research and marketing activities; in other words to improve both their innovative and business capabilities. In the case of Astellas, in-licensing allows the company to have access to promising new drugs and R&D capabilities in biologics. Following the strategy, Astellas in-licensed Regeneron's velocimmune® technology for discovering human monoclonal antibodies and Kirin's immunosuppressive fully human anti-CD40 antagonisticmonoclonal antibody in 2007. With Kirin, the company also agreed to collaborate on research and development where the costs will be shared equally. In 2006, Immuno-Biological Laboratories Co. Ltd. granted Astellas the exclusive rights to develop, manufacture, and market anti-human osteopontin antibodies, for therapeutic use. Astellas entered into collaboration with the Chemo-Sero-Therapeutic Research Institute (KAKETSUKEN) in order to prepare clinical studies of its licensed compound on a humanised version of the neutralised antibody.

On the other hand, Eisai's in-licensing activities focus more on the marketing and distribution. For instance, the company in-licensed the rights to commercialise Solstice Neurosciences Inc.'s NeuroBloc (Botulinum toxintype B agent) in Europe in 2007, the exclusive distribution of Ajinomoto's osteoporosis treatment drug Actonel in 2006, and the exclusive US rights to Pfizer's promotean anti-coagulant Fragmin in 2005.

Gilead Sciences, **Lundbeck** and **Shire** give the utmost significance to in-licensing in their externalisation strategies. Shire was very strong in M&As as well (Table 7). The company seems to prefer or is dependent on externalisation strategies that only allow proprietary rights to the company. The approaches of Gilead and Lundbeck are different from each other, too.

As early as 1991 and 1992, **Gilead** licensed the rights to a family of nucleotide analogue compounds and structures from the Institute of Organic Chemistry and Biochemistry at the Academy of Sciences of the Czech Republic (IOCB) (with which the company entered into R&D collaboration in 2006) and the Rega Institute for Medical Research of the Catholic University in Leuven, Belgium. These compounds became the foundation for Gilead's research and development program, and soon led to the development of Gilead's first products for HIV and hepatitis B (HBV). For this reason, when Gilead in-licenses, for instance, small molecule therapeutics against selected hepatitis C virus (HCV) drug targets from Chiron Corporation, it in-licenses with the rights to R&D and commercialisation.

On the other hand, **Lundbeck** in-licenses with the purpose of developing its pipeline by means of already developed compound and its marketing and distribution. Memantine, one of the best selling products of Lundbeck in treatment of Alzheimer's disease, was in-licensed from Merz Co. GmbH in 2000 for the quick launch of the compound through marketing and distribution. In the same way, in 2005, Lundbeck in-licensed marketing rights to PAION's Phase III product Desmoteplase for stroke in Europe, Japan and the rest of the world except the United States (USA) and Canada for which Forest Laboratories holds the marketing and development rights. In 1999, Lundbeck, as part of a research and development agreement with the Canadian biotech company, Neurochem, acquired the global rights to the drug candidate NC 531 - a new and innovative compound for the treatment of Alzheimer's disease.

UCB defines its R&D activities as 70% reliance on its own research and 30% reliance on in-licensing and describes the outcome as one new pharmaceutical product every 3-5 years. In 2006, the company in-licensed worldwide development, collaboration and license rights from Immunomedics Inc for epratuzumab for all auto-immune disease indications (Annual Report 2006, p.53).

The news releases do not reveal enough to understand the extent to which Mid-Pharma companies use in-licensing to enhance and complement their already existing capabilities. The analysis here only gives us an idea as to how much the companies use it to expand their portfolios and move into new areas. More in-depth analysis is needed to determine the extent of capability development through in-licensing.

Out-licensing

On the other hand, we have out-licensing, used a good deal less frequently in our group of companies but whose boundaries reflect the level of capabilities of the pharmaceutical companies. Here, **Gilead** is the leader in Mid-Pharma, with 10 out-licensed compounds and drugs between 1996-2007. It seems to be a supplier of compounds to Big Pharma. Some of its out-licensing customers are Roche, Pharmacia & Upjohn, Japan Tobacco Inc., GlaxoSmithKline and Pfizer. After out-licensing Tamiflu, the only oral antiviral for the treatment and prevention of influenza A and B, which was invented by Gilead and licensed to Roche in 1996, the two companies collaborated on the development of the product, advancing Tamiflu through clinical trials, initiated in 1997, to its first market approval approximately two and a half years later (the FDA approved Tamiflu in October 1999, and it is a registered trademark of F. Hoffmann-La Roche Ltd.).[41] As mentioned earlier (in section 3.1), Gilead is the only company that out-licensed the non-exclusive rights to produce and distribute generic versions of tenofovir DF (brand name Viread) to Indian generic drug producer companies. The license agreements require that the Indian generic companies meet certain national and international regulatory standards and include a technology transfer to enable expeditious production of large volumes of high-quality generic versions of tenofovir DF. In addition, these agreements allow the manufacture of commercial quantities of both active pharmaceutical ingredient (API) and finished product.

Shire follows Gilead with 7 out-licensing agreements in roughly 15 years. Merck KGaA and Novo Nordisk have been engaging in out-licensing since the early 2000s. **Merck KGaA** out-licenses mostly drugs to Big Pharma such as GlaxoSmithKline and Eli Lilly for marketing and distribution, while Novo Nordisk out-licenses mostly compounds (total 6 and 5 respectively). In early 2007, **Novo Nordisk** announced its decision to focus all its research and development resources on the company's growing pipeline of protein-based pharmaceuticals. As a result of this decision, the company said it would out-license existing preclinical and clinical small-molecule projects, including its GKA programme which is currently in clinical testing. One of Novo Nordisk's out-licensing agreements consists of novel, orally administered compounds discovered during a strategic research collaboration initiated in 2001 between TransTech and Novo Nordisk utilising TransTech's proprietary small-molecule discovery engine, TTP Translational Technology®.

Lundbeck had out-licensed many of its drugs between 1996-2004 (Table 8). Its out-licensing relationship with **Forest Laboratories** is a long-term alliance which began with Lundbeck's out-licensing the antidepressant Celexa (citalopram HBr) for marketing in the United States in 1996 and then was extended to include the antidepressant Lexapro (escitalopram oxalate) in1998.[42] Forest, being a Mid-Pharma company that relies mostly on

[41] In June 2005, Gilead delivered a notice of termination to Roche for the companies' 1996 Development and License Agreement for Tamiflu(R) (oseltamivir phosphate) and the companies subsequently entered into arbitration. However, with increasing public concern over the threat of an influenza pandemic, in particular related to the growing incidence of avian influenza, Gilead and Roche have soon reached a settlement in the interest of working together to address public health needs. Under the terms of the amended agreement, Gilead and Roche establish joint committees to oversee manufacturing, commercial and pandemic planning for the product. Gilead also has the option to co-promote Tamiflu in specialized areas in the United States. Gilead has not yet decide whether it will exercise its option for co-promotion in 2007 or beyond.

[42] There seems to be a symbiotic relationship between Lundbeck and Forest Laboratories, which is based on R&D by Lundbeck and marketing and distribution by Forest Laboratories. It is therefore worth investigating this

in-licensing with marketing capabilities, successfully brought both Celexa and Lexapro to market, eventually creating the fastest-growing antidepressant franchise in the United States. This was the first-ever approval of Lundbeck in the USA for a product preparation in 1998. Their co-operation with Forest Laboratories, which became strategic partner for Lundbeck in the USA, continued with the approval of US Food and Drug Administration (FDA) for Cipramil.

Allergan provides another example of an agreement for development of a drug out-licensed together with the licensee where the companies also collaborate on the overall product strategy and management (e.g. in its out-licensing to Japanese companies for the Japanese market Senju Pharmaceuticals[43] and Kyorin Pharmaceutical Co., Ltd.[44] in 2004). The company also out-licensed Botox in Japan and China to GlaxoSmithKline in 2005, which in addition to gratifying sales in Japan in 2006, has brought U.S. co-promotion rights from GSK for Imitrex StatDose System and Amerge, indicated for migraine treatment, and enabled the company to double the size of its neurosciences sales force (Allergan, Annual Report 2006, p.6). In 1999, when the company was not in the ranks of Big Pharma yet (derived out of the figures in Table A.1.3.1), Boehringer Ingelheim granted the rights for the development and commercialization of epinastine[45] for the treatment of ocular allergies to Allergan. Besides the rights to develop and commercialise the compound, Boehringer Ingelheim agreed to provide its expertise in allergy product development as well as a file in late stage Phase II clinical trials. In exchange, Boehringer Ingelheim received milestone payments when the product was approved in both the United States and the EU and royalties on future product sales. Allergan marketed the product worldwide except for Japan.

In short, Mid-Pharma out-licensors most often aim at international market expansion of their drugs. Drug development does not seem to be as important a part of the licensing as in the in-licensing. More analysis is needed to determine whether the domination of in-licensing over out-licensing in Mid-Pharma implies a low degree of interest in the results of the latter's R&D efforts. In conducting such analysis, one would need to additionally consider R&D collaborative agreements, to which we now turn.

R&D collaboration

The pharmaceutical industry in general follows the route of many other industries, which have abandoned the 'go-it-alone' approach and value the importance of collaboration as a competitive advantage.[46] Many pharmaceutical companies have started to explore

relationship to understand issues such as complementary partnering (or complementarities) among mid-pharma companies, the level of capabilities of mid-pharma companies in comparison to Big Pharma (what they lack, e.g. in marketing and distribution in the case of Lundbeck and R&D in the case of Forest Laboratories), and the contribution of a possible disaggregation of the value chain in the pharmaceutical sector in the case of mid-pharma companies. Moreover, it would be interesting to look into opportunities for such disaggregation for Big Pharma, which is largely based on vertical integration model of business.

[43] The drug out-licensed to Senju Pharmaceuticals, a leader within the Japanese ophthalmic pharmaceutical market, is Lumigan (Bimatoprost Ophthalmic solution - 0.03 percent), an eye drop medication for lowering intraocular pressure (IOP) with global sales of $181 million in 2003. It was first launched in the United States in 2001 and marketed in more than 40 countries around the world by 2004.

[44] The drug out-licensed to Kyorin Pharmaceutical, Co., Ltd. is Alphagan/ Alphagan P Franchise (Brimonidine Tartrate solution 0.2 percent and Brimonidine Tartrate Purite solution 0.15 percent), the third largest selling glaucoma franchise in the world as measured by 2003 revenue ($287 million), according to IMS Health Inc.

[45] Boehringer Ingelheim currently commercializes the oral form of epinastine under the brand name Flurinol in South American countries and under the brand name Alesion in Japan, for the treatment of seasonal allergies. The latter is the company's number one prescribed allergy product in Japan and one of its leading prescription products within its ethical product portfolio.

[46] A consultant from Windhover Information suggests 'disaggregated' business model for the pharmaceuticals industry to focus on a few core areas of competence, such as drug discovery, development or marketing (see The Economist, 'Billion dollar pills', Jan 25, 2007. http://www.economist.com/research/articlesBySubject/displaystory.cfm?subjectid=531766&story_id=8585891)

opportunities for growth by other than organic means, in order to improve their finances and pipelines through developing new products and technologies together with external partners. However, despite Big Pharma's well-known in-house R&D reliance, **Boehringer Ingelheim** surprisingly outperforms all the Mid-Pharma companies in its R&D collaborations (Table 10). **Abbott Laboratories** has distinctive forms of R&D collaboration such as the one with Dharmacon in oncology started in 2006 to develop new therapeutic agents based on a gene silencing technology of RNA interference (RNAi). The research aims to extend drug discovery efforts for the two companies to disease targets where traditional discovery technologies have not been successful. Another oncology research collaboration of Abbott Laboratories is with Genentech, established in 2007. The collaboration aims at the global research, development and commercialisation of two investigational anti-cancer compounds discovered by Abbott scientists.

Nevertheless, Mid-Pharma companies are very actively involved in R&D collaborations with pharma, biopharma and biotech companies of various sizes.[47] R&D collaboration with Big Pharma succeeds out-licensing of compounds and therapies developed by mid-Pharma to Big Pharma (as mentioned above), though there are exceptional cases such as Gilead's R&D collaboration with GSK (as discussed below) and Schering-Plough's joint venture with Merck & Co. in developing cholesterol-reducing drug Vytorin, as a combination of Zetia (ezetimibe) of Schering-Plough and Zocor (simvastatin) of Merck & Co., that significantly reduces LDL ("bad") cholesterol (Schering Plough Annual Report 2004, p.5).[48]

On the other hand, there is cooperation across mid-pharma companies. Some examples are:

- Lundbeck's continuous drug development collaboration with Teva Pharmaceutical Industries, dating back to 1999; its cooperation with Solvay Pharmaceuticals B.V. on the development and marketing of an atypical antipsychotic for the treatment of schizophrenia;[49] as well as the development of another compound for treating psychosis and Parkinson's disease (started in 2000 and 2002 respectively);
- Eisai's R&D collaboration with Solvay Pharmaceuticals' subsidiary Solvay Seiyaku K.K. in Japan in co-development and exclusive distribution of a pancreatic exocrine insufficiency treatment SA-001 (started in 2006);
- Allergan's collaboration to develop and commercialise a compound of Boehringer Ingelheim, when the latter was considered to be a mid-pharma company in 1999, and again Allergan's collaboration to develop two novel

[47] A distinction between size of the company collaborated with and the content of the collaboration in the Mid Pharma sector might be an interesting research question. In other words, who benefits from whom; is it Mid-Pharma who learns from Big Pharma or is it Big Pharma who exploits the scientific capabilities of Mid-Pharma?

[48] This is just one side of the relationships between mid- and Big Pharma, where mid-pharma provides Big Pharma with new, innovative compounds and therapies to be developed (e.g. UCB's out-licensing the world-wide rights of the compound fesoterodine for the treatment of overactive bladder, which has been approved by the European authorities and has received an approval letter from the US regulatory authorities, to Pfizer, which plans to launch it in second half of 2008 in Europe and early 2009 in the US (UCB Annual Report 2007, p. 12)). This kind of relationship is not constrained to mid-pharma, but also includes small pharma companies. As mentioned in section on out-licensing, there are rare counterexamples of out-licensing by Big Pharma to mid-pharma companies. The other side of the relationship with Big Pharma consists of the marketing and distribution of a drug that is approved by authorities, yet due to lack of marketing capabilities, does not make its way to the market. Again, although the common form of cooperation in marketing and distribution seems to be with Big Pharma (e.g., Allergan with GSK, Astellas's co-promotion of different drugs with Nippon Boehringer IngelheimCo. Ltd., and Hoffman La Roche Inc. in Japan (Astellas Annual Report 2006, p.18), Shire's marketing partner for Reminyl, Johnson & Johnson (Shire Annual Report 2001, p. 4)), such relationships are not limited to Big Pharma companies. There are mid-pharma companies that are specialised in marketing and distribution of innovations of other companies. Lundbeck's marketing relations with Forest Laboratories, Allergan's co-promotion agreement for ELESTAT with Inspire Pharmaceuticals are very good examples of this phenomenon (Allergan, Annual Report 2003, p.14-15).

[49] Solvay was the originator of the compound and retained the marketing rights in the US, Canada, Mexico and Japan, while Lundbeck gained the marketing rights for Europe and the rest of the world.

> therapeutic treatments for dry eye with Inspire Pharmaceuticals, based on Inspire's INS365 Ophthalmic and Allergan's Restasisä cyclosporine ophthalmic emulsion, 0.05%, both in Phase III clinical development for dry eye in 2001. I

Indeed, R&D collaboration appears to be as widespread as in-licensing. Here are some examples:

Even before the acquisition of Serono, a company with strong R&D history, **Merck KGaA** had an impressive track record of R&D collaboration. The company also used incentive systems such as making milestone payments to ImClone Systems on achieving a clinical-trial milestone for BEC2 Cancer-Vaccine and for early achievement of a clinical milestone in their R&D agreement of development of IMC-C225 in patients with pancreatic cancer, refractory head and neck cancer, and refractory colorectal cancer in their R&D Agreement in 2001. The R&D collaborations of Merck KGaA primarily focus on its therapeutic areas of oncology and immunology, but differentiate the technologies used in the studies. For instance, it collaborated with Archemix in Aptamer-Based Cancer Therapeutics in 2007,with Jerini to develop small molecule cancer drugs in 2004, with Biomira (Canadian biotech company) to develop the L-BLP25 liposomal vaccine for treating NSCLC in 2004, with ProMetic for Monoclonal Antibody Purification in 2001, and with Gedeon Richter to join research forces in developing a treatment for ischaemic stroke in 2000.

Baxter values collaborative R&D as much as the contribution of M&As to in-house R&D. In 2006, the company agreed to co-develop a product for bone regeneration under a long term R&D agreement with Swiss biotech company, Kuros Biosurgery AG. With support from Baxter, Kuros initiated a Phase II clinical trial involving the regeneration of bone using a product that combines the capabilities of TISSEEL (Baxter's fibrin sealant that contains two plasma-based proteins which, when mixed, replicate the start of the tissue-repairing process) with proprietary biologics.

Table 10. R&D collaborations by Mid-Pharma

Number of contract-based R&D undertaken, 1996-2007

	R&D		*R&D and commercialisation*	
Companies	*years*	*total number*	*years*	*total number*
Abbott	2006-2007	6		0
Alcon	2005	3	2006	1
Allergan	2001-2002	2	2001-2005	5
Astellas	2005-2007	3	2005-2007	8
Bausch & Lomb	2005	1	2005-2006	3
Baxter	2001-2007	14	2005-2007	6
Boehringer	1999-2007	28	1997-2003	5
Eisai	2004-2006	7	2003-2007	6
Forest	2004-2005	3	2004-2007	4
Gilead Sciences	1990-2006	7	1997-2007	12
Lundbeck	1999-2007	8	1999-2007	7
Merck KGaA	2000-2007	18	2001-2006	4
Serono	before 2006	10	before 2006	5
Novo Nordisk	2001-2007	7	2001-2006	3
Schering Plough	2002-2007	5	2003-2007	9
Shire	before 1999	1	1996-2007	5
Solvay	1997-2005	10	2001-2006	3
UCB	2005-2006	2	2005-2006	3

** Serono's external sourcing relationships before Merck KGaA's acquisition in 2006. Figures for Merck KGaA represent Serono only after 2006.*

Source: Calculated from the information released in the company websites (news releases) and various annual reports

Solvay Pharmaceuticals performs a little better than Novo Nordisk and Lundbeck. **Solvay Pharmaceuticals**' R&D collaboration with **Abbott Laboratories** has proved to be fruitful. The two companies jointly developed new compounds, in particular the next generation fenofibrate SLV348/ABT335, and moved to Phase III clinical trials. A joint development partnership between Abbott and AstraZeneca for fixed-dose combination was also concluded in 2006, after Solvay out-licensed the fenofibrate to Abbott. Another joint development agreement Solvay is involved in is with Denmark's Novozymes, started in 2004, to develop a new, biotechnologically engineered treatment for pancreatic exocrine insufficiency. In 1997 Solvay and Innogenetics (Ghent, Belgium) entered into a biotech alliance consisting of an agreement in molecular biology focusing on the discovery of novel genes encoding potential drug targets expected to be involved in human disease processes. In 2004, Solvay also made an agreement with Quintiles / Pharmabio Development that effectively doubled the capacity to process Solvay's early clinical projects. Under the agreement, Pharmabio will bear around 50% of the normal costs and the uncertainties of the outcomes for selected phase two projects. In return, Pharmabio will receive a milestone payment from Solvay for each of the compounds reaching positive clinical proof-of-principle and moving into further development.

In addition to the above mentioned R&D partnering across mid-pharma companies, it appears that sometimes Mid-Pharma companies have joined forces to increase their R&D efficiency. In 1999, **Lundbeck** and **Novo Nordisk** made an agreement to establish a joint library of chemical compounds. Moreover, the agreement permits Lundbeck to identify new, innovative drug candidates using Novo Nordisk's high-throughput screening technology. The

collaboration will give both companies access to a larger pool of chemical compounds that can be screened to identify initial leads for further development within various therapeutic areas. However, the agreement is based on the fact that Novo Nordisk and Lundbeck focus on different therapeutic areas.

Lundbeck, in the early 2000s, has collaborated with small biotech companies such as Maxygen ApS to research and develop a protein pharmaceutical product, which could be used for central nervous system diseases, including multiple sclerosis and the biotech company M&E Biotech A/S to develop a phamaccine (therapeutic vaccine) for the treatment of human neurodegenerative disorders (e.g. Alzheimer's disease) by using M&E Biotech's AutoVac™ technology.

Since 2003, **Novo Nordisk** and Innate Pharma SA (French small biotech company) collaborate "to develop medicines targeting one of the body's first lines of defence against cancer and infections: natural killer cells. In contrast to most typical company collaborations focusing on a single disease, technology or therapy, the Innate Pharma/Novo Nordisk partnership is broadly strategic, involving wide-ranging R&D based on NK cell biology. Innate Pharma founders' recent discoveries in the field of NKs hold promising potential for therapeutic applications in cancers, autoimmune disorders and infectious diseases. Having already collaborated on an initial project for three years, the partners have established competitive and complementary competences in this area of immunology, which effectively advanced one project through research and preclinical development. Building on this synergy, the partnership also takes advantage of the individual strengths of the two companies: Innate Pharma's expertise in immune-based therapies targeting innate immune system and Novo Nordisk's experience and technologies for developing and producing protein-based therapies. By now combining forces on a broader scale, the partnership will strive to build a portfolio of new drug candidates in the area, originating from their own research or by further in-licensing from third parties."[50]

With its strong stress on M&As and in-licensing as externalisation strategies, there is no place for R&D collaborations for **Shire**. **Gilead** uses both in- and out-licensing extensively as tools for externalisation, but it also balances their extent with that of R&D collaborations in its strategy. Gilead has historically been a good R&D collaborator for the Big Pharma. In 1990, the company had a collaborative research agreement with GlaxoWellcome for the research and development of genetic code blockers, also known as antisense, to identify and develop new pharmaceutical compounds that prevent the production of disease-causing proteins at the genetic level. The collaboration between the two companies was extended several times and Glaxo Wellcome continued to fund Gilead's research efforts in this field. In 1996, Gilead entered into a worldwide collaboration with Roche to develop and market therapies to treat and prevent viral influenza. Roche funded all research and development costs and pays Gilead undisclosed royalties on the net sales of any products developed under the collaboration. Different from collaboration with other pharmaceuticals companies, in 2006, Gilead and the Institute of Organic Chemistry and Biochemistry at the Academy of Sciences of the Czech Republic (IOCB) established the Gilead Sciences Research Centre. Gilead provides a $1.1 million annual donation to IOCB for an initial five-year term to fund the Centre's operations and ongoing research activities. IOCB has used the donations to establish and support the Gilead Sciences Research Centre, which consists of selected research groups led by the scientists at IOCB. In addition, Gilead and IOCB have established

[50] Innate Pharma and Novo Nordisk announce strategic partnership to research and develop drugs targeting natural killer cells (5 Apr 2006), Novo Nordisk Press Releases, http://www.novonordisk.com/press/sea/sea.asp?sLanguageCode=en-GB&lYear=0&lMonth=0&sNewsTypeGUID=6A4ECEE6-AB16-4A45-902A-09090C29C553&sSearchText=alliance

the Gilead Distinguished Chair in Medicinal Chemistry. Dr. Antonin Holy, IOCB, is going to be the first to hold the position of Distinguished Chair and continue to lead research efforts in nucleoside and nucleotide drug discovery. In 1991 and 1992, Gilead's cooperation with the institute played a crucial role in the successful development of Gilead and dates back to 1991-1992 (see section on in-licensing above).

Eisai focuses on in-house R&D and in-licensing but balances R&D collaboration with other companies. Between 2005-2006, Eisai, with a strict focus on Alzheimer's disease, has been involved in several R&D collaborations. These are joint research on drug discovery with Swedish BioArtic Neuroscience Inc. for immunotherapy for Alzheimer's disease, with DNAVEC Corporation in its home town in Japan for vaccine therapy for Alzheimer's disease, with ToreyPines Therapeutics, Inc. (US) for a new genetic research program for Alzheimer's disease, and joint development of a transdermal patch formulation of Aricept.

In 2005, **Astellas** has participated in an industry-government collaborative research program in Asia, a first of its kind, with the National Institute of Technology and Evaluation and Chugai Pharmaceutical Co. Ltd. to jointly search for, collect and isolate microorganisms in Vietnam and assess their potential for industrial use. Also in 2005, the company engaged in a collaborative R&D agreement to discover and develop new drug candidates derived from natural products chemistry with MerLion Pharmaceuticals. The collaboration was based on the use of the partner's technology on the Astellas pipeline of validated drug candidates for the identification of new chemical seeds. Astellas then conducts the optimisation of such novel compounds and generates drug candidates for future development.

Forest Laboratories, a company that strategically values in-licensing, has developed its R&D collaborations with one particular partner, Gedeon Richter Inc. in 2004 and 2005. Gedeon Richter is a major pharmaceutical company in Hungary and one of the largest in Central and Eastern Europe, with the largest R&D unit in Central and Eastern Europe focusing exclusively on CNS disorders. It has manufacturing sites in Hungary, Russia, Romania, Poland, India and a recently acquired German R&D biotechnology production facility. The product portfolio of the company covers almost all important therapeutic areas. With its widely acknowledged steroid chemistry expertise the company is a significant player in the gynaecological field worldwide. 16 % of the company's revenue results from original drug research and development activity. Following reorganization of the proprietary R&D in 2000, main clinical targets are schizophrenia, anxiety and chronic pain. Complementing its own preclinical excellence R&D collaboration agreements were signed with Mitsubishi Pharma Corporation (Japan) and Forest Laboratories in 2004 and 2005. The company has an original R&D portfolio with 16 ongoing projects including four compounds in either Phase I or Phase II clinical trials. The R&D collaboration of Forest with Gedeon Richter focuses on a group of compounds for the development of a treatment of chronic pain and other CNS conditions, on another group of novel compounds for the treatment of anxiety, depression and other CNS conditions, and on Richter's atypical antipsychotic and related compounds in development for schizophrenia and bipolar mania as well as for other psychiatric conditions, which all key therapeutic areas of Forest.

UCB has started collaborating in R&D rather late in 2005 but with biotech companies such as ImClone to develop an oncology compound for a novel investigational therapy targeting the development of tumor vasculature and then in 2006 with Amgen to develop a novel and promising large molecule (sclerostin (CDP7851)) for osteoporosis (bone loss disorders), combining CB's genomic research with Amgen's expertise in bone biology. A Phase I trial is ongoing with results expected in the third quarter of 2007.
In conclusion, one asks what really differentiates Mid-Pharma companies with respect to their choice of types of externalization strategy. For Forest Laboratories, in-house R&D is expensive and challenging, so it openly prefers in-licensing to foster its pipeline. But what makes Shire value M&As and in-licensing more than R&D collaborations when it is already a

successful research-driven company? Shire explains why it prefers M&As and in-licensing over other types of externalisation strategies in its 2006 Annual Report (p.7). The company is concerned with the issues associated with the loss or expiry of patent protection or market exclusivity, and to play on the low-risk side and be able to benefit of long-term patent protection and market exclusivity of the products and projects it has**.** Then, why are Merck KGaA and Baxter International satisfied with a combination of M&As and R&D collaboration while Schering Plough, Eisai, Gilead, Lundbeck and, to some extent, Novo Nordisk are happy with the combination of in-licensing and R&D collaboration as external sourcing? And finally, with the hope that the answers to all these questions might lie behind the finance question, one asks what determines which kind of relationship is responsible for the largest influx of product revenues to Mid-Pharma? Or is the reason rather related to the company path dependency, routines and innovation culture?

4. Future Trends: Innovation Strategies and Trajectories

4.1 Narrowing down or Expanding

Some Mid-Pharma companies, especially among those already at the low end of the lower Mid-Pharma with respect to sales, determine their long-term strategic goal as focusing on the research, development and commercialisation of therapies in their key therapeutic areas. They pursue focused strategies and divest their non-core businesses. Good examples are **Shire,** which as part of its strategy of focusing on the development and marketing of smaller, specialty products with long-term patent protection in its core therapeutic areas, disposed of its non-core assets, and **UCB**, which divested its Specialty Surfaces, Chemical peptide and OTC businesses, to pursue focused strategies in biopharmaceuticals (Table A.9 in the appendix). **Shire** believes that a carefully selected portfolio of products with an operating model of cross-functional global teams responsible for each of its main therapeutic areas, and a strategically aligned and relatively small-scale sales force, will deliver strong results. Such a structure would be sufficiently flexible to allow the companies to target new therapeutic areas to the extent opportunities permit. For Shire, these opportunities mean acquisitions and in-licensing that are focused on products in niche markets with strong intellectual property protection either in the US or Europe. The company believes this is the best way to minimise the challenges posed by the decline in the industry's overall productivity.[51] Similarly, the acquisition of Serono has led **Merck KGaA** to narrow its focus to pharmaceutical business so that soon after the acquisition of Serono, Merck sold its generics division to Mylan Laboratories, Inc. in October 2007 and exited its Orthopedics JV (see Table A.9 in the appendix).[52] Merck KGaA started narrowing down its focus on clinical areas as early as 2002 in order to follow the route of Big Pharma by launching a single successful global blockbuster, which it achieved one year later with the launch of its innovative medicine (monoclonal antibody) Erbitux as its first product in the oncology therapeutic area, particularly for the treatment of colorectal cancer (Merck KGaA Annual Report 2002, p.23).

On the other hand, some Mid-Pharma companies like **Astellas** aim to become a "mega global pharmaceutical company" (Astellas, Annual Report 2006, p.1). As the Big Pharma turns into an 'enormous Big Pharma' with the wave of M&A it undergoes,[53] this ultra-goal should not perhaps be viewed as idiosyncratic. Whichever route the Mid-Pharma companies choose, the pharmaceuticals industry offers significant growth opportunities as long as they manage to keep their innovation levels high. We also see a transformation in **Gilead Sciences** from a lower mid-pharma cooperating with Big Pharma to an upper mid-pharma

[51] Shire plc. Annual Report 2005 and http://www.shire.com/
[52] http://www.merck-pharmaceuticals.co.uk/
[53] The Economist, 'Billion dollar pills', Jan 25, 2007.
http://www.economist.com/research/articlesBySubject/displaystory.cfm?subjectid=531766&story_id=8585891

that uses small biotech and pharmaceutical companies for its own growth. **Solvay** based its company strategy in 2002 on many activities (such as internal development of the existing product portfolio; acquisitions and/or development of new products; and contribution from newly developed molecules and increased effectiveness of R&D carried out alone or in partnership). It acquired medium-sized companies; expanded and optimised its sales force, alone or in partnership; and expanded geographically; particular in Northern America.[54] With the acquisition of Schwarz Pharma, **UCB** aims to transform into a global biopharmaceutical company with a rich late stage pipeline.

4.2 Innovation Strategies

All of the Mid-Pharma companies researched officially declare that they will continue increasing their R&D expenditures in the coming years as long-term strategy. In general, their primary R&D goals consist of pursuing drug discovery and development in order to create products in new therapeutic areas, strengthen their key therapeutic areas by keeping large volume of projects in their pipeline and moving them through rapidly; and maximising the value of certain products by developing their uses for new indications.

Small molecules vs biologicals

Expanding the drug development portfolio of pharmaceutical companies is one of the key elements of their innovation strategies. This is determined strongly by their choice of technology focus (small molecule vs biologicals). It is well-known that in the last decade, Big Pharma firms have begun to move from small molecules to biologics, and assumed a strong position particularly within the antibody market, and initiated a change in the rest of the industry.[55] "The world of biopharmaceutical production has in the last five years grown immensely due to ever-increasing market demand for monoclonal antibodies (MAbs) and other therapeutic proteins. As many antibody-based therapies are applied in high doses -for example in oncology- there is a need to ensure high production capacity with high yield."[56]

Boehringer Ingelheim aims at meeting this need by continuously improving biopharmaceutical production of therapeutics derived from mammalian cell culture in its R&D site in Biberach, Germany and bacterial fermentation in Vienna, Austria.

The Mid-Pharma companies that have been focusing on small molecules are now moving into biologicals by the externalisation strategies mentioned above. **Schering-Plough** aims at maintaining a diverse discovery and development portfolio to ensure a balanced mix of both small molecules and biologics in its pipeline (esp. in oncology and inflammatory diseases). The company has established Centres of Excellence in each of these areas (see section 3.1 in-house R&D above).

As well as maintaining its leadership in diabetes and haemostasis, **Novo Nordisk** invests in R&D to expand its biopharmaceutical research pipeline to cover the therapeutic areas of inflammation and oncology. The company is interested in innovative biologics projects at all stages of development, from early discovery to clinical phases.

Eisai calls the medium term strategic development for the period 2006-2011 a 'dramatic leap into biologic therapeutics', particularly shaped with its acquisition of Morphotek, Inc., a company specialised in monoclonal antibodies. Eisai also covers translational research

[54] Solvay Pharmaceuticals, Annual Report 2002, p.12
[55] A major attraction of antibodies is the total absence of generic risk. In contrast, bio-similars are an emerging threat for members of the therapeutic protein class.
[56] http://www.boehringer-ingelheim.com/

through contact with academia; a research portfolio including biologics accompanies their small molecule research.

Baxter offers Biologic API contract manufacturing (both clinical & commercial) as well as biopharmaceuticals including monoclonal antibodies and recombinant proteins in various culture media in the form of protein expression (cell banking, protein design, cell line optimization) and process development (molecular biology, purification, characterization, yield improvement). This might well be the underlying reason behind its large number of R&D collaborations.

Roughly half of the entities in the current pipeline of **Merck KGaA** are biological candidates. Serono's acquisition contributes to biological molecule development since biology is at the heart of all Serono does. The key developing substances of Merck's research include the monoclonal antibodies Cetuximab and Matuzumab, as well as a therapeutic cancer vaccine.

UCB has expertise in both large and small molecules (see section 2.4, products on market above). The company aims at creating a radically different generation of novel chemical entities; building 'biological scaffolds' to create more potent, tolerable antibody-based therapies; investigating the multiple value of chemical 'PEGs' for antibody fragments (UCB, Annual Report 2006, p.17). In 2006, the company developed A2HitTM,[57] considered to be a breakthrough combination of biology and chemistry.

4.3 Innovation Trajectories

Therapeutic priorities

The therapeutic priorities of all the Mid-Pharma companies are shaped by the still-unsatisfied medical needs and demand in the market as well as scientific opportunities. The mid-pharma companies are faced with the choice of sticking to niche therapeutic areas or extending into new therapeutic areas. Mid-Pharma companies tend to prioritise among their key therapeutic areas, rather than enter radical new markets. These companies mostly build their specialisation on in-house capabilities, yet they make use of external sourcing. In order to deepen their niche therapeutic areas, some companies out-license the compounds that are outside their niches. However, this does not exclude the mid-pharma companies that seek to extend into new therapeutic areas, particularly through mergers and acquisitions as well as collaborations.

Novo Nordisk has prioritised its biopharmaceuticals operations by expanding its portfolio with *haemostasis management, growth deficiency and hormone replacement therapy*. The company also aims at building a presence in *immunotherapies*. With this purpose, Novo Nordisk not only allocates an increasing share of its revenues to R&D, but also assigns high priority to further rejuvenating the portfolio with new and patent-protected molecular entities that offer additional benefits to people with haemophilia. An example is an improved, next-generation factor VII analogue known as NN1731. The engineered analogue recombinant molecule imitates normal clot formation in the patient more closely than the original rFVIIa molecule (Novo Nordisk Annual Report 2006, p.34).

Some mid-pharma companies divide their in-house R&D and external sourcing efforts selectively between different therapeutic activities. For instance, **Solvay** internalises all the R&D activities of its therapeutic areas, and indeed prioritises, cardiometabolics and neuroscience, while preferring to enter R&D and licensing agreements in the therapeutic

[57] "A2HitTM is using antibodies to guide us to the exact site on a protein where a disease can be inhibited (antibodyto-hit, A2HitTM) so that we can design a new generation of novel chemical entities." (UCB Annual Report 2006, p. 18).

areas of flu vaccines and pancreatic enzymes. The shares of R&D expenditures on cardiometabolics and neuroscience in the company's total R&D expenditures of 2006 are 36% and 32% respectively. When compared to that of flu vaccines and pancreatic enzymes, which are 5% and 8% respectively, it is clear that the former are therapeutic priorities of Solvay (Solvay Annual Report 2006, p.18).

Like Big Pharma, some lower mid-pharma companies have deepened their therapeutic priorities through M&As. For instance, the acquisition of Schwarz Pharma has provided **UCB** with two highly promising late-stage therapies in four important indications in *central nervous system* treatment, supplementing its existing therapeutic areas and taking it into new growth markets, such as *Parkinson's disease*. These include: Neupro, the first once-a-day, non-ergolinic dopamine agonist for Parkinson's, delivered via a novel transdermal patch; rotigotine (the same chemical entity as Neupro patch) for restless legs syndrome; and lacosamide for epilepsy and diabetic neuropathic pain (UCB Annual Report 2006, p. 28).

In November 2006, to support its niche therapeutic area of infectious diseases based on small molecule therapeutics, **Gilead Sciences** acquired Raylo Chemicals Inc. (which generated the raw materials and manufactured the active pharmaceutical ingredients (API) for several antiviral compounds for more than 17 years) and most of its assets from the German specialty chemicals company Degussa AG (Gilead Sciences, Annual Report 2006, p. 5).

Out-licensing becomes the norm for the compounds that fall outside the strategic therapeutic foci of some mid-pharma companies, helping them to deepen their focus on particular niche markets while gaining extra income through licensing fees, milestone payments, and so on. **Allergan** is a case in point. It has entered into discussions to potentially out-license the compounds that are part of its proton pump inhibitor program for the treatment of gastric ulcers.

Shire is an example of expanding into new therapeutic areas by acquisition. For instance, the company added *human genetic therapies* (HGT) to its therapeutic priorities by the acquisition of US biotech company Transkaryotic Therapies Inc. (TKT) in 2005. Within just a year of the acquisition, Shire launched Elaprase, its first HGT product, while significantly increasing sales of a second therapy, Replagal. In HGT, the company has a number of other exciting projects in the pipeline, including enzyme replacement therapies for Gaucher disease (GA-GCB), currently in Phase III of development, and three additional Lysosomal Storage candidates, including Sanfilippo Syndrome and Metachromatic Leukodystrophy (Shire Annual Report 2006, p.5). **Gilead Sciences** has broadened its focus beyond its key therapeutic area with the acquisitions of two specialty biopharmaceutical companies Corus and Myogen in 2006. These acquisitions allowed the company to enter into new therapeutic areas, namely respiratory and cardiopulmonary, in a strong position with late-stage clinical candidates for the treatment of cystic fibrosis-related lung infections. These new items in its pipeline provide near- and long-term revenue potential as well as an approved drug for the treatment of primary pulmonary hypertension (Gilead Sciences, Annual Report 2006, p.5 and 16). **Baxter International,** a mid-pharma company that aims at expanding into new therapeutic areas, collaborates with biotech companies to position its bioscience segment to enter the orthobiologic market.

Among the companies in our sample that stick to a niche therapeutic area, we observe that oncology and neuroscience are the most prioritised areas in the companies whose therapeutic areas include either or both of them. For instance, as a result of the company's special emphasis on Aricept (a drug for a treatment for mild-to-moderate Alzheimer's disease), **Eisai** prioritises neurology as the company's focus area to allocate its R&D resources. Eisai is now emphasizing cancer research as a strong candidate in its research in the Tsukuba Research Laboratories together with the Eisai Research Institute of Boston. For

instance, **Merck KGaA** is one of the mid-pharma companies that are currently able to afford researching in four biological areas of oncology: *monoclonal antibodies*, which inhibit cancer growth; *therapeutic cancer vaccines*, which mobilize the body's own immune defense system against the tumor; *immunocytokines*, which recognize cancer cells and stimulate a local immune response; and *angiogenesis inhibitors*, which starve the tumor by cutting off its nutrient supply. The company works on the development of therapies that specifically target cancer cells without damaging healthy cells by exploiting the potential offered by immunology, biotechnology and molecular biology to help the body in its fight against cancer cells. **UCB**'s research allows some selective indications in oncology, too. Taking advantage of a dual pipeline of large and small molecules, UCB argues that "with small chemical molecules, for example, it is possible to inhibit the signals that instruct cancerous cells to multiply or survive by targeting kinases, while large molecules give us the facility to deliver toxins in a highly targeted way, reducing side effects. Using biological scaffolds, which combine biology and chemistry, they argue that they can also deliver higher payloads of toxins via antibodies, the rationale for CMC544" (UCB Annual Report 2006, p.32). The company has also advanced a novel antibody (CDP791) through Phase II trials for non-small-cell lung cancer. Oncology is also on the priority list of other Mid-Pharma companies that pursue strategies to expand their therapeutic areas, such as Novo Nordisk and Astellas.

Another minor observation in ophthalmology, based on the two mid-pharma companies in our sample, is related to the mid-Pharma companies' strategy to prioritise a niche area within therapeutic area, namely ophthalmology, in order to be distinct and to reap the benefits from the highly specialised market. For instance, **Alcon**'s R&D efforts have focused on the treatment of one of the leading causes of blindness in the developed world – age-related macular degeneration (AMD) – for the last fifteen years, with the aim to develop drugs that address currently untreated or undertreated conditions such as macular degeneration, macular edema, diabetic retinopathy and dry eye. **Allergan**'s R&D efforts, on the other hand, focus on developing drugs for eye treatment using the drug innovations in other therapeutic areas. For instance, the company has just finished the first Phase III clinical trial for memantine, a compound already approved by the FDA for the treatment of Alzheimer's disease, as a prospective treatment for glaucoma.[58]

Current Pipeline

Table 11 below presents the most recent available pipeline information for Mid-Pharma companies. Japanese companies (Astellas and Eisai) and Solvay Pharmaceuticals are distinguished from the rest of the sample of Mid-Pharma companies with respect to their submission for product approval. The companies that have more projects in Phase III generally have quite a number of projects in Phase II, too. These are, in descending order, Schering-Plough (15 and 10 respectively), Merck KGaA (12 and 13), Solvay Pharmaceuticals (12 and 8), Allergan (10 and 7), UCB (7 and 8). Despite high submission rate, Astellas has more (32 preclinical/phase I and JP:9 / US:6 / EU:9 phase II) projects at the early stages of R&D. Merck KGaA and Shire follow Astellas with 13 and 9 Phase I projects respectively. In general they all have rich pipelines with a lot of compounds. However, approval rates differ significantly among the companies. Most of the data regarding approval was calculated by the author using the information released through company news (this is indicated in Table

[58] "While memantine did not show a benefit as assessed by the functional measure chosen as the primary endpoint in the first of our two clinical trials, memantine did show a clinical benefit of the highest dose compared to placebo in the functional measure chosen as a secondary endpoint. With a pioneering program that can potentially transform the current treatment paradigm, it was not surprising that it was the secondary functional measure that showed clinical benefit. If eventually proven effective in glaucoma, memantine would be the first breakthrough treatment to directly address the protection of the optic nerve rather than by alleviating intraocular pressure as a means of slowing the glaucomatous loss of visual function." (Allergan Annual Report 2006, p.7).

10). With quite low level of projects at clinical trials, Alcon has the highest approval rate. Despite its high R&D collaborations, Baxter does not have so impressive clinical trials and yet has 6 approvals in 2006-2007, and on the contrary, Astellas has only one approval in Japan in 2007. Eisai, Solvay and Allergan have 5, 4 and 3 approvals respectively.
We tried to examine the impact of R&D collaboration and in-licensing relations of the mid-pharma companies on their current pipeline through a closer look at these relations. The information regarding these relations of the companies is not exhaustive, so based on the information gathered through on-line press releases and annual reports of the companies studied, we have determined the relationships that include compounds or products at some phase of clinical trial with the prospect of contributing to the current pipeline of the companies studied here. We have focussed on the relationships after 2000.

External sourcing (in the form of in-licensing and especially R&D collaboration with or without commercialisation possibilities) contributes to the development of strong pipelines in mid-pharma companies. Those with high number of in-licensing and R&D collaboration (see Tables 9 and 10) also have high numbers of compounds in different phases of their pipelines (e.g., Schering-Plough, Eisai, Astellas, Solvay, Merck KGaA, Shire and Lundbeck). As mentioned earlier in section 2.4, in just one year (2006), **Novo Nordisk** has increased the number of compounds in its current pipeline from one to four in the areas of oncology and inflammation as a result of increase in its R&D partnerships in these areas that were resulted in two compounds in clinical trials. **Merck KGaA**'s exceptionally high number of compounds in its pipeline is also speculated to be a result of incorporation of Serono (which had a lot of in-licensing and R&D collaboration of its own). However, it is impossible to say if one strategy is more productive than another, since we do not have exhaustive information, and especially since strategies are often combined (e.g., in-licensing is practised simultaneously with co-development, as when a company licenses the right to market and distribute a product from its original developer but also continues to work on developing the drug jointly with the licensor). A few examples follow:

- **Abbot Laboratories** and Genentech *collaborate for the global research, development and commercialization* of two of Abbott's investigational anti-cancer compounds in 2007. The companies will work together on all aspects of further development and commercialization of ABT-263 and ABT-869, which were discovered by Abbott scientists. Both compounds are currently in Phase I clinical trials in a number of tumor types. Phase II clinical trials for ABT-869 in several tumor types are going to begin in 2007.
- **Alcon** collaborates with Amgen since 2006 in a *joint research, development, and commercialisation* of therapeutics for the treatment of eye diseases, with multiple biological targets and disease areas within the field of ophthalmology. Amgen is responsible for providing existing and future molecules that have been or are identified to have potential effects on eye disease, while Alcon leads clinical development and commercialization activities for molecules jointly selected by the companies.
- In 2006, **Astellas** signed a definitive agreement for the *exclusive rights to develop and market* FG-2216 for the treatment of anemia in Japan in June 2005 and is now conducting Phase I clinical trials targeting renal anemia associated with chronic renal insufficiency at the pre-dialysis and dialysis stage.
- **Boehringer Ingelheim** has *in-licensed* Medivir's innovative HIV antiviral MIV-310. Currently, it is in phase II clinical development.
- 2005 **Forest** and Gedeon Richter entered a *collaboration agreement* on a group of compounds that target the NMDA 2B receptor and will be developed for the treatment of chronic pain and other CNS conditions. RGH-896 is the first of this group and is currently in early clinical development. Forest and Richter has initiated a Phase IIb study in neuropathic pain in the United Stated in the second half of 2006. In January 2004, Cypress entered into a collaboration agreement with Forest Laboratories for

the development and marketing of milnacipran. In 2007, Forest Laboratories, Inc. and Cypress Bioscience, Inc. announced positive results of Phase III study for Milnacipran as a treatment for Fibromyalgia Syndrome 2004.

- In 2007 **Gilead** and LG Life Sciences entered an *exclusive license agreement* focused on the development of caspase inhibitors for the treatment of fibrotic diseases. The agreement grants Gilead *commercialization* rights to LGLS' caspase inhibitors, including LB84451, LGLS' lead compound. LB84451 is an investigational pan-caspase inhibitor currently being evaluated in a Phase IIa clinical trial in patients chronically infected with the hepatitis C virus.
- In 2005 **H. Lundbeck A/S** and PAION Deutschland GmbH announced an *exclusive partnership agreement* for the *development and marketing* of PAION's Phase III product Desmoteplase for stroke in Europe, Japan and the rest of the world except the United States (USA) and Canada. Forest Laboratories holds the marketing and development rights in the USA and Canada. In 2007 Lundbeck and Takeda formed a *strategic alliance* for the *exclusive co-development and co-commercialization* of a portfolio of novel compounds (LU AA21004 and LU AA24530) in the US and Japan for the treatment of mood and anxiety disorders.

In several cases, company acquisitions serve the purpose of strengthening pipelines in existing therapeutic areas while extending the pipeline by entering into new therapeutic areas. Supporting examples are:

- **Allergan**'s acquisition of Oculex Pharmaceuticals in 2003 and the acquisition of Posurdex, a bioerodable, which showed significant improvement in signs and symptoms of macular edema (swelling of the retina) compared with patients who did not receive the treatment during Phase II studies;
- **Gilead**'s acquisition of Myogen in 2006 and filing a New Drug Application (NDA) based on the two completed pivotal Phase III studies (ARIES 1&2) that evaluated the safety and efficacy of the product as a potential treatment for PAH;
- **UCB**'s acquisition of Schwarz Pharma in 2007, bringing in two highly promising late-stage neurological therapies in four important indications and thereby supplementing UCB's existing therapeutic areas and late-stage pipeline as well as taking the company into new growth markets, such as Parkinson's disease, and
- **Schering-Plough**'s acquisition of Organon Biosciences in 2007 by adding five compounds in Phase III development to its late-stage pipeline.

5. Conclusion

In this report, we have been concerned with companies that possess full in-house drug discovery and development capabilities – these are not producers of generics. Based on revenues we can divide this group into upper mid-pharma and lower mid-pharma, but over the last five years, in general most of Mid-Pharma companies have enjoyed sustainable growth (although it is clear that the upper mid-pharma grows more dynamically than lower mid-pharma companies). Moreover, all these companies are increasing both their R&D spending and their R&D intensity (indeed, for the years for which we have data on the industry as a whole, 2002-2004, R&D intensity in our group of companies was mostly stable, whereas the industry trend was declining, as discussed in section 2.4). There appear to be grounds for speculating that the research intensity might be determined to a great extent by the firm's size and the number of therapeutic foci, but more research is needed. In general, the primary R&D goals of these companies consist of pursuing drug discovery and development in order to create products in new therapeutic areas, strengthening their key therapeutic areas by keeping a large volume of projects in their pipeline and moving them through it rapidly; and maximising the value of certain products by developing their uses for other indications than the ones they were developed for. In this sense, they are not much different from Big Pharma.

Mid-Pharma companies seem to have significant reliance on individual products - a property that makes them 'mid', instead of 'big' pharma companies. A large portion of their total product sales depends on these individual products, which makes them vulnerable to the threat of generics and the like.

The pharmaceutical industry in general is forced to follow the route of many other industries, which have abandoned the 'go-it-alone' approach and value the importance of collaboration and external knowledge sourcing as a competitive advantage. There is no single mid-pharma company among those studied here that does not give importance to developing partnerships with other pharmaceutical companies, academic institutions and research laboratories.

Mid-Pharma companies do not seem to undertake M&As as intensively as Big Pharma does. One group of companies in our sample uses mergers and acquisitions strategically to complement their organic growth; the other 'latecomers' started M&As in 2002 or later, and with some reservations. As in the case of Big Pharma; mergers and acquisitions seem to be one of the main vehicles for Mid-Pharma companies to grow strategically, to extend their key therapeutic areas, and improve their pipeline. However, they are also the targets of M&As, such as Organon being acquired by Schering-Plough, Serono being acquired by Merck KGaA, Schwarz Pharma acquired by UCB, Altana acquired by Nycomed Pharma, and Sankyo and Daiichi merging to form Daiichi Sankyo, and Fujisawa and Yamanouchi merging to form Astellas. Joint ventures are not common between Mid-Pharma companies; however, Mid-Pharma companies do often enter joint ventures with Big Pharma companies.

Licensing has been thought to be the norm in the pharmaceutical industry. However, a different kind of external sourcing than licensing has been detected during the research on mid-pharma sector, namely product acquisition, which has been the norm for smaller companies. Pharmaceutical companies acquire the patent of a product and sometimes continue to collaborate with the ex-owner to develop it further. In-licensing is another commonly used tool of pharmaceutical companies to complement their internal R&D efforts for new drug discovery and development, as well as to build strength in their global operations through not only internal research but also external licensing opportunities. The companies openly declare that they actively pursue new compounds, new therapies and technologies through in-licensing. While the approach of Big Pharma to in-licensing is more on the R&D and drug development side, Mid-Pharma companies are also interested in in-

licensing for enhancing their marketing and distribution around the world. Out-licensing, which is used a good deal less frequently in our group of companies than in-licensing, is the flip side of the coin. It reflects the level of in-house capabilities of companies rather than a quest for acquiring knowledge from external sources. This also implies that mid-pharma companies are big enough to go all the way to market with a new product, which is not the case for a small company.

Mid-Pharma companies are actively involved in R&D collaborations with pharma, biopharma and biotech companies of various sizes, and indeed such collaboration appears to be as widespread as in-licensing. However, a number of questions about what really differentiates Mid-Pharma companies with respect to their choice of types of externalization strategy remain to be answered by further research. For example, what makes a successful research-driven company value M&As and in-licensing more than R&D collaborations? And why are some firms satisfied with a combination of M&As and R&D collaboration while others prefer the combination of in-licensing and R&D collaboration as external sourcing? And finally, what determines which kind of relationship is responsible for the largest influx of product revenues to Mid-Pharma? Is the reason related to the company path dependency, routines and innovation culture?

Some Mid-Pharma companies, especially among those already at the low end of the lower Mid-Pharma with respect to sales, determine their long-term strategic goal as focusing on the research, development and commercialisation of therapies in their key therapeutic areas. They pursue focused strategies and divest their non-core businesses (e.g., UCB, Shire, Merck KGaA). More than radical shifts into new therapeutic areas, Mid-Pharma companies primarily prioritise among their key therapeutic areas (e.g. Novo Nordisk, Solvay, UCB, Allergan, Gilead Sciences, Alcon). Other Mid-Pharma companies are pursuing the goal of joining the ranks of Big Pharma; particularly the Japanese mid-pharma company Astellas.

With respect to the direction of research, we observe in this group of companies a trend seen in the industry in general; namely that companies that have been focusing on small molecules are now moving into biologicals by the externalisation strategies mentioned above. With regard to current pipeline information, the Mid-Pharma companies in our sample seem relatively healthy as they tend to have a high volume of compounds in late stage clinical trials.

Table 11. The most recent pipeline data of the Mid-Pharma

Number of products in clinical trial phases							
Company	Preclinical	Phase I	Phase II	Phase III	Submission (filed for approval)	Approved by FDA 2006 - 2007	Source and notes
Boehringer Ingelheim	na	na	na	na	na	na	
Abbott Laboratories	na	na	na	na	na	na	
Schering-Plough	0	0	10	15	4	1*	Downloaded from the Company website, Product Pipeline, October 2007 http://www.schering-plough.com/pdf/Pipeline_October_2007.pdf * calculated from information gathered from press releases.
Baxter Intl	0	4	4	1	0	6	Downloaded from the Company website, Product Pipeline, 2007
Astellas	32		J:9 U:6 E:9	J:4 U:4 E:1	J:10 U:6 E:2	J:1 (Aug 07)	Downloaded from the Company website, R&D Pipeline, as of November, 2007 http://www.astellas.com/global/ir/library/pdf/2q_rd2008_eg.pdf (J: Japan; U:US; E: Europe)
Novo Nordisk	0	5	7	6	3	1*	Downloaded from the Company website, Product Pipeline, 2007 http://www.novonordisk.com/science/pipeline/rd_pipeline.asp * calculated from information gathered from press releases.
Eisai Co.	0	J: 0 U: 5	J: 9 U:8	J: 8 U:1	J:11 U:2	3 (main areas) + 2 (other)	Downloaded from the Company website, Product Pipeline, as of October 30, 2007 http://www.eisai.co.jp/pdf/eir/epipeline.pdf (The pipeline of the US subsidiary Eisai Co. Ltd.'s information is in paranthesis http://www.eisai.com/pipeline.asp?ID=173) (J: Japan; U:US)
Merck KGaA	0	13	13	12	3	2*	Downloaded from the Company website, as of November, 2007 http://www.merckserono.net/en/images/pipeline_tcm226-10144.jpg * calculated from information gathered from press releases and products approaved by EMEA
Alcon Inc.	0	0	3	4	1	19 (2006)	Calculated from the pipeline table in the Company Website, as of May 07, 2007
Solvay Pharmaceuticals	15	5	8	12	9 (filed/approved)	4*	Calculated from the pipeline table in the Company Website, 2007. * calculated from information gathered from press releases.
Forest Laboratories	na	4*		6**	na	na	* Information from news releases about the company's R&D collaboration **Calculated from the information released in the company website regarding the product pipeline, 2007.
UCB Biopharma	0	INF:1	CNS:5; INF:2; ONC:1	CNS:5; INF:1; ONC:1	CNS:8; INF:2; OTH:1	2*	Downloaded from the Company Website, 2008 (CNS: Central Nervous System; INF: Inflammation; ONC: Oncology; OTH: Other) * calculated from information gathered from press releases.
Allergan	0	0	7	10	5	3*	Calculated from Annual Report 2006, p.12 * calculated from information gathered from press releases.
Gilead Sciences	4	4	2	1	2	2*	Calculated from the Company website, 2007 http://www.gilead.com/research * calculated from information gathered from press releases.
Bausch & Lomb	na	na	na	na	na	na	
Lundbeck	0	5	3	3	1	0	Downloaded from the Company Website, 2007
Shire	SP: 6 HGT: 3	SP:1 HGT: 1	SP: 2 HGT: 2	HGT:1	SP: 2	1	Downloaded from the Company Website, 2007, http:www.shire.com/shire/RandD/projects.jsp (SP:Specialty Pharma HGT: Human Gene Therapies)

Source: Downloaded or calculated from the information revealed in the company websites and/or annual reports.

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Appendix to Mid-Pharma Report

Table A.1.1 List of Top 50 Pharmaceuticals and Biotech Companies

Revenue Rank 2006	Company	Country	Healthcare Revenue 2006 (USD millions)	Healthcare R&D 2006 (USD millions)	Net income/ (loss) 2006 (USD millions)	Employees 2006
1	Johnson & Johnson	USA	53,324	7,125	11,053	138,000
2	Pfizer	USA	48,371	7,599	19,337	122,200
3	GlaxoSmithKline	United Kingdom	42,813	6,373	10,135	106,000
4	Novartis	Switzerland	37,020	5,349	7,202	102,695
5	Sanofi-Aventis	France	35,645	5,565	5,033	100,735
6	Hoffmann–La Roche	Switzerland	33,547	5,258	7,318	100,289
7	AstraZeneca	United Kingdom	26,475	3,902	6,063	98,000
8	Merck & Co.	USA	22,636	4,783	4,434	74,372

9	**Abbott Laboratories**	**USA**	**22,476**	**2,255**	**1,717**	**66,800**
10	Wyeth	USA	20,351	3,109	4,197	66,663
11	Bayer	Germany	18,216	1,791	1,577	61,880
12	Bristol-Myers Squibb	USA	17,914	3,067	1,585	60,000
13	Eli Lilly and Co.	USA	15,691	3,129	2,663	50,060
14	Amgen	USA	14,268	3,366	2,950	48,000
15	**Boehringer Ingelheim**	**Germany**	**13,284**	**1,977**	**2,163**	**43,000**
16	**Schering-Plough**	**USA**	**10,594**	**2,188**	**1,057**	**41,500**
17	**Baxter International**	**USA**	**10,378**	**614**	**1,397**	**38,428**
18	Takeda Pharmaceutical Co.	Japan	10,284	1,620	2,870	35,000
19	Genentech	USA	9,284	1,773	2,113	33,500
20	Procter & Gamble	USA	8,964	n/a	10,340	29,258

21	Teva Pharmaceutical Industries	Israel	8,408	495	546	26,670
22	**Astellas Pharma**	**Japan**	**7,850**	**1,435**	**1,122**	**23,613**
23	Daiichi Sankyo	Japan	7,158	1,459	671	20,100
24	**Novo Nordisk**	**Denmark**	**6,520**	**1,063**	**1,086**	**15,358**
25	**Eisai**	**Japan**	**5,583**	**926**	**604**	**14,993**
26	**Merck KGaA**	**Germany**	**5,175**	**772**	**1,258**	**13,900**
27	**Alcon**	**Switzerland**	**4,897**	**512**	**1,348**	**13,500**
28	Akzo Nobel	Netherlands	4,694	741	1,449	13,000
29	**UCB**	**Belgium**	**4,426**	**1,024**	**492**	**12,741**
30	Nycomed	Switzerland	4,264	n/a	-105	10,533
31	**Forest Laboratories**	**USA**	**3,442**	**941**	**454**	**9,649**
32	**Solvay**	**Belgium**	**3,268**	**533**	**1,026**	**9,000**
33	Genzyme	USA	3,187	650	-17	8,477

34	**Allergan**	**USA**	**3,063**	**1,056**	**-127**	**8,423**
35	**Gilead Sciences**	**USA**	**3,026**	**384**	**-1,190**	**6,772**
36	CSL	Australia	2,788	161	454	6,400
37	Chugai Pharmaceutical Co.	Japan	2,787	467	328	5,962
38	Biogen Idec	USA	2,683	718	218	5,907
39	**Bausch & Lomb**	**USA**	**2,292**	**197**	**15**	**5,830**
40	Taisho Pharmaceutical Co.	Japan	2,069	244	132	5,756
41	King Pharmaceuticals	USA	1,989	254	289	5,191
42	Watson Pharmaceuticals	USA	1,979	131	-445	5,126
43	Mitsubishi Pharma	Japan	1,945	403	208	5,111
44	**Shire**	**United Kingdom**	**1,797**	**387**	**278**	**4,958**

45	Cephalon	USA	1,764	403	145	4,913
46	Dainippon Sumitomo Pharma	Japan	1,763	350	193	3,750
47	Kyowa Hakko Kogyo	Japan	1,698	268	108	2,895
48	Shionogi & Co.	Japan	1,640	320	159	2,868
49	Mylan Laboratories	USA	1,612	104	217	2,800
50	**H. Lundbeck**	**Denmark**	**1,552**	**329**	**186**	**2,515**

Original Source: *Top 50 pharmaceutical companies*, MedAdNews, September 2007
Note in the original document: Some companies (eg, Bayer and Procter & Gamble) have additional revenue not included here.
Note of the author: The bold highlighted companies in the list are examined in this report.
Source: Retrieved from http://en.wikipedia.org/wiki/List_of_pharmaceutical_companies

Table A.1.2 General information about pharmaceutical companies, categorised by size

Big Pharma companies

- Abbott Laboratories, a top-20 pharma company based in the United States
- Amgen, a top-20 pharma company based in the United States
- AstraZeneca, a top-20 pharma company based in the United Kingdom formed in 1999 through the merger of Astra AB and Zeneca Group PLC
- Bayer, a top-20 pharma company based in Germany
- Boehringer-Ingelheim, a top-20 pharma company based in Germany
- Bristol-Myers Squibb, a top-20 pharma company based in the United States
- Eli Lilly and Company, a top-20 pharma company based in the United States
- GlaxoSmithKline, also known as GSK, Britain's biggest pharmaceutical company
- Hoffmann-La Roche, or Roche, a top-20 pharma company based in Switzerland

- Johnson & Johnson, a top-20 pharma company based in the United States
- Merck & Co., a top 10 pharmaceutical company, based in USA
- Novartis
- Pfizer
- Procter & Gamble
- Roche
- Sanofi-Aventis, a global top-20 pharmaceutical company based in France
- Schering-Plough, an American company created during World War II through seizure of assets from Schering
- Takeda, a top-20 pharma company based in Japan
- Wyeth, formerly American Home Products, a top-20 pharma company based in the United States

Mid-Pharma companies

- Alcon, a Swiss pharmaceutical company specialising in ophthalmology
- Allergan, an American multinational
- Almirall Prodesfarma, a Spanish multinational
- Astellas Pharma, a Japanese company formed in 2005 through the merger of Fujisawa Pharmaceutical and Yamanouchi Pharmaceutical
- Biovail, the largest Canadian pharmaceutical company
- Gilead Sciences, an American biopharmaceutical company
- King Pharmaceuticals, an American company
- Lundbeck, a Danish company
- Merck KGaA, a top 30 pharmaceutical company, based in Germany
- Millennium Pharmaceuticals
- Novo Nordisk Global leader in Diabetes care. Currently has the highest global market share of insulin & insulin delivery devices. Also caters for Growth Hormone and Hemophilia care.
- Organon International (Organon) products, the healthcare division of Akzo Nobel
- Pierre Fabre Group
- Schering, a German company that merged in 2006 with Bayer to form Bayer Schering Pharma
- Shire Pharmaceuticals Group, a British company
- Solvay Group
- Servier Laboratories
- Teva Pharmaceutical Industries, a global (top-20) manufacturer of mainly generic pharmaceuticals, based in Israel.
- UCB, a Belgian biopharmaceutical company

Small-sized pharma companies (most of them are assumed to be generic producers)

- 3M, now called iNova is a diversified global technology company based in the United States which produces pharmaceuticals as part of its health care business

- Acambis, a vaccine development company with offices in Cambridge, US and Cambridge UK
- Active Biotech, a Swedish pharmaceutical company specialising in immunology
- Alkermes, an American company
- Alliance Pharmaceuticals, an emerging British pharmaceutical company
- Amico Laboratories, a pharma company based in Bangladesh
- Antara Biosciences, a biotechnology company based in the United States
- Ardana Bioscience, a Scottish pharmaceutical company specialising in reproductive health
- Axcan Pharma, a specialty pharma company based in Quebec, Canada
- Bargn Farmaceutici Phils. Co., a pharmaceutical / cosmeceutical company based in the philippines maker of COSMO Skin
- Beximco Pharmaceuticals Ltd, pharma company based in Bangladesh
- Bial, a Portuguese pharmaceutical company
- Biolex, an American company
- BioPort, an American vaccine manufacturer and a subsidiary of Emergent BioSolutions
- BioSciMed, a Korean company*
- Biotecnol, a Portuguese company*
- Biovail, the largest Canadian pharmaceutical company
- Biovitrum, a Swedish company
- Bio-X Healthcare, a Belgian pharmaceutical company specialising in oral healthcare
- Bosch Pharmaceuticals Pvt Ltd. (external link), , Pakistan's leading pharmaceutical company specializing in Cephalosporins, Penicillins, Quinolones and Biotech products
- Catalytica, a former American company which merged with Synotex Company in 2000 to form DSM Catalytica Pharmaceuticals, now known as DSM Pharmaceuticals
- Christian Bioscientific, an American company health that is focused on health and medically relevant. A Limited Liability Corporation ready to make strides in any sector of the biotechnology industry including interests in nanotechnology, occupational/environmental health, and industrial hygiene
- Cipla, an Indian company best known as a manufacturer of anti-AIDS drugs
- Crucell, a Dutch biotechnology company specialising in vaccines
- Dow Pharmaceutical Sciences (external link), an American company focused on topical therapeutics
- DSM Pharmaceuticals
- Emcure Pharma, A pharma company based in the India
- Ethypharm (external link) a French company specialized in the development of drug delivery solutions for the pharmaceutical industry
- Ferozsons Laboratories, A Pakistani based company which is exclusively focused on Gastroenterology.
- Galderma, A French based company which is exclusively focused on Dermatology

- Galen Limited, a Northern Irish pharmaceutical company
- Getz Pharma, a Pakistani company, the th largest Pharmaceutival company in Pakistan
- Grindex external link, the largest pharmaceutical company in the Baltic States.
- Hexal Australia, an Australian generic pharmaceutical manufacturer, part of the Hexal International Group
- Hexal International Group (external link), a German generic pharmaceutical manufacturer
- Hospira, a specialty pharmaceutical and medication delivery company
- Institute for OneWorld Health, a nonprofit American pharmaceutical company focused on developing infectious disease drugs for developing countries
- Intercytex, a British healthcare company using its proprietary cell therapy technology to develop innovative regenerative medicine products to restore skin and hair
- Isis Pharmaceuticals (external link), an American company focused on development of RNA-based therapeutics
- Jelfa SA (external link), a Polish generic pharmaceutical manufacturer
- Krka, d. d., a Slovenian generic pharmaceutical and cosmetics manufacturer
- Kurve Technology, Inc. (external link) an American company specialized in the development of drug delivery solutions for the pharmaceutical industry
- LEO Pharma, a Danish pharmaceutical company
- Mansfield-King
- Mayne Pharma, an Australian pharmaceutical company acquired by Hospira in 2007
- Menarini (external link)
- Medopharm, an Indian pharmaceutical company
- Merix Pharmaceutical Corp. (Merix Health Care Products) Based in USA
- MGI Pharma
- Millennium Pharmaceuticals
- Napp Pharmaceuticals (external link)
- Nucleics DNA sequencing reagents, services & software
- Ordain Health Care[2]
- Ortho-McNeil Pharmaceutical
- Otsuka Pharmaceutical Co. (external link), based in Japan
- Ovation Pharma
- Pharmacosmos, a pharmaceutical company based in Denmark
- Pharma Focus Asia Pharma Industry
- Pharmed Medicare, Among top five fastst growing companiesPharmedPharmed
- Pliva
- Purdue Pharma, private company, maker of Oxcycontin
- Global Pharmaceutical Company
- Ranbaxy
- Sara Pharmaceuticals A growing pharmaceutical company from India

- Searle Pharmaceutical, A leading Pharmaceutical of Pakistan
- Sepracor, a growing pharmaceutical company whose products include Lunesta and Xopenex
- Stiefel Laboratories One of the world leaders in dermatology.
- Sun Pharmaceutical Industries
- ThePharmaNetwork, (external link) TPN capitalizes on its knowledge, flexibility, speed and ability to execute strategic plans that offer concrete and innovative solutions to companies throughout the global pharmaceutical supply chain.
- Valeant, formerly ICN Pharmaceuticals, an American company
- Vertex Pharmaceuticals, an American company
- Viasys Healthcare, formerly Huntleigh Healthcare and subsequently sold to Cardinal Health in 2007
- Vion Pharmaceuticals, Inc., an American company
- ViroPharma, an American company
- Wesly Pharmaceuticals a Chennai based Indian company with a global vision.
- Zeltia, a Spanish holding company which includes Pharma Mar, Genomica, Zelnova, XYLazel, Promax and NeuroPharma.
- Zentiva, a Czech company

Companies that are merged and/or acquired by BigPharma companies

- Alphapharm, an Australian generic pharmaceutical manufacturer and a wholly owned subsidiary of Merck KGaA
- ALZA Corporation, an American company acquired by Johnson & Johnson in 2001
- Astra AB, a former Swedish company which in 1999 merged with Zeneca Group PLC to form AstraZeneca
- Aventis, a former French company which in 2004 merged with Sanofi-Synthélabo to form Sanofi-Aventis
- Janssen Pharmaceutica Products, a subsidiary of Johnson & Johnson
- Janssen-Cilag, a subsidiary of Johnson & Johnson
- Knoll Pharmaceuticals, formerly the pharmaceutical division of BASF, acquired by Abbott in 2001
- Pharmacia, now part of Pfizer
- Sugen, purchased by Pfizer in 2003
- TAP Pharmaceutical Products, Inc, a joint-venture of Abbott and Takeda, created without discovery or manufacturing capabilities

Companies that are merged and/or acquired by Mid-Pharma companies

- Altana Pharma AG, formerly part of Altana AG. Since January 1st, 2007, Altana Pharma is part of the Nycomed Group
- Catalytica, a former American company which merged with Synotex Company in 2000 to form DSM Catalytica Pharmaceuticals, now known as DSM Pharmaceuticals

- Celltech, a former British company acquired by the Belgian company UCB in 2004
- Daiichi Pharmaceuticals, a former Japanese company which merged with Sankyo Co., Ltd. in 2005 to form Daiichi Sankyo
- Daiichi Sankyo, a Japanese holding company established in 2005 for the management integration of Sankyo and Daiichi Pharmaceuticals
- Diosynth, a Dutch company, merged in 2005 with sister company Organon, both were part of the Dutch Akzo Nobel. In 2007, Akzo Nobel announced the intended sale of Organon to Schering-Plough
- Serono, a Swiss biopharmaceutical company now part of Merck KGaA

Source: Retrieved from http://en.wikipedia.org/wiki/List_of_pharmaceutical_companies

Table. A.1.3.1 Rankings of Pharmaceutical Executive Top 50 companies according to their human prescription drug sales only, (billion $) 2001-2006 (highlights show changes in the rankings of the companies studied here, double underline shows the companies with sales below $10 billion)

2001		2002		2003		2004		2005		2006	
1 Pfizer	25.5	1 Pfizer	28.28	1. Pfizer	39.6	1 Pfizer	46.13	1 Pfizer	44.28	1 Pfizer	45.08
2 GlaxoSmithKline	24.8	2 GlaxoSmithKline	28.2	2. GlaxoSmithKline	29.8	2 GlaxoSmithKline	31.37	2 GlaxoSmithKline	33.96	2 GlaxoSmithKline	39.2
3 Merck	21.35	3 Merck	21.6	3. Merck	22.5	3 Sanofi-Aventis	30.9	3 Sanofi-Aventis	32.34	3 Sanofi-Aventis	37.43
4 AstraZenca	16.48	4 AstraZeneca	17.8	4. Johnson & Johnson	19.5	4 Johnson & Johnson	22.13	4 Novartis	24.96	4 Novartis	29.5
5 Bristol-Myers Squibb	15.6	5 Aventis	17.3	5. Aventis	19	5 Merck	21.5	5 AstraZeneca	23.95	5 AstraZeneca	26.48
6 Aventis	15.35	6 Johnson & Johnson	17.2	6. AstraZeneca	18.9	6 AstraZeneca	21.43	6 Johnson & Johnson	22.32	6 Johnson & Johnson	23.27
7 Johnson & Johnson	14.9	7 Novartis	15.36	7. Novartis	16	7 Novartis	18.5	7 Merck	22.01	7 Merck	22.64
8 Novartis	14.5	8 Bristol-Myers Squibb	14.7	8. Bristol-Myers Squibb	15	8 Bristol-Myers Squibb	15.5	8 Wyeth	15.32	8 Roche	16.86
9 Pharmacia	11.97	9 Pharmacia	12.03	9. Wyeth	12.6	9 Wyeth	13.96	9 Bristol-Myers Squibb	15.25	9 Lilly	15.69
10 Lilly	11.54	10 Wyeth	11.7	10. Eli Lilly	12.6	**10 Abbott Labs**	**13.76**	10 Eli Lilly	14.65	10 Wyeth	15.68
11 Wyeth	11.71	11 Eli Lilly	11.07	**11. Abbott Labs**	**12.3**	11 Eli Lilly	13.06	**11. Abbott Labs**	13.99	11 Bristol-Myers Squibb	13.86
12 Roche	8.53	12 Roche	10.81	12. Roche	12.2	12 Roche	17.3	12 Roche	12.9	12 Amgen	13.86
13 Schering-Plough	**8.36**	**13 Abbott Labs**	**9.27**	13. Sanofi-Synthélabo	9.1	13 Amgen	10.6	13 Amgen	12.02	**13 Abbott**	**12.4**
14 Abbott Laboratories	**8.17**	**14 Schering-Plough**	**8.7**	**14. Boehringer Ingelheim**	**8**	**14 Boehringer-Ingelheim**	**8.7**	**14 Boehringer-Ingelheim**	**10.84**	**14 Boehringer-Ingelheim**	**10.96**
15 Takeda	7.77	15 Sanofi-Synthelabo	8.01	15. Amgen	7.9	15 Takeda	8.3	15 Takeda	8.53	15 Bayer	9.87
16 Sanofi-Synthelabo	5.7	**16 Boehringer Ingelheim**	**7.92**	16. Takeda	7.4	**16 Schering Plough**	**6.4**	**16 Astellas Pharma**	**8.04**	16 Takeda	8.68
17 Boehringer Ingelheim	**5.6**	17 Takeda	7.15	**17. Schering-Plough**	**6.7**	17 Schering AG	6.09	**17 Schering Plough**	7.56	**17 Schering-Plough**	**8.56**
18 Bayer	5.04	18 Schering AG	5.4	18. Schering AG	5.5	18 Bayer	5.44	18 Bayer	7.56	18 Teva	7.82
19 Schering AG	3.9	19 Bayer	5.12	19. Bayer	5.4	**19 Eisai**	**5**	19 Schering AG	6.29	19 Genentech	7.64
20 Akzo Nobel	3.55	20 Amgen	4.99	20. Sankyo	3.81	20 Teva	4.3	20 Genentech	5.49	20 Schering AG	7.48
21 Amgen	3.5	21 Sankyo	3.57	**21. Eisai**	**3.79**	**21 Merck KGaA**	**3.85**	**21 Novo Nordisk**	**5.36**	**21 Astellas Pharma**	**7.09**
22 Sankyo	3.3	22 Akzo Nobel	3.4	22. Yamanouchi	3.53	22 Genentech	3.75	**22. Eisai**	**4.77**	**22 Novo Nordisk**	**6.85**
23 Merck KGaA	**2.89**	**23 Eisai**	**3.39**	**23. Novo Nordisk**	**3.44**	23 Yamanouchi	3.73	23. Teva	2.7	**23 Merck KGaA**	**4.91**
24 Novo Nordisk	**2.8**	24 Yamanouchi	3.2	**24. Merck KGaA**	**3.37**	24 Otsuka	3.72	**24 Merck KGaA**	**4.61**	**24 Eisai**	**4.85**
25 Shionogi	2.8	**25 Merck KGaA**	**3.19**	25. Teva	**3.276**	**25 Novo Nordisk**	**3.51**	25 Sankyo	4.25	25 Otsuka	4.14
26 Baxter	**2.79**	**26 Novo Nordisk**	**3.17**	**26. Baxter**	**3.271**	**26 Baxter**	**3.5**	26 Otsuka	3.3	**26 Baxter**	**3.88**
27 Daiichi Pharmaceutical	2.56	**27 Baxter**	**3.1**	27. Akzo Nobel	3.112	27 Fujisawa	3.2	**27 Forest**	**3.16**	**27 Solvay**	**3.43**
28 Yamanouchi	2.53	28 Shionogi	3.08	28. Fujisawa	2.937	28 Sankyo	2.9	28. Daiichi	3.06	28 Altana	2.98
29 Eisai	**2.4**	29 Daiichi	2.7	29. Daiichi	2.769	**29 Forest Labs**	**2.65**	**29 Baxter**	**3.02**	**29 UCB**	**2.89**
30 Fujisawa	2.3	30 Teva	2.51	30. Genentech	2.621	30 Chugai	2.62	30 Akzo Nobel	2.87	**30 Forest**	**2.79**
31 Teva	1.84	31 Fujisawa	2.49	31. Shionogi	2.308	31 Akzo Nobel	2.37	31 Altana	2.84	31 Chugai	2.73
32 Purdue Pharma	1.8	32 Genentech	2.16	**32. Forest Labs**	**2.206**	32 Altana	2.23	32 Chugai	2.77	**32 Allergan**	**2.64**
33 Genentech	1.74	**33 Solvay**	**2**	33. Purdue Pharma	2.2	33 Serono	2.18	**33 Solvay**	**2.69**	33 Genzyme	**2.63**
34 Chugai Pharmaceutical	1.64	34 Purdue Pharma	1.9	**34. Solvay**	**2.071**	**34 Solvay**	**2.16**	**34 UCB**	**2.42**	**34 Gilead Sciences**	**2.59**
35 Solvay	**1.54**	35 Altana	1.68	35. Serono	2.018	**35 UCB**	**2.08**	35 Genzyme	2.41	35 Serono	2.5
36 Otsuka	1.47	36 Otsuka	1.67	36. Altana	1.949	36 Genzyme	1.98	36 Serono	2.34	36 Akzo Nobel	2.24
37 Elan	1.4	37 Tanabe Seiyaku	1.58	**37. Allergan**	**1.755**	**37 Allergan**	**1.84**	**37 Allergan**	**2.32**	**37 Alcon**	**2.01**
38 Tanabe Seiyaku	1.27	**38 Forest Labs**	**1.56**	38. Schwarz Pharma	1.691	38 Mitsubishi Pharmaceutica	1.81	38 Mitsubishi Pharmaceutica	1.89	38 CSL	1.97
39 Serono	1.25	39 Serono	1.53	39. King	1.521	39 Shionogi Seiyaku	1.641	**39 Gilead Sciences**	**1.81**	39 King Pharmaceuticals	1.89
40 Forest Laboratories	**1.17**	**40 Allergan**	**1.38**	40. Otsuka	1.476	40Watson	1.6405	**40 Lundbeck**	**1.65**	40 Watson	1.86
41 Allergan	**1.13**	41 Watson	1.22	41. Genzyme	1.474	41 Ivax Corporation	1.56	41 Watson	1.65	41 Biogen Idec	1.78
42 Altana	1.13	42 Kyowa	1.18	42. Watson	1.46	**42 Alcon Labs**	**1.54**	42 Biogen Idec	1.62	42 Mitsubishi Pharma	1.73
43 Kyowa Hakko Kogyo	1.09*	43 King	1.17	43. Tanabe Seiyaku	1.378	**43 Lundbeck**	**1.52**	**43 Shire**	**1.6**	43 Cephalon	1.72
44 Ono Pharmaceutical	1.05	44 Biogen	1.14	44. Biogen Idec	1.355	44 Biogen Idec	1.49	44 Shionogi Seiyaku	1.57	**44 Lundbeck**	**1.66**
45 Biogen	1.04	45 Ono	1.11	**45. Alcon Labs**	**1.309**	45 Mylan Labs	1.37	45 King Pharmaceuticals	1.54	45 Dainippon Sumitomo	1.64
46 Immunex	0.986	46 Elan	1.11	46. Mylan Labs	1.269	**46 Shire**	**1.36**	46 Tanabe Seiyaku	1.48	**46 Shire**	**1.54**
47 Genzyme	0.982	**47 Alcon Labs**	**1.08**	47. Shire	1.237	47 Ono	1.34	47. Kyowa	1.36	47 Nycomed Pharma	1.5
48 3M Worldwide	0.883*	48 Schwarz Pharma	1.03	48. Kyowa	1.209	48 King Pharmaceuticals	1.31	48 Mylan Labs	1.25	48 Shionogi Seiyaku	1.43
49 ICN Pharmaceuticals	0.721	49 3M	1	49. Chiron	1.181	49 Tanabe Seiyaku	1.304	49 Medimmune	1.24	49 Actavis	1.4
50 Schwarz Pharma	0.673	50 Genzyme	0.907	50. Ono	1.16	50 Purdue	1.296	50. Ono	1.24	50 Tanabe Seiyaku	1.35

* estimated

Source: Pharmaceutical Executive, Special Report on the World's Top 50 companies May 2002, May 2003, May 2004, May 2005, May 2006, May 2007
http://pharmexec.findpharma.com/pharmexec

Table. A.1.3.2 Rankings of Pharmaceutical Executive Top 50 companies according to their sales growth compared to the previous year, 2001-2006 (highlights show changes in the rankings of the companies studied here)

2001	growth compared to 2000 sales (%)	2002	growth compared to 2001 sales (%)	2003	growth compared to 2002 sales (%)	2004	growth compared to 2003 sales (%)	2005	growth compared to 2004 sales (%)	2006	growth compared to 2005 sales (%)
44 Ono Pharmaceutica	*NA*	***26 Novo Nordisk***	***NA***	15. Amgen	57	*38 Mitsubishi Pharma*	*NA*	***16 Astellas Pharma***	***NA***	49 Actavis	219
41 Allergan	**67**	*42 Kyowa*	*NA*	38. Schwarz Pharma	55	22 Genentech	43	20 Genentech	46	15 Bayer	105
14 Abbott Laboratorie	**40**	20 Amgen	40	49. Chiron	45	12 Roche	41.5	**39 Gilead Sciences**	**45**	47 Nycomed Pharma	70
45 Biogen	36	43 King	35	**32. Forest Labs**	**40**	13 Amgen	35	31 Altana	27	18 Teva	65
31 Teva	34	**38 Forest Labs**	**33**	1. Pfizer	40	36 Genzyme	34	**37 Allergan**	**26**	43 Cephalon	48
40 Forest Laboratorie	**34**	48 Schwarz Pharma	25	39. King	34.8	**19 Eisai**	**32**	25 Sankyo	25	45 Dainippon Sumitom	44
37 Elan	33	32 Genentech	24	41. Genzyme	32	20 Teva	30.5	**33 Solvay**	**24**	**34 Gilead Sciences**	**43**
42 Altana	30	35 Altana	22	35. Serono	31	41 Ivax Corp*	29	**24 Merck KGaA**	**21**	19 Genentech	39
47 Genzyme	30	**23 Eisai**	**21**	25. Teva	30	30 Chugai	28	30 Akzo Nobel	21	8 Roche	31
29 Eisai	**23**	**40 Allergan**	**21**	**37. Allergan**	**26**	24 Otsuka	20	**27 Forest**	**19**	**14 Boehringer-Ingelh**	**29**
49 ICN Pharmaceutica	21	31 Fujisawa	19	30. Genentech	21	**29 Forest Labs**	**20**	**17 Schering Plough**	18	**22 Novo Nordisk**	**28**
32 Purdue Pharma	20	30 Teva	17	**45. Alcon Labs**	**20**	**42 Alcon Labs**	**18**	18 Bayer	18	**26 Baxter**	**28**
7 Johnson & Johnson	19	**47 Alcon Labs**	**17**	42. Watson	19.6	1 Pfizer	16	45 King Pharmaceutic	18	**27 Solvay**	**28**
6 Aventis	15	6 Johnson & Johnsc	15.5	47. Shire	19	**35 UCB**	15	**43 Shire**	**17**	25 Otsuka	25
8 Novartis	15	15 Sanofi-Synthelab	14.8	7. Novartis	18	**21 Merck KGaA**	**14**	4 Novartis	16	28 Altana	22
23 Merck KGaA	**14**	36 Otsuka	13.8	44. Biogen Idec	16.6	32 Altana	14	**11. Abbott Labs**	16	36 Akzo Nobel	22
24 Novo Nordisk	**14**	**13 Abbott Labs**	**13.4**	12. Roche	16	6 AstraZeneca	13.5	**34 UCB**	**16**	33 Genzyme	20
35 Solvay	**14**	49 3M*	13	36. Altana	15	4 Johnson & Johnson	13	46 Tanabe Seiyaku	14	20 Schering AG	19
46 Immunex	14	**16 Boehringer Inge**	**13**	46. Mylan Labs	14.9	48 King Pharmaceutica	13	13 Amgen	13	**29 UCB**	**19**
1 Pfizer	13	39 Serono	12.4	**11 Abbott Labs**	**14.4**	3 Sanofi-Aventis	12	5 AstraZeneca	12	4 Novartis	18
2 GlaxoSmithKline	12	1 Pfizer	12	4. Johnson & Johnsc	13.8	15 Takeda	12	10 Eli Lilly	12	3 Sanofi-Aventis	16
20 Akzo Nobel	12	5 Aventis	11	33. Purdue Pharma	13.6	40Watson	12	**29 Baxter**	**11**	**32 Allergan**	**16**
9 Pharmacia	11	**27 Baxter**	**11**	10. Eli Lilly	13.5	**10 Abbott Labs**	**11.6**	8 Wyeth	10	**46 Shire**	**16**
26 Baxter	**11**	18 Schering AG	10	28. Fujisawa	11.9	17 Schering AG	11	23. Teva	10	2 GlaxoSmithKline	15
28 Yamanouchi	11	44 Biogen	10	16. Takeda	11.6	9 Wyeth	10.5	35 Genzyme	9	12 Amgen	15
36 Otsuka	10.9	4 AstraZeneca	9	**21. Eisai**	**8.9**	44 Biogen Idec	9.5	42 Biogen Idec	9	**37 Alcon**	**14**
48 3M Worldwide*	10	50 Genzyme	9	13. Sanofi-Synthélat	8	27 Fujisawa	9	49 Medimmune	9	40 Watson	14
11 Wyeth	10	2 GlaxoSmithKline	8	9. Wyeth	7.5	**14 Boehringer-Ingelhe**	**8**	2 GlaxoSmithKline	8	**17 Schering-Plough**	**13**
16 Sanofi-Synthelabo	9	10 Wyeth	7	22. Yamanouchi	7	45 Mylan Labs	8	36 Serono	7	39 King Pharmaceutica	13
21 Amgen	9	41 Watson	6	**26. Baxter**	**5.6**	**46 Shire**	**8**	**40 Lundbeck**	**7**	5 AstraZeneca	11
39 Serono	8.7	34 Purdue Pharma	5.3	6. AstraZeneca	5	**26 Baxter Internationa**	**7**	47. Kyowa	7	10 Wyeth	10
4 AstraZenca	8	24 Yamanouchi	5	3. Merck	5	33 Serono	7	32 Chugai	6	41 Biogen Idec	10
17 Boehringer Ingelh	**8**	**33 Solvay**	**5**	**23. Novo Nordisk**	**5**	2 GlaxoSmithKline	5	12 Roche	5	38 CSL	8
38 Tanabe Seiyaku	7.7	45 Ono	5	20. Sankyo	5	23 Yamanouchi	5	38 Mitsubishi Pharma	4	9 Lilly	7
19 Schering AG	7	28 Shionogi	4.4	2. GlaxoSmithKline	5	**37 Allergan**	**5**	15 Takeda	3	35 Serono	7
33 Genentech	7	17 Takeda	4.3	**24. Merck KGaA**	**4.8**	8 Bristol-Myers Squibb	4	19 Schering AG	3	**23 Merck KGaA**	**6**
5 Bristol-Myers Squibb	6	7 Novartis	4	40. Otsuka*	1	11 Eli Lilly	4	50. Ono	3	6 Johnson & Johnson	4
10 Lilly	6	**14 Schering-Plougl**	**4**	8. Bristol-Myers Squ	1	**16 Schering Plough**	**4**	7 Merck	2	7 Merck	3
3 Merck	5	29 Daiichi	4	50. Ono	1	**34 Solvay**	**4**	**14 Boehringer-Ingell**	**2**	1 Pfizer	2
15 Takeda	4	12 Roche	3	19. Bayer	-0.4	7 Novartis	2.5	6 Johnson & Johnson	1	16 Takeda	2
25 Shionogi	3.6	22 Akzo Nobel	3	48. Kyowa	-1.2	**25 Novo Nordisk**	**2**	**21 Novo Nordisk**	**1**	**24 Eisai**	**2**
27 Daiichi Pharmaceut	3	21 Sankyo	2.4	43. Tanabe Seiyaku	-1.4	18 Bayer	1	41 Watson	0.3	**44 Lundbeck**	**0.3**
30 Fujisawa	2.9	3 Merck	1	**34. Solvay**	**-1.6**	5 Merck	-4	9 Bristol-Myers Squibl	-1	31 Chugai	-2
12 Roche	1	9 Pharmacia	1	**14. Boehringer Inge**	**-2**	50 Purdue	-6	28. Daiichi	-1	**21 Astellas Pharma**	**-8**
34 Chugai Pharmaceu	1	37 Tanabe Seiyaku	0	29. Daiichi	-3	**43 Lundbeck**	**-8**	**22. Eisai**	**-3**	11 Bristol-Myers Squib	-9
13 Schering-Plough	**0**	8 Bristol-Myers Squi	-2	18. Schering AG	-3	49 Tanabe Seiyaku	-14	1 Pfizer	-4	**13 Abbott**	**-9**
50 Schwarz Pharma	-2	**25 Merck KGaA**	**-2.9**	5. Aventis	-4.5	31 Akzo Nobel	-23	44 Shionogi Seiyaku	-4	**30 Forest**	**-9**
43 Kyowa Hakko Kogy	-6	11 Eli Lilly	-4	27. Akzo Nobel	-5	28 Sankyo	-24	3 Sanofi-Aventis	-5	42 Mitsubishi Pharma	-9
18 Bayer	-6.7	19 Bayer	-16	**17. Schering-Ploug**	**-24**	39 Shionogi Seiyaku	-29	48 Mylan Labs	-9	48 Shionogi Seiyaku	-9
22 Sankyo	-9.6	46 Elan	-22	31. Shionogi	-32	47 Ono	-39	26 Otsuka	-11	50 Tanabe Seiyaku	-9

* estimated

Source: Pharmaceutical Executive, Special Report on the World's Top 50 companies May 2002, May 2003, May 2004, May 2005, May 2006, May 2007 http://pharmexec.findpharma.com/pharmexec

Table A.1.3.3 Rankings of Pharmaceutical Executive Top 50 companies according to their R&D spending ($ billion), 2001-2006 (highlights show changes in the rankings of the companies studied here)

Sales Rank	2001	Sales Rank	2002	Sales Rank	2003	Sales Rank	2004	Sales Rank	2005	Sales Rank	2006
42 Altana	NA	**26 Novo Nordisk**	**NA**	1. Pfizer	7.13	**35 UCB**	**NA**	1 Pfizer	7.44	1 Pfizer	7.6
48 3M Worldwide	NA	49 3M	NA	4. Johnson & Johnson	4.68	3 Sanofi-Aventis	9.31	6 Johnson & Johnson	6.31	2 GlaxoSmithKline	6.55
1 Pfizer	4.8	1 Pfizer	5.17	2. GlaxoSmithKline	4.54	1 Pfizer	7.52	2 GlaxoSmithKline	5.71	3 Sanofi-Aventis	5.84
2 GlaxoSmithKline	3.8	2 GlaxoSmithKline	4.3	12. Roche	3.47	12 Roche	5.4	5 AstraZeneca	5.36	4 Novartis	5.47
6 Aventis	3.03	5 Aventis	3.67	6. AstraZeneca	3.45	2 GlaxoSmithKline	5.2	3 Sanofi-Aventis	4.79	6 Johnson & Johnson	5
4 AstraZenca	2.7	4 AstraZeneca	3.06	5. Aventis	3.23	4 Johnson & Johnso	5.2	4 Novartis	4.48	7 Merck	4.78
3 Merck	2.4	3 Merck	2.7	3. Merck	3.17	5 Merck	4.01	7 Merck	3.85	5 AstraZeneca	3.9
8 Novartis	2.2	6 Johnson & Johnsoı	2.7	7. Novartis	3.07	6 AstraZeneca	3.8	12 Roche	3.79	20 Schering AG	3.5
10 Lilly	2.2	7 Novartis	2.6	19. Bayer	2.73	7 Novartis	3.48	13 Amgen	3.2	12 Amgen	3.37
9 Pharmacia	2.07	12 Roche	2.42	10. Eli Lilly	2.35	11 Eli Lilly	2.69	10 Eli Lilly	3.03	9 Lilly	3.13
5 Bristol-Myers Squibb	1.9	9 Pharmacia	2.32	8. Bristol-Myers Squibb	2.27	8 Bristol-Myers Squil	2.5	9 Bristol-Myers Squibb	2.75	11 Bristol-Myers Squil	3.07
11 Wyeth	1.8	8 Bristol-Myers Squil	2.2	20. Sankyo	2.14	9 Wyeth	2.46	**17 Schering Plough**	1.87	10 Wyeth	2.9
14 Abbott Laboratorie	**1.6**	11 Eli Lilly	2.14	9. Wyeth	2.09	**29 Forest Labs**	**2.25**	**11. Abbott Labs**	1.82	8 Roche	2.695
12 Roche	1.3	10 Wyeth	2.08	**11 Abbott Labs**	**1.73**	13 Amgen	1.99	15 Takeda	1.32	**13 Abbott**	**2.255**
13 Schering-Plough	**1.3**	**13 Abbott Labs**	**1.5**	15. Amgen	1.65	**10 Abbott Labs**	**1.69**	8 Wyeth	1.26	**17 Schering-Plough**	**2.19**
7 Johnson & Johnson	1.1	**14 Schering-Plough**	**1.4**	13. Sanofi-Synthélabo	1.48	**16 Schering Plough**	**1.6**	**16 Astellas Pharma**	**1.26**	**14 Boehringer-Ingell**	**2.015**
18 Bayer	1.09	**16 Boehringer Ingel**	**1.4**	**17. Schering-Plough**	**1.46**	18 Bayer	1.53	20 Genentech	1.26	15 Bayer	1.88
16 Sanofi-Synthelabo	0.908	15 Sanofi-Synthelabo	1.3	**14. Boehringer Ingelhe**	**1.33**	**14 Boehringer-Ingel**	**1.5**	19 Schering AG	1.16	19 Genentech	1.77
17 Boehringer Ingelhe	**0.866**	20 Amgen	1.1	16. Takeda	1.06	15 Takeda	1.2	**14 Boehringer-Ingelh**	**1.15**	16 Takeda	1.44
21 Amgen	0.865	19 Bayer	1.09	18. Schering AG	1.04	22 Genentech	0.95	18 Bayer	1.13	**24 Eisai**	**1.33**
19 Schering AG	0.76	18 Schering AG	1.01	**37. Allergan**	**0.763**	17 Schering AG	0.75	**21 Novo Nordisk**	**0.81**	**21 Astellas Pharma**	**1.19**
22 Sankyo	0.594	17 Takeda	0.843	30. Genentech	0.722	**19 Eisai**	**0.724**	25 Sankyo	0.81	25 Otsuka	0.883
33 Genentech	0.526	21 Sankyo	0.72	**23. Novo Nordisk**	**0.685**	27 Fujisawa	0.695	42 Biogen Idec	0.747	**29 UCB**	**0.811**
23 Merck KGaA	**0.503**	**25 Merck KGaA**	**0.662**	27. Akzo Nobel	0.64	49 Tanabe Seiyaku	0.679	**22. Eisai**	**0.73**	**23 Merck KGaA**	**0.797**
20 Akzo Nobel	0.472	22 Akzo Nobel	0.654	22. Yamanouchi	0.575	44 Biogen Idec	0.67	**24 Merck KGaA**	**0.67**	41 Biogen Idec	0.718
24 Novo Nordisk	**0.47**	32 Genentech	0.623	**26. Baxter**	**0.553**	**25 Novo Nordisk**	**0.664**	**34 UCB**	**0.61**	**22 Novo Nordisk**	**0.689**
26 Baxter	**0.427**	24 Yamanouchi	0.546	44. Biogen Idec	0.545	23 Yamanouchi	0.66	36 Serono	0.594	28 Altana	0.653
28 Yamanouchi	0.419	**27 Baxter**	**0.501**	28. Fujisawa	0.536	28 Sankyo	0.66	28. Daiichi	0.54	33 Genzyme	0.65
30 Fujisawa	0.419	31 Fujisawa	0.479	**21. Eisai**	**0.498**	31 Akzo Nobel	0.64	**29 Baxter**	**0.53**	36 Akzo Nobel	0.639
29 Eisai	**0.371**	**23 Eisai**	**0.462**	**24. Merck KGaA**	**0.472**	33 Serono	0.6	30 Akzo Nobel	0.52	**26 Baxter**	**0.614**
34 Chugai Pharmaceuti	0.332	46 Elan	0.397	35. Serono	0.467	**21 Merck KGaA**	**0.597**	35 Genzyme	0.5	35 Serono	0.56
27 Daiichi Pharmaceuti	0.323	29 Daiichi	0.386	36. Altana	0.465	**26 Baxter Internatic**	**0.52**	31 Altana	0.496	**27 Solvay**	**0.556**
32 Purdue Pharma	0.323	39 Serono	0.386	29. Daiichi	0.459	24 Otsuka	0.5	26 Otsuka	0.49	18 Teva	0.495
37 Elan	0.321	44 Biogen	0.367	**34. Solvay**	**0.456**	32 Altana	0.5	38 Mitsubishi Pharmac	0.47	**32 Allergan**	0.476
45 Biogen	0.315	35 Altana	0.361	49. Chiron	0.409	38 Mitsubishi Pharm	0.48	32 Chugai	0.43	31 Chugai	0.457
39 Serono	0.309	36 Otsuka	0.325	41. Genzyme	0.389	30 Chugai	0.45	**33 Solvay**	**0.39**	**30 Forest**	**0.41**
41 Allergan	**0.257**	**47 Alcon Labs**	**0.323**	33. Purdue Pharma	0.359	**42 Alcon Labs**	**0.4**	**37 Allergan**	**0.39**	42 Mitsubishi Pharma	0.408
25 Shionogi	0.236	34 Purdue Pharma	0.306	**45. Alcon Labs**	**0.349**	36 Genzyme	0.39	49 Medimmune	0.385	43 Cephalon	0.403
36 Otsuka	0.224	**33 Solvay**	**0.291**	42. Watson	0.32	**34 Solvay**	**0.36**	23. Teva	0.37	**46 Shire**	**0.387**
46 Immunex	0.205	28 Shionogi	0.256	40. Otsuka	0.276	**37 Allergan**	**0.35**	**40 Lundbeck**	**0.324**	**34 Gilead Sciences**	**0.384**
43 Kyowa Hakko Kogyc	0.2	42 Kyowa	0.244	48. Kyowa	0.27	20 Teva	0.34	**27 Forest**	**0.29**	**44 Lundbeck**	**0.351**
35 Solvay	**0.193**	45 Ono	0.237	31. Shionogi	0.269	**43 Lundbeck**	**0.3**	**43 Shire**	**0.286**	**37 Alcon**	**0.292**
47 Genzyme	0.188	**40 Allergan**	**0.233**	50. Ono	0.253	47 Ono	0.294	50. Ono	0.286	39 King Pharmaceutic	0.254
44 Ono Pharmaceutical	0.176	50 Genzyme	0.23	39. King	0.238	39 Shionogi Seiyaku	0.28	**39 Gilead Sciences**	**0.28**	45 Dainippon Sumitor	0.252
31 Teva	0.169	37 Tanabe Seiyaku	0.174	47. Shire	0.215	48 King Pharma*	0.25	44 Shionogi Seiyaku	0.274	40 Watson	0.131
38 Tanabe Seiyaku	0.149	30 Teva	0.165	25. Teva	0.213	50 Purdue	0.232	47. Kyowa	0.268	38 CSL	0.12
40 Forest Laboratories	**0.106**	**38 Forest Labs**	**0.157**	**32. Forest Labs**	**0.204**	**46 Shire**	**0.196**	45 King Pharmaceutic	0.263	49 Actavis	0.088
15 Takeda	0.072	48 Schwarz Pharma	0.133	43. Tanabe Seiyaku	0.201	41 Ivax Corporation	0.16	46 Tanabe Seiyaku	0.26	47 Nycomed Pharma	0.049
50 Schwarz Pharma	0.063	41 Watson	0.081	38. Schwarz Pharma	0.162	40Watson	0.134	41 Watson	0.125	50 Tanabe Seiyaku	0.002
49 ICN Pharmaceutical	0.031	43 King	0.028	46. Mylan Labs	0.086	45 Mylan Labs	0.1	48 Mylan Labs	0.088	48 Shionogi Seiyaku	0

* estimated

Source: Pharmaceutical Executive, Special Report on the World's Top 50 companies May 2002, May 2003, May 2004, May 2005, May 2006, May 2007 http://pharmexec.findpharma.com/pharmexec

Table. A.1.4 Wood Mackenzie's ProductView: Ranking, sales, market share and sales growth of pharma companies, 2005-2006 (highlights show changes in the rankings of the companies studied here)

Wood Mackenzie's Productview™

Rank Company 2005	Sales $(m)	Market Share %	Sales Growth 04-05 $(%)	Rank Company 2006	Sales $(m)	Market Share %	Sales Growth 05-06 $(%)
1 Pfizer	44,269	9	-4	1 Pfizer	45,083	8.6	1.8
2 sanofi-aventis	33,933	6.9	83.3	2 GlaxoSmithKline	36,947	7.1	8.9
3 GlaxoSmithKline	33,917	6.9	8	3 sanofi-aventis	35,605	6.8	4.9
4 Novartis	24,487	5	15.3	4 Novartis	28,868	5.5	17.9
5 AstraZeneca	23,303	4.7	11.7	5 Roche	26,560	5.1	21.4
6 Johnson & Johnson	22,322	4.5	0.9	6 AstraZeneca	25,741	4.9	10.5
7 Merck & Co	22,012	4.5	-4	7 Johnson & Johnson	23,267	4.4	4.2
8 Roche	21,880	4.5	25.3	8 Merck & Co	22,636	4.3	2.8
9 Bristol-Myers Squibb	15,254	3.1	-2	9 Wyeth	15,683	3	9.8
10 Wyeth	14,281	2.9	9.7	10 Eli Lilly	14,816	2.8	7.5
11 Eli Lilly	13,782	2.8	5.5	11 Bristol-Myers Squibb	13,861	2.6	-9.1
12 Abbott	**13,302**	**2.7**	**14.8**	12 Amgen	13,858	2.6	15.3
13 Amgen	12,022	2.4	20.5	**13 Abbott**	**12,395**	**2.4**	**-6.8**
14 Boehringer Ingelheim	**9,029**	**1.8**	**17.5**	**14 Boehringer Ingelheim**	**10,401**	**2**	**15.2**
15 Takeda	8,999	1.8	5.7	15 Takeda	9,429	1.8	4.8
16 Schering-Plough	**7,564**	**1.5**	**17.9**	16 Bayer Schering Pharma	8,681	1.7	85.3
17 Astellas Pharma	**7,488**	**1.5**	**0**	**17 Schering-Plough**	**8,561**	**1.6**	**13.2**
18 Daiichi-Sankyo	6,683	1.4	0	**18 Astellas Pharma**	**7,723**	**1.5**	**3.1**
19 Novo Nordisk	**5,629**	**1.1**	**16.1**	19 Daiichi-Sankyo	6,859	1.3	2.6
20 Eisai	**5,049**	**1**	**9.3**	**20 Novo Nordisk**	**6,518**	**1.2**	**15.8**
21 Schering AG	**4,733**	**1**	**8.4**	**21 Eisai**	**5,345**	**1**	**5.9**
22 Bayer Schering Pharma	4,685	1	1.1	**22 Merck KGaA**	**4,669**	**0.9**	**6.8**
23 Merck KGaA	**4,371**	**0.9**	**13.5**	**23 Solvay**	**3,264**	**0.6**	**15.7**
24 Solvay	**2,820**	**0.6**	**30.1**	**24 Forest**	**3,101**	**0.6**	**11**
25 Forest	**2,794**	**0.6**	**-8.5**	25 Akzo Nobel	2,957	0.6	8.3

Source: Wood Mackenzie's Productview™ March 2007, Wood Mackenzie, Wednesday, July 04, 2007

Table A.2.1 The website information of the companies researched

Boehringer Ingelheim	Germany	http://www.boehringer-ingelheim.com/
Abbott Laboratories*	USA	http://www.abbott.com/
Schering-Plough	USA	http://www.schering-plough.com/
Baxter International	USA	http://www.baxter.com/
Astellas Pharma	Japan	http://www.astellas.com/
Novo Nordisk	Denmark	http://www.novonordisk.com/
Eisai	Japan	http://www.eisai.com/
Merck KGaA*	Germany	http://www.merck.de/
MerckSerono	UK	http://www.merck-pharmaceuticals.co.uk/
Solvay*	Belgium	http://www.solvay.com/
		http://www.solvaypharmaceuticals-us.com/
Forest Laboratories	USA	http://www.frx.com/index.aspx
UCB	Belgium	www.ucb-group.com
Allergan*	USA	http://www.allergan.com/
Gilead Sciences	USA	http://www.gilead.com/
H. Lundbeck A/S	Denmark	http://www.lundbeck.com
Shire plc	UK	http://www.shire.com/
Bausch & Lomb	USA	http://www.bausch.com/
Alcon	Switzerland	http://www.alcon.com/

Table A.2.2 The sample of companies, by country, year of foundation and therapeutic area in pharmaceutical sector

Company	Country	Year of foundation	Therapeutic foci in Pharmaceuticals
Boehringer Ingelheim	Germany	1885	CNS, respiratory, metabolism, Cardiovascular, immunology and inflammation, Oncology, Virology, Molecular biology, Chemical synthesis
Abbott Laboratories	USA	1888	Anesthesia, Anti-infective, Cardiovascular, Immunology, Metabolics, Neuroscience, Oncology, Pain care, Renal care, Virology
Schering-Plough	USA	1940s	Oncology, Infectious Diseases, Inflammatory Diseases, Cardiovascular and Metabolic Diseases, Respiratory Diseases, Central Nervous System (CNS), Women's health
Baxter International	USA	1931	Haemophilia, Immune disorders, Plasma-based therapies (plasma proteins and vaccines), Infectious diseases, Regenerative medicine, Bisurgery and Cellular therapies (technologies used in adult stem-cell therapies);
Astellas Pharma	Japan	1923	Urology, Immunology and inflammation, Diabetes, Central nervous system and Pain, Infectious diseases including viruses and cancer
Novo Nordisk	Denmark	1989	Diabetes, growth hormone and growth disorders, haemostasis, inflammation, protein technologies and delivery, oncology, hormone replacement therapy
Eisai	Japan	1941	Neuroscience, oncology and gastroenterology; and to some extent immunology and vascular biology
Merck KGaA	Germany	1827	Oncology, Neurology, CardioMetabolic care, Autoimmune and inflammatory, Reproductive Health + (Serono) fertility treatments, growth and metabolic disorders, psoriasis, and above all multiple sclerosis.
Alcon	Switzerland	1947	Ophthalmology
Solvay Pharmaceuticals	Belgium	1863	Cardiometabolics, Neuroscience, Flu vaccines, Pancreatic enzymes, Gastroenterology, Women's and men's health
Bausch & Lomb	USA	1853	Ophthalmic pharmaceuticals (Rx); Cataract, Vitreoretinal, Refractive; Contact lens, Lens care
Forest Laboratories	USA	1954	Cardiovascular, Central Nervous System, Endocrinology, Ob/Gyn – Pediatrics, Pain Management, Respiratory
UCB Biopharma	Belgium	1928	Central nervous system (epilepsy, Crohn's disease), inflammation and allergy + (Schwarz Pharma) Parkinson's disease.
Allergan	USA	1950s	Ophthalmology (excluding retinal therapeutics), neurosciences, medical dermatology, gastroenterology and urology
Gilead Sciences	USA	1987	Antivirals (such as HIV/AIDS and chronic hepatitis), Cardiovascular conditions (such as pulmonary arterial hypertension and resistant hypertension) and Respiratory diseases (such as influenza and cystic fibrosis).
H. Lundbeck A/S	Denmark	1950s	Central Nervous System (psychiatric and neurological disorders such as anxiety, depression, alzheimers, schizophrenia, parkinsons)
Shire plc	United Kingdom	1986	Attention Deficit and Hyperactivity Disorder (ADHD), Human genetic therapies, Gastrointestinal and Renal diseases
Source: Web sites and Annual Reports of the Companies			

Table A.2.3 The sample of companies, by business segments (%), 2006

Company	Business segments	2006
Boehringer Ingelheim	prescription medicines	78.6%
	consumer health care	10.1%
	biopharmaceuticals	4.8%
	pharma chemicals and pharmaceuticals production	2.9%
	industrial customer	7.7%
	other sales	0.2%
Abbott Laboratories	medical products	22.5%
	pharmaceuticals	55.1%
	nutritional products	19.2%
Schering-Plough	Prescription Pharmaceuticals	80.8%
	Consumer Helath care	10.6%
	Animal Health	8.6%
Baxter International	bioscience	42.4%
	medication delivery	37.7%
	renal	19.9%
Novo Nordisk	diabetes care	71.9%
	biopharmaceuticals	28.1%
Eisai	pharmaceuticals	96.9%
	other areas	3.1%
Merck KGaA	total pharmaceuticals	65.8%
	ethicals within pharmaceuticals	46.2%
Allergan	Specialty pharmaceuticals	87.7%
	medical devices	12.3%
Alcon	pharmaceutical	41.0%
	surgical	45.0%
	consumer eye care	14.0%
Bausch & Lomb	pharmaceutical	28.7%
	Vision care	49.1%
	Surgery devices	22.3%
Source: Calculated from the Company Annual Reports, 2006		

Figure A.1 Size-based Continuum of Mid-Pharma Companies, by R&D expenditure (USD billion), 2006

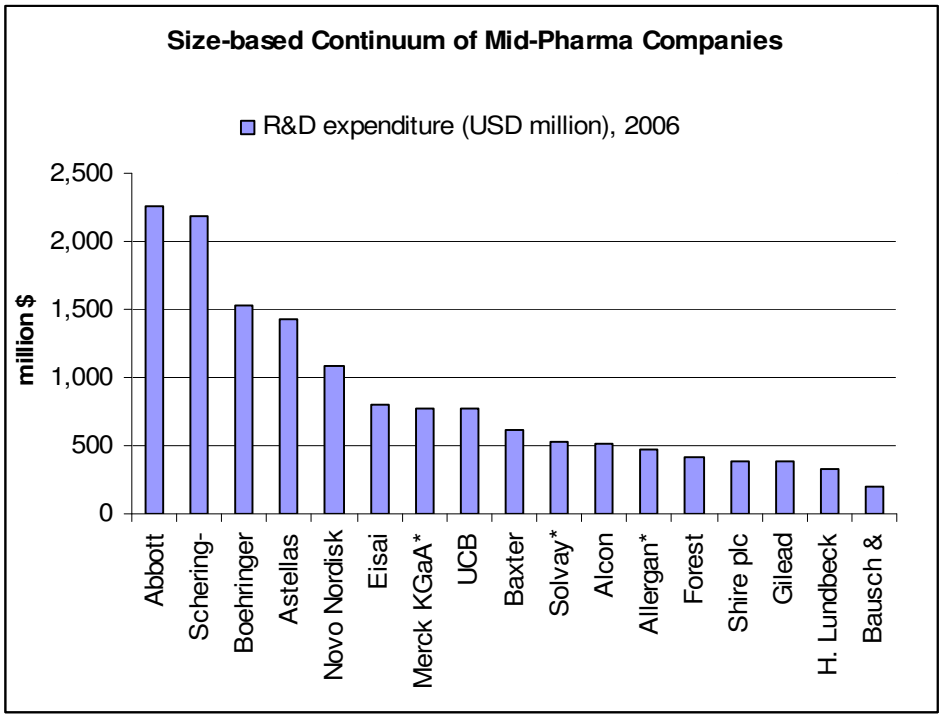

Table A.3 Mid-pharma companies ranked by total sales, 2002-2006

		Total Sales (USD millions)				
Company	**Country**	**2002**	**2003**	**2004**	**2005**	**2006**
Abbott Laboratories	USA	15,280	17,280	19,680	22,338	**22,476**
Boehringer Ingelheim^	Germany	7,959	9,301	11,094	11,251	**13,270**
Solvay^	Belgium	8,315	9,522	9,889	10,103	**11,796**
Schering-Plough	USA	10,180	8,334	8,272	9,508	**10,594**
Baxter International	USA	8,099	8,904	9,509	9,849	**10,378**
Merck KGaA^	Germany	7,770	9,075	7,968	6,927	**7,855**
Astellas Pharma^	Japan	4,215	4,837	8,056	7,516	**7,802**
Novo Nordisk^	Denmark	3,514	4,435	5,307	5,347	**6,518**
Eisai^	Japan	3,240	3,882	4,733	4,963	**5,738**
Alcon	Switzerland	3,009	3,407	3,914	4,369	**4,897**
Allergan	USA	1,436	1,781	2,059	2,343	**3,010**
Forest Laboratories	USA	1,567	2,207	2,650	3,052	**2,794**
UCB^	Belgium	2,640	3,737	4,172	2,411	**2,746**
Gilead Sciences	USA	na	na	na	1,809	**2,590**
Bausch & Lomb	USA	1,817	2,020	2,234	2,354	**2,292**
H. Lundbeck A/S^	Denmark	1,203	1,511	1,625	1,513	**1,551**
Shire plc	UK	859	1,030	1,113	1,328	**1,536**

^ These firms have presented their financial figures in their national currencies, so they are converted into US dollar by using http://www.oanda.com/convert/fxhistory (interbank rate and annual average) for Yen/USD and DKK/USD, and UCB Annual Reports for Euro/USD

na Not available

Source: Company Annual Reports and websites (see appendix for a list of company website addresses).

Table A.4.1 Mid-pharma companies ranked by sales of their pharmaceuticals operations only and their growth rate, 2002-2006

Sales Rank	Company	Country	Sales in Pharmaceuticals only (USD millions) 2002	2003	2004	2005	2006	Growth 2002-2006
1	Abbott Laboratories	USA	9,270*	12,300*	11,913	13,691	12,395	33.7%
2	Boehringer Ingelheim^	Germany	7,920*	8,000*	8,700*	9,174	10,200	28.8%
3	Schering-Plough	USA	8,788	6,672	6,417	7,564	8,561	-2.6%
4	Astellas Pharma**^	Japan	4,215	4,837	8,056	7,516	7,802	85.1%
5	Novo Nordisk^	Denmark	3,514	4,435	5,307	5,347	6,518	85.5%
6	Baxter International	USA	3,100*	3,271*	5,462	4,859	6,461	108.4%
7	Eisai^	Japan	3,240	3,882	4,733	4,963	5,738	77.1%
8	Merck KGaA^	Germany	3,311	4,162	4,695	4,595	5,169	56.1%
9	Solvay^	Belgium	1,956	2,308	2,373	2,679	3,264	66.9%
10	Forest Laboratories	USA	1,567	2,207	2,650	3,052	2,794	78.3%
11	UCB^	Belgium	2,640	3,737	4,172	2,411	2,746	4.0%
12	Allergan	USA	1,385	1,755	2,046	2,319	2,639	90.5%
13	Gilead Sciences	USA	na	na	na	1,809	2,590	43.2%***
14	Alcon	Switzerland	1,090	1,310	1,543	1,768	2,007	84.1%
15	H. Lundbeck A/S^	Denmark	1,203	1,511	1,625	1,513	1,551	28.9%
16	Shire plc	UK	859	1,030	1,113	1,328	1,536	78.7%
17	Bausch & Lomb	USA	396	468	528	585	658	66.3%

na Not available

* Pharmaceutical Executive magazines May 2003, May 2004, and May 2005 http://pharmexec.findpharma.com/pharmexec/Special+Reports/

** Astellas Pharma is created through the merger of Yamanouchi and Fuijsawa in April 2005. The figures for the previous years are simple addition of two companies' sales.

*** Growth 2005-2006

^ These firms have presented their financial figures in their national currencies, so they are converted into US dollar by using http://www.oanda.com/convert/fxhistory (interbank rate and annual average) for Yen/USD and DKK/USD, and UCB Annual Reports for Euro/USD

Source: Company Annual Reports and websites (see appendix for a list of company website addresses).

Table A.4.2 Mid-pharma companies by percentage change in sales of their pharmaceuticals operations only, 2003-2006

Company	Country	Percentage change in Sales in Pharmaceuticals only compared to previous year 2003	2004	2005	2006
Abbott Laboratories	USA	33%	-3%	15%	-9%
Boehringer Ingelheim^	Germany	1%	9%	5%	11%
Schering-Plough	USA	-24%	-4%	18%	13%
Astellas Pharma**^	Japan	15%	67%	-7%	4%
Novo Nordisk^	Denmark	26%	20%	1%	22%
Baxter International	USA	6%	67%	-11%	33%
Eisai^	Japan	20%	22%	5%	16%
Merck KGaA^	Germany	26%	13%	-2%	13%
Solvay^	Belgium	18%	3%	13%	22%
Forest Laboratories	USA	41%	20%	15%	-8%
UCB^	Belgium	42%	12%	-42%	14%
Allergan	USA	27%	17%	13%	14%
Gilead Sciences	USA	na	na	na	43%
Alcon	Switzerland	20%	18%	15%	14%
H. Lundbeck A/S^	Denmark	26%	8%	-7%	3%
Shire plc	UK	20%	8%	19%	16%
Bausch & Lomb	USA	18%	13%	11%	13%

na Not available

Source: Table A.4.1

Table A.5.1 Mid-pharma companies by R&D expenditures (USD million), 2002-2006

			R&D Expenditure (USD millions)				
Company	**Country**	**Sales rank 2006**	**2002**	**2003**	**2004**	**2005**	**2006**
Abbott Laboratories**	USA	1	1,475	1,624	1,697	1,821	**2,255**
Schering-Plough**	USA	3	1,425	1,469	1,607	1,865	**2,188**
Boehringer Ingelheim*^	Germany	2	1,304	1,140	1,195	1,318	**1,527**
Astellas Pharma^	Japan	4	502	582	1,202	1,322	**1,430**
Novo Nordisk^	Denmark	5	494	622	751	869	**1,088**
Eisai^	Japan	7	413	497	653	729	**793**
Merck KGaA*^	Germany	8	456	527	610	719	**772**
UCB^	Belgium	11	283	340	467	635	**772**
Baxter International**	USA	6	501	553	517	533	**614**
Solvay Pharmaceuticals*^	Belgium	9	290	358	365	436	**532**
Alcon**	Switzerland	14	323	350	390	422	**512**
Allergan*	USA	12	228	305	343	384	**476**
Forest Laboratories	USA	10	158	205	234	294	**410**
Shire plc	UK	16	189	216	200	339	**387**
Gilead Sciences	USA	13	na	na	na	278	**384**
H. Lundbeck A/S^	Denmark	15	200	294	296	297	**329**
Bausch & Lomb**	USA	17	128	150	163	178	**197**

* only pharmaceuticals segment of their business.

** The Group R&D expenditure. **Notes:** The figures of Abbott Laboratories and Solvay are Group R&D expenditures; however, Abbott Lab states that "The majority of R&D expenditures are concentrated on pharmaceutical products" (Abbott Laboratories, Annual Report 2006: p.69), 75% of Solvay's Group R&D expenditure in 2006 is for the pharmaceutical segment oits business (Solvay, Annual Report 2006, Key figures), and 57% of 2006 R&D expenditure is in pharmaceuticals segment of their business (Alcon Inc., Annual Report 2006, p.29). Baxter Intl has increased its R&D expenditures in 2006 to invest in the company's adult stem-cell program as well as to advance the company's pipeline in the specialty plasma therapeutics, hemophilia and other recombinant products, and to expand the product portfolio in to the area of regenerative medicine (Baxter Intl Annual Report 2006, p.39).

^ These firms have presented their financial figures in their national currencies, so they are converted into US dollar by using http://www.oanda.com/convert/fxhistory (interbank rate and annual average) for Yen/USD and DKK/USD, and UCB Annual Reports for Euro/USD

Source: Company annual reports and websites

Table A.5.2 Mid-pharma by percentage change in R&D expenditures compared to previous year (%), 2003-2006

		percentage change in R&D Expenditure compared to previous year			
Company	**Country**	**2003**	**2004**	**2005**	**2006**
Abbott Laboratories**	USA	10.1%	4.5%	7.3%	23.8%
Schering-Plough**	USA	3.1%	9.4%	16.1%	17.3%
Boehringer Ingelheim*^	Germany	-12.6%	4.8%	10.3%	15.9%
Astellas Pharma^	Japan	16.0%	106.3%	10.0%	8.2%
Novo Nordisk^	Denmark	26.0%	20.8%	15.8%	25.1%
Eisai^	Japan	20.3%	31.4%	11.7%	8.8%
Merck KGaA*^	Germany	15.4%	15.9%	17.8%	7.3%
UCB^	Belgium	20.3%	37.4%	35.8%	21.6%
Baxter International**	USA	10.4%	-6.5%	3.1%	15.2%
Solvay Pharmaceuticals*^	Belgium	23.3%	2.1%	19.3%	22.1%
Alcon**	Switzerland	8.4%	11.5%	8.0%	21.4%
Allergan*	USA	33.8%	12.5%	12.0%	24.0%
Forest Laboratories	USA	29.7%	14.1%	25.6%	39.5%
Shire plc	UK	14.1%	-7.5%	69.9%	14.1%
Gilead Sciences	USA	na	na	na	38.1%
H. Lundbeck A/S^	Denmark	46.9%	1.0%	0.2%	10.8%
Bausch & Lomb**	USA	17.2%	8.7%	9.2%	10.7%

Source: Table A.5.1

Table A.6 Mid-pharma companies by R&D expenditure as % of sales in pharmaceuticals only , %, 2002-2006

		R&D spending as % of Pharmaceutical Sales				
Company	**Country**	**2002**	**2003**	**2004**	**2005**	**2006**
UCB	Belgium	10.7%	9.1%	11.2%	26.3%	28.1%
Shire plc	UK	22.0%	21.0%	17.9%	25.5%	25.2%
H. Lundbeck A/S	Denmark	16.6%	19.4%	18.2%	19.6%	21.2%
Schering-Plough*	USA	14.0%	17.6%	19.4%	19.6%	20.7%
Astellas Pharma	Japan	11.9%	12.0%	14.9%	17.6%	18.3%
Allergan	USA	16.5%	17.4%	16.8%	16.6%	18.0%
Boehringer Ingelheim	Germany	na	na	na	14.4%	17.5%
Novo Nordisk	Denmark	14.0%	14.0%	14.2%	16.3%	16.7%
Solvay	Belgium	14.8%	15.5%	15.4%	16.3%	16.3%
Merck KGaA	Germany	13.8%	12.7%	13.0%	15.7%	14.9%
Gilead Sciences	USA	na	na	na	15.4%	14.8%
Forest Laboratories	USA	10.1%	9.3%	8.8%	9.6%	14.7%
Eisai	Japan	12.7%	12.8%	13.8%	14.7%	13.8%
Alcon*	Switzerland	10.7%	10.3%	10.0%	9.7%	10.5%
Abbott Laboratories*	USA	9.7%	9.4%	8.6%	8.2%	10.0%
Bausch & Lomb*	USA	7.0%	7.4%	7.3%	7.6%	8.6%
Baxter International*	USA	6.2%	6.2%	5.4%	5.4%	5.9%

* Group R&D expenditure / net sales of the Group,

otherwise; R&D expenditure only in pharmaceutical segment / net sales in pharmaceuticals only

Source: Tables A.3, A.4 and A.5

Table A.7 Mid-pharma companies by net income (USD million), 2002-2006

Company	Country	Net income (profit after tax) 2002	2003	2004	2005	2006
Boehringer Ingelheim^	Germany	595	677	1,129	1,880	**2,170**
Abbott Laboratories*	USA	2,794	2,753	3,236	3,372	**1,717**
Baxter International	USA	771	866	388	956	**1,397**
Alcon	Switzerland	467	595	872	931	**1,348**
Merck KGaA*^	Germany	232	275	835	836	**1,256**
Schering-Plough	USA	1,974	-92	-947	269	**1,143**
Astellas Pharma^	Japan	450	499	563	966	**1,118**
Novo Nordisk^	Denmark	598	819	838	977	**1,086**
Solvay*^	Belgium	533	542	672	1,013	**1,025**
Forest Laboratories	USA	338	622	736	839	**709**
Eisai^	Japan	274	341	474	517	**678**
UCB^	Belgium	358	428	451	938	**461**
Shire plc.	UK	251	276	236	-578	**278**
H. Lundbeck A/S^	Denmark	160	210	282	263	**186**
Bausch & Lomb	USA	73	126	154	19	**15**
Allergan*	USA	75	-53	377	404	**-127**
Gilead Sciences	USA	na	na	na	814	**-1,190**

* net income of the Group

^ These firms have presented their financial figures in their national currencies, so they are converted into US dollar by using http://www.oanda.com/convert/fxhistory (interbank rate and annual average) for Yen/USD and DKK/USD, and UCB Annual Reports for Euro/USD

na Not available

Source: Company Annual Reports and websites (see appendix for a list of company website addresses).

Table A.8 Mid-pharma companies by number of employees, 2002-2006

			Number of Employees				
Company	**Country**	**Sales Rank 2006**	**2002**	**2003**	**2004**	**2005**	**2006**
Abbott Laboratories*	USA	1	57,819	58,181	60,617	59,735	**66,663**
Schering-Plough	USA	3	na	na	na	na	**50,000**
Baxter International	USA	6	55,000	51,300	48,300	46,900	**48,000**
Boehringer Ingelheim	Germany	2	31,843	34,221	35,529	37,406	**38,428**
Merck KGaA*	Germany	8	34,504	34,206	28,877	29,133	**29,999**
Novo Nordisk	Denmark	5	18,372	19,241	20,725	22,460	**23,613**
Astellas Pharma	Japan	4	na	na	na	na	**13,900**
Alcon	Switzerland	14	almost 12,000	almost 12,000	na	12,700	**13,500**
Bausch & Lomb	USA	17	na	na	na	na	**approx 13,700**
Solvay*	Belgium	9	7,557	7,530	7,988	10,004	**10,088**
Eisai	Japan	7	7,260	7,433	7,700	8,295	**9,081**
UCB	Belgium	11	10,326	11,559	11,403	8,525	**8,477**
Allergan*	USA	12	na	4,900	5,000	more than 5000	**5,200**
H. Lundbeck A/S	Denmark	15	4,534	5,233	5,155	5,022	**5,171**
Forest Laboratories	USA	10	na	na	na	na	**5,000**
Gilead Sciences	USA	13	na	na	na	na	**more than 2900**
Shire plc	UK	16	1,847	1,815	1,833	2,090	**2,868**
na Not available							
Source: Company Annual Reports and websites (see appendix for a list of company website addresses).							

Table A.9. Details of divestiture activities by Mid-Pharma

Year	Company	Partner	description of the partnership
2007	Abbott Labs	Core lab diagnostics	sharpening focus on innovation-driven business
2006	Astellas	OTC Business Subsidiary, Zepharma Inc.	Astellas Sells All Outstanding Shares of Its OTC Business Subsidiary, Zepharma Inc., to Daiichi Sankyo Co., Ltd.
2002	Baxter Intl	Services Component of Renal Business	
2001	Gilead	OSI Pharmaceuticals	an agreement, valued at up to $200 million in cash and stock, under which Gilead will sell assets from its oncology business to OSI. OSI will acquire Gilead's pipeline of clinical candidates in oncology and all related intellectual property, as well as Gilead's Boulder, Colorado operations, including clinical research and drug development personnel, infrastructure and facilities. In consideration of these assets, OSI will pay to Gilead $130 million in cash and $40 million in shares of OSI common stock upon the closing of the transaction. OSI will also pay to Gilead up to an additional $30 million in either cash or a combination of cash and OSI common stock upon the achievement of certain milestones related to the development of NX211, the most advanced of Gilead's oncology product candidates.
2007	Merck KGaA	sale of its generic pharmaceutical business to Mylan Laboratories Inc.	
2004	Merck KGaA	Exit Orthopedics Joint Venture to Focus on Core Businesses	
2006	Shire	Duramed Pharmaceuticals Inc (Duramed), a subsidiary of Barr,	As part of its strategy of focusing on drugs with long-term patent protection in its core therapeutic areas, the Group continued its disposal program of non-core assets with the sale to Duramed of ADDERALL for $63 million in August 2006. ADDERALL was Shire's immediate-release ADHD product which has been subject to generic competition since 2002.
2006	UCB	Bioproducts Manufacturing Division to Lonza AG of Switzerland	specializing only in biopharmaceuticals. This division, active in chemical peptide manufacturing, employed approximately 300 people.
2007	UCB	Fabre, a pharmaceutical leader in the European Over-The-Counter (OTC) market	the OTC business of UCB in France, the Benelux, Switzerland and Greece in ord to specialize only in biopharmaceuticals
2005	UCB	all activities of its Surface Specialties business segment (Specialty Chemicals)	specializing only in biopharmaceuticals, and divesting the business segment Surface Specialties
2004	UCB	all activities of its Surface Specialties business segment (Specialty Films)	specializing only in biopharmaceuticals, and divesting the business segment Surface Specialties

Source: News releases in Company Websites and various issues of Annual Reports

Table A.10 Selected examples of M&As by Mid-Pharma

Selected examples of M&As by Mid-Pharma

Year	Company	Partner acquired	Reasons to acquire
1999	Abbott Labs	Perclose	entering vascular care
2001	Abbott Labs	Knoll Pharmaceuticals	adding biologics expertise and Humira
2004	Abbott Labs	TheraSense	solidifying diabetes care leadership
2006	Abbott Labs	Guidant vascular	propelling Abbott to the forefront of vascular care
2006	Abbott Labs	Kos Pharmaceuticals	expanding on-market presence and pipeline in lipid management.
2006	Abbott Labs	Guidant's vascular business	With Abbott's current vascular business, this acquisition creates one of the leading global vascular devices companies.
2003	Allergan	Oculex Pharmaceuticals, Inc.,	Key to the transaction was the acquisition of Posurdex®, a bioerodable, extended release implant that Oculex was developing to deliver dexamethasone to the targeted disease site at the back of the eye.
2006	Allergan	Inamed Corporation	Combines two global specialty companies with complementary portfolios of leading medical aesthetics products, creates cross-marketing and cross-selling opportunities and fits with Allergan's strategy of focusing on high-growth specialty markets and leadership in specialty pharmaceuticals.
2007	Allergan	Esprit Pharma Holding Company, Inc	supports Allergan's U.S. growth strategy; strengthens the company's core pharmaceutical businesses by creating a dedicated urologics division; allows entering into another core specialty market with significant growth potential.
2005	Bausch & Lomb	Shandong Chia Tai Freda Pharmaceutical Group	to accelerate the company's expansion into the rapidly growing ophthalmic pharmaceuticals market in China
1998	Baxter Intl	Ohmeda Pharmaceutical, New Province, New Jersey	to enter into the area of anesthetics business, both gases (inhaled anesthetics) and injectables
2001	Baxter Intl	AUTROS Healthcare Solutions Inc.	to Expand its Offering of Patient Safety Technologies
2002	Baxter Intl	ESI Lederle	to Significantly Expand Its Injectable Drug Portfolio and Manufacturing Capability
2007	Eisai Co.	Morphotek Inc.	to make a full-fledged entry into the field of biologics; to pursue the development of potential cutting-edge cancer therapies,
2003	Gilead	Triangle Pharmaceuticals	Triangle Pharmaceuticals, Inc. (Nasdaq:VIRS) by merging Triangle with a wholly owned subsidiary of Gilead.
1999	Gilead	NeXstar Pharmaceuticals, Inc.	The combined organization will operate under the name Gilead Sciences, with NeXstar subsidiaries operating at existing sites in the United States, Europe and Australia. Gilead's current Board of Directors will serve as the Board for the merged company.

Table A.10 (cont.) Selected examples of M&As by Mid-Pharma

Year	Company	Partner acquired	Reasons to acquire
2002	Lundbeck	Synaptic, US research company	establishing an American research unit as a bridgehead in the US
2006	Merck KGaA	Serono	raise Merck's competitiveness in the global pharmaceutical market
2007	Schering Plough	Organon BioSciences N.V., the human and animal health care businesses of Akzo Nobel N.V.	builds on the company's strength in primary care; enhances Schering-Plough's strength in human and animal biologic products; fills a gap in the company's late-stage pipeline by adding five compounds in Phase III development and a number of promising projects in Phase II development
2005	Schering Plough	NeoGenesis Pharmaceuticals, Inc., a drug discovery company	an agreement for Schering-Plough to acquire most of NeoGenesis' assets, subject to normal closing conditions
2005	Shire	Transkaryotic Therapies Inc. (TKT)	fits Shire's profile, significantly builds Shire's pipeline while bringing the company a new, sustainable area of specialty pharmaceutical expertise in a market where there are only a small number of players.
2007	Shire	New River Pharmaceuticals Inc.	to gain full control/economic benefit of VYVANSE, its future flagship product for ADHD, add to shire's product pipeline and broadens technology platform
2001	Shire	BioChem Pharma	Royalty products; Building market capabilities
1995	Shire	Imperials	Allow UK flotation in 1996
1997	Shire	Pharmavene	Key for CARBATROL, ADDERALL XR
1997	Shire	Richwood	US marketing; ADHD franchise
1999	Shire	Fuisz EU	marketing in France, Germany and Italy; strengthen research
1999	Shire	Roberts	Gi/ARGYLIN; Building market capabilities
2002	Shire	Atlantic Pharmaceutical	became one of the principal manufacturing sites for Shire in the US; support strategy of dualsourcing for key products
2005	Solvay	Fournier Pharma	becomes the global leader in fenofibrate; adds a strong and unique product line in Solvay's cardiology business
1998	Solvay	Unimed Pharmaceuticals, US	a key step in the Solvay's strategy to rapidly expand its pharmaceutical business in the U.S.
2004	UCB	Celltech	to create a pure biopharma, focusing on severe diseases
2006	UCB	Schwarz Pharma, Germany	transformation into becoming a global biopharmaceutical company with one of the richest late stage pipelines

Source: Calculated from the information released in the company websites (news releases) and various annual reports

Table A.11 Details of JV relations by Mid-Pharma

Year	Company	Partner	Description of the JV
2005	Astellas	Sanofi-aventis	Established in 1982, FSA is a joint venture company 51% owned by sanofi-aventis and 49% by Astellas. FSA owns the rights to manufacture and sell certain products originating from sanofi-aventis such as Myslee® (zolpidem), Dogmatyl® (sulpiride), Primperan® (metoclopramide) and Gramalil® (tiapride) .
2006	Baxter Intl	Guangzhou Baiyunshan Pharmaceuticals Co.Ltd.	to produce and sell parenteral nutrition products of the partner first and then gradually expand the portfolio to include Baxter products in China, aiming at growth in that emerging market.
2001	Baxter Intl	Nutricia and Andreas Rudolph	to serve the growing homecare market in Germany
2004	Gilead	Bristol-Myers Squibb	to develop and commercialize the fixed-dose combination of Bristol-Myers Squibb's Sustiva(R) (efavirenz) and Gilead's Truvada(TM) (emtricitabine and tenofovir disoproxil fumarate) in the United States. If approved, the new product would be the first complete Highly Active Antiretroviral Therapy (HAART) treatment regimen for HIV available in a fixed-dose combination taken once daily. The joint venture established by the two companies is the first of its kind in the field of HIV therapy.
2000	Schering-Plough	Merck & Co., Inc	JV named Merck/Schering-Plough Pharmaceuticals: to develop and market in the United States new prescription medicines in cholesterol management. The collaboration includes worldwide markets (excluding Japan).

Source: Calculated from the information released in the company websites (news releases) and various annual reports

Table A.12. In-licensing by Mid-Pharma

Number of in-licensing undertaken 1990-2007

	In-licensing		*In-licensed category*			
Companies	*years*	*total number*	*compound*	*drug*	*patent*	*technology*
Abbott	2005-2006	5	1	0	2	2
Alcon	1993-2007	3	2	1	0	0
Allergan	2001-2002	2	1	1	0	0
Astellas	2005-2006	8	3	4	0	1
Bausch & Lomb	2005-2006	5	2	1	0	2
Baxter	2005-2007	4	0	2	0	2
Boehringer	1997-2006	14	6	3	0	5
Eisai	2004-2007	10	6	4	0	0
Forest	1998-2007	5	2	3	0	0
Gilead Sciences	1991-2007	12	10	2	0	0
Lundbeck	1999-2007	9	4	4	0	1
Merck KGaA*	2002-2006	3	1	2	0	0
Serono*	before 2006	9	4	4	0	1
Novo Nordisk	2006-2007	3	2	0	0	1
Schering Plough	2003-2007	11	6	4	0	1
Shire	1998-2007	9	1	4	2	2
Solvay	1997-2003	4	2	2	0	0
UCB	2006	4	1	2	1	0

** Serono's external sourcing relationships before Merck KGaA's acquisition in 2006.*
Figures for Merck KGaA represent Serono only after 2006.
Source: Calculated from the information released in the company websites (news releases) and various annual reports

Table A.13 Out-licensing by Mid-Pharma

Number of out-licensing undertaken 1990-2007

	Out-licensing		*Out-licensed category*		*Cross-licensing*		*Return of rights*	
Companies	*years*	*total number*	*compound*	*drug*	*years*	*total number*	*years*	*total number*
Abbott		0	0	0		0		0
Alcon	2007	1	0	1	2001	1		0
Allergan	2004-2005	4	0	4		0		0
Astellas		0	0	0		0		0
Bausch & Lomb		0	0	0		0		0
Baxter	2006	1	0	1	2003	1		0
Boehringer	1997-2003	4	1	3		0		0
Eisai	2006	2	2	0		0		0
Forest		0	0	0		0		0
Gilead Sciences	1996-2007	10	6	4		0		0
Lundbeck	1996-2004	5	1	4		0		0
Merck KGaA*	2001-2007	6	1	5		0	2004	1
Serono*		0	0	0		0		0
Novo Nordisk	2000-2007	5	5	0		0		0
Schering Plough	2007	1	0	0		0		0
Shire	1990-2007	7	2	5		0		0
Solvay	2002	1	0	1		0		0
UCB	2000-2006	2	2	0		0	2006	1

** Serono's external sourcing relationships before Merck KGaA's acquisition in 2006.*

Figures for Merck KGaA represent Serono only after 2006.

Source: Calculated from the information released in the company websites (news releases) and various annual reports

Table A.14 Patents by Mid Pharma

Assignee of the patent	2007	2006	2005	2004	2003	2002	2001	2000
Boehringer Ingelheim	17	21	72	104	196	271	305	479
Abbott Laboratories	2	10	34	70	93	147	236	633
Schering Plough (exc animal health)	0	0	0	0	1	2	1	5
Schering Plough	0	1	3	3	19	15	27	47
Baxter International	5	6	11	16	62	121	119	251
Astellas Pharma	0	1	17	28	40	52	51	52
Novo Nordisk	20	11	16	24	60	74	118	329
Eisai	4	9	12	24	37	80	97	185
Merck KGaA	0	0	0	1	0	1	5	2
Serono	5	10	17	10	17	18	33	46
Alcon	0	26	17	44	90	113	137	234
Solvay	0	2	7	19	22	26	34	36
Forest Laboratories	0	0	0	0	0	0	0	1
UCB	0	0	0	0	2	3	3	3
Allergan	0	3	17	59	88	116	173	303
Gilead Sciences	0	0	3	7	12	18	28	60
Bausch & Lomb	0	0	0	0	0	0	0	0
H. Lundbeck	0	3	11	12	14	48	55	73
Shire Biochem	0	1	1	2	2	8	7	6

Source: US Patent Office website, http://www.uspto.gov/patft/