

## Chapter 2

# Can Innovation Still Be the Main Growth Driver of the Pharmaceutical Industry?

Alexander Schuhmacher

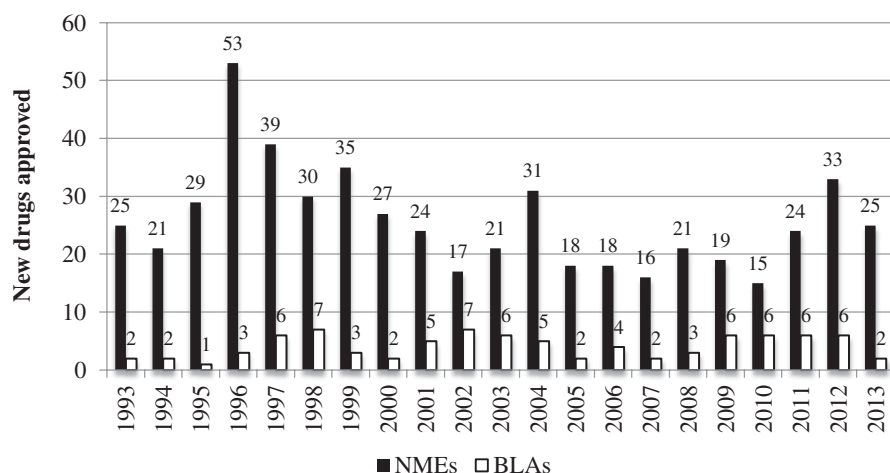
### Innovation as a Driver of Growth for the Pharmaceutical Industry in the Past

In the period from the 1950s to 2013, the American Food and Drug Administration (FDA) approved 1346 new molecular entities (NMEs) or new biologics entities (NBEs). On average, the approval rate was 20 NMEs per year. In the past 40 years, the number of new drugs launched into the market increased slightly from 15 NMEs in the 1970s to 25–30 NMEs since the 1990s (Munos 2009). The highest number of new drugs approved by FDA was in 1996 and 1997 (see Fig. 2.1), which might be related to the enactment of the Prescription Drug User Fee Act (PDUFA) in 1993 (Kaitin and DiMasi 2011).

It has been reported that in 2009 approximately 4300 pharmaceutical companies performed research and development (R&D) worldwide (Munos 2009). Compared to this figure, it is interesting to note that from 1950 to 2009 only 261 pharmaceutical companies have been successful in launching at least one new drug into the market (Munos 2009). Out of this group, only 12 % of the companies were in the pharmaceutical market for all 60 years (Munos 2009). The other organizations either failed, merged with a competitor, or were acquired. About 600 NMEs were launched by the companies that disappeared due to merger and acquisition (M&A; Munos 2009). Twenty-one pharmaceutical companies have launched 50 % of all new drugs until today, whereby 360 NMEs have been produced by nine pharmaceutical companies that have existed since 1950 (Munos 2009). Out of this group, Merck & Co. (www.merck.com), Eli Lilly (www.lilly.com), and Roche (www.roche.com) have been the most successful companies worldwide so far (Munos 2009). The fact that some companies were able to survive over a period of six decades shows that the health-care sector has provided a basis for the sustainable growth of pharmaceutical

---

A. Schuhmacher (✉)  
Reutlingen University, Reutlingen, Germany  
e-mail: alexander.schuhmacher@reutlingen-university.de



**Fig. 2.1** New drugs approved by FDA between 1993 and 2013. (Data derived from Hughes 2009; Munos 2009; Mullard 2012b, 2014b; www.fda.org); NMEs new molecular entities, BLAs biologic license applications, FDA Food and Drug Administration

companies up to this point. But is there also ground for future growth and sustainability for pharmaceutical companies in the future?

## The Pharmaceutical Industry Today

### *The R&D Investments of Top Pharmaceutical Companies*

Today, the multinational pharmaceutical companies that perform R&D come from the traditional, main pharmaceutical markets, namely the USA, Europe, and Japan. Of the 15 companies listed in Table 2.1, seven companies are based in the USA, two in Japan, and six in Europe. None of these major players in the pharmaceutical industry come from emerging countries such as China, India, Russia, Brazil, or South Africa.

The pharmaceutical sector is still polypolic. The top 15 pharmaceutical companies have a combined market share of 51.8%. Today's leading pharmaceutical company worldwide is the Swiss Novartis with total group sales of US\$ 50.8 billion in 2012. Its R&D investments have been enormous in recent years with the totals of US\$ 8–9 billion annually (see Table 2.2).

On average, the top pharmaceutical companies have invested 15–20% of their total sales into R&D in the past years, which has translated into R&D costs of more than US\$ 5 billion annually (see Table 2.3). The overall average R&D rate of

**Table 2.1** Top pharmaceutical companies ranked in accordance with their total pharmaceutical sales in 2012. Not included are revenues generated by nonpharmaceutical activities

Rank	Company	Headquarter (city, country)	Total sales (USD billion, 2012)	Market share (%)
1	Novartis	Basel, CH	50.8	5.9
2	Pfizer	New York, USA	46.9	5.5
3	Merck & Co.	Whitehouse Station, USA	40.2	4.7
4	Sanofi	Paris, FR	37.7	4.4
5	Roche	Basel, CH	34.8	4.1
6	GlaxoSmithKline	Brentford, GB	32.7	3.8
7	AstraZeneca	London, GB	32.0	3.7
8	Johnson & Johnson	New Brunswick, USA	27.9	3.3
9	Abbott	North Chicago, USA	26.8	3.1
10	Teva	Petach Tikwa, IS	24.8	2.9
11	Eli Lilly	Indianapolis, USA	21.9	2.6
12	Amgen	Thousand Oaks, USA	17.2	2.0
13	Boehringer Ingelheim	Ingelheim, DE	17.1	2.0
14	Bayer	Leverkusen, DE	16.2	1.9
15	Takeda	Osaka, JP	15.9	1.9

USD US Dollars

the pharmaceutical and biotechnology industry has been described to be 14.4 % in 2012 (European Commission 2013). Companies such as Novartis, Pfizer, Roche, and Sanofi have even invested more than US\$ 8 billion per year showing the importance of R&D as a major driver of growth in the industry.

According to the European Commission, 15 of the top 50 companies that invest most in R&D worldwide are pharmaceutical companies (European Commission 2013). Thus, the pharmaceutical branch is one of the top investors in R&D worldwide. Roche (6), Novartis (7), Merck & Co. (8), Johnson & Johnson (9), and Pfizer (10) are within the top ten of the world leading R&D investors (European Commission 2013).

In total, the pharmaceutical industry is the sector that invests most in R&D worldwide. The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) reported that in 2010 the pharmaceutical and biotechnology industries had R&D investments of more than US\$ 85 billion (IFPMA 2012) with US\$ 48.5 billion R&D investments reported by Pharmaceutical Research and Manufacturers of America (PhRMA) members (PhRMA 2013).

Resulting from increasing R&D expenditures during the years 2005–2012, the European Commission reported an investment in R&D of up to US\$ 100 billion

**Table 2.2** R&D investments and R&D rate of Novartis (2001–2013). R&D rate is the relative proportion of R&D costs to total sales per year

Year	Novartis		
	Total sales (USD million)	R&D costs (USD million)	R&D rate (%)
2001	32.038	4.189	13.1
2002	20.877	2.843	13.6
2003	24.864	3.765	15.1
2004	28.247	4.207	14.9
2005	29.400	4.800	16.3
2006	34.400	5.300	15.4
2007	38.100	6.400	16.8
2008	41.500	7.200	17.3
2009	44.300	7.300	16.5
2010	50.600	8.100	16.0
2011	58.600	9.200	15.7
2012	56.700	9.100	16.0
2013	57.900	9.600	16.6

USD US Dollars

worldwide for the pharmaceutical and biotechnology sectors in 2012 (European Commission 2013). In the same report, the analysis showed that most of the multinational pharmaceutical companies have invested significantly more in R&D during the period between 2005 and 2012 (see Table 2.4; European Commission 2013).

The huge amounts pharmaceutical companies are spending in new drug R&D and the enormous total R&D investments of the whole industry have put pressure on the return on R&D investment and brought the sustainability of pharmaceutical R&D in question if the output, namely the number of new drugs launched, is not comparably high.

### *The Output of Pharmaceutical R&D*

In the past 12 years, Novartis ([www.novartis.com](http://www.novartis.com)), Pfizer ([www.Pfizer.com](http://www.Pfizer.com)), and GlaxoSmithKline ([www.gsk.com](http://www.gsk.com)) have been the most successful pharmaceutical companies, as they launched 16, 13, and 12 new drugs into the market, respectively. Figure 2.2 summarizes the number of NMEs from the most efficient pharmaceutical companies that have been approved by the FDA over the period of 2001–2012.

The statistics of new drugs launched into the market in Fig. 2.2 include the NMEs per company that have been generated from internal sources and also the ones that come from external sources, such as licensing of drug candidates and acquiring new drugs by M&A. The total externally sourced pipeline of multinational pharmaceutical companies has been analyzed to be sourced on average by 50% (29–80%)

**Table 2.3** Key R&D figures of the top pharmaceutical companies

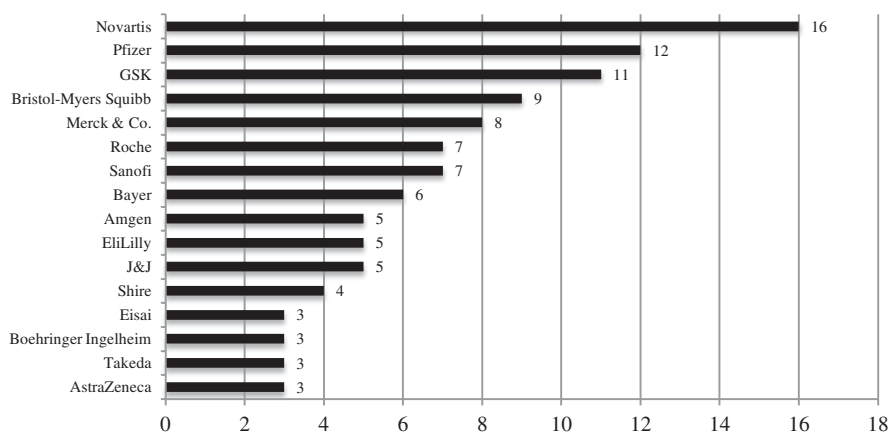
Year	AstraZeneca		GSK	Merck & Co.		Pfizer		Roche		Sanofi	
	R&D costs (USD million)	R&D rate (%)	R&D costs (BP million)	R&D rate (%)	R&D costs (USD million)	R&D rate (%)	R&D costs (USD million)	R&D costs (CHF million)	R&D rate (%)	R&D costs (EUR million)	R&D rate (%)
2005	3379	14.1	3136	14.5	3848	17.5	7256	5705	15.3	4044	14.8
2006	3902	14.7	3457	14.9	4783	21.1	7599	7365	15.7	4430	15.6
2007	5089	21.6	3327	14.6	4883	20.2	8089	8385	16.7	4537	16.2
2008	5179	16.4	3681	15.1	4805	20.1	7945	8845	16.5	4150	16.8
2009	4409	13.4	4106	14.5	5845	21.3	7845	9874	15.7	4091	15.8
2010	5318	16.0	4457	15.7	11,111	24.2	9413	9050	13.9	3884	14.6
2011	5523	16.4	3687	13.5	8467	17.6	8681	8073	14.2	4101	14.7
2012	5243	18.7	3979	15.1	8168	17.3	7482	8475	13.7	4905	14.0
2013	4821	18.8	3923	14.8	7503	17.0	6678	8700	12.9	4770	14.5

GSK GlaxoSmithKline, CHF Swiss Franks, BP British Pounds, USD US Dollars, EUR Euros, R&D research and development

**Table 2.4** Top ten pharmaceutical companies and R&D investments in 2005 and 7 years later (European Commission 2013)

Company	R&D costs (2012/2005, %)
Pfizer	−9%
Johnson & Johnson	+9%
GSK	−7%
Novartis	+69%
Sanofi	+21%
Roche	+91%
Merck & Co.	+84%
Eli Lilly	+56%
Boehringer Ingelheim	+106%
Takeda	+180%

R&D research and development



**Fig. 2.2** New molecular entities (NMEs) approved by Food and Drug Administration (FDA) between 2001 and 2012 by major pharmaceutical companies (data derived from Frantz and Smith 2003; Frantz 2004, 2006; Owens 2007; Hughes 2008, 2009, 2010; Mullard 2011, 2012b, 2013, 2014a; <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/NDAandBLAApprovalReports/ucm373420.htm>). GSK GlaxoSmithKline, J&J Johnson & Johnson

from external sources (Schuhmacher et al. 2013); 25% of the drug candidates have been licensed and the other 25% were acquired from outside of the companies (Schuhmacher et al. 2013). Analyzing the sources of new drugs of three of the multinational pharmaceutical companies, namely Pfizer, Roche, and Sanofi, it becomes apparent that M&A activities have played a major role in the number of new drugs launched. For example, ten NMEs have been approved by the FDA for Pfizer between 2001 and 2012. Two additional new drugs improve Pfizer's statistics directly, as two drugs had been registered for Pharmacia and Wyeth after the companies were

**Table 2.5** Number of NMEs approved by FDA in 2001–2012 for Pfizer, Roche, and Sanofi

Company	Pfizer	Phar- macia	Wyeth	Roche	Genen- tech	Sanofi	Aventis	Gen- zyme
Year of M&A		2003	2009		2009		2004	2011
Total number of NMEs approved by the FDA (2001–2012) per single company	10	2	4	3	5	6	1	4
2001	1	1						
2002	1					1		
2003		1		1		1		
2004	1				1		1	1
2005			1					
2006	1				1			1
2007	1		1	1				
2008	1		1					1
2009						1		
2010					1	1		1
2011	1		1	1				
2012	3				2	2		
Total number of NMEs approved by the FDA (2001–2012) since acqui- sition of peer companies	12			6		7		
Total number of NMEs approved by the FDA (2001–2012)	16			8		11		

*M&A* mergers and acquisitions, *NMEs* new molecular entities, *FDA* Food and Drug Administration

acquired by Pfizer in 2003 and 2009, respectively. And four additional new drugs could be added to Pfizer as these drugs have been approved for Pharmacia or Wyeth at least 4 years before the companies have been acquired (see Table 2.4) (Table 2.5).

The multinational pharmaceutical companies listed in Fig. 2.2 have launched on average 0.6 NMEs per year between 2001 and 2012, with Novartis and Pfizer launching 1.3 and 1.16 NMEs, respectively. These figures are far below the industry goal to produce 2–3 NMEs per year per company that has been reported as a need of pharmaceutical companies to meet their growth objectives (Kola and Landis 2004;

Preclinical research		Clinical development			FDA review	Launch
Drug discovery	Preclinical testing	Phase I	Phase II	Phase III		
>100,000 compounds screened and 5,000 – 10,000 compounds tested	250 compounds tested	5-10 compounds tested			1 approved drug	
IND Submitted		NDA submitted				
		Number of volunteers or patients				
		20-100	100-500	1,000-5,000		
		6-8 years				
3-6 years					0.5-2 years	

**Fig. 2.3** Traditional pharmaceutical R&D process, R&D phases, and principle timelines. IND investigational new drug, NDA new drug application, FDA food and drug administration, R&D research and development

Munos 2009). Assuming a growth target of 5% per year, a pharmaceutical company with total sales of US\$ 15 billion would need to deliver 2.5–3 NMEs per year over a period of 10 years to meet this target (Kola and Landis 2004). A bigger pharmaceutical company of the size of Pfizer with total pharmaceutical sales of US\$ 45 billion would need to launch 7.5–9 NMEs per year, if expecting to generate a growth of 5% per year through pharmaceutical innovation (Kola and Landis 2004). None of the pharmaceutical companies have achieved this goal in the past years, bringing into question the dogma, that the main driver of growth in the pharmaceutical industry is innovation.

## The Pharmaceutical Innovation Process

The pharmaceutical R&D process is highly regulated, lengthy, and risky. Traditionally, the process of discovering and developing a new drug is divided into preclinical research and clinical development, followed by a review and launch phase (see Fig. 2.3).

### *The Success Rates of Pharmaceutical R&D*

As indicated in Fig. 2.3, pharmaceutical R&D has a low probability of success (PoS). Only one out of more than 100,000 compounds that have been screened



in discovery research and, thereof, 10,000 compounds that have been tested during preclinical research make it to the market. In total, the probability of discovering, developing, and registering an NME has been estimated to be around 4% (Paul et al. 2010; also see 2013 CMR International Pharmaceutical R&D Factbook, <http://cmr-thomsonreuters.com/pdf/fb-exec-2013.pdf>). Table 2.6 summarizes some articles and highlights the probabilities per phase of drug R&D.

CMR reported for the preclinical phase, Phase I and Phase II of clinical development, success rates per phase of 67, 46, and 19%, respectively (2013 CMR International Pharmaceutical R&D Factbook, <http://cmr-thomsonreuters.com/pdf/fb-exec-2013.pdf>). In particular, the low PoS for the early clinical phases represents the goal that potentially unsuccessful compounds should fail early and inexpensively.

The underlying causes of the high attrition rates are manifold. Differences may depend on the drug class, the therapeutic area, the type of disease, the source of the drug candidate, and the size of the company. It has been reported that adverse pharmacokinetics and bioavailability were a major cause of attrition in the 1990s (Kola and Landis 2004). In the same opinion letter, it was stated that the lack of efficacy and safety were the major reasons for the low PoS in clinical development in 2000. In an analysis of ten big pharmaceutical companies in the period of 1991–2000, the reasons for attritions have been analyzed as being primarily efficacy and safety issues (Kola and Landis 2004).

In a review of the FDA approvals in 2012, it was reported that most of the failures in Phase II and Phase III resulted from the lack of efficacy (56%), followed by safety (28%) (Arrowsmith and Miller 2013). The lack of efficacy may be related in some therapeutic areas, such as oncology and central nervous system (CNS), with a lack of predictive animal models in the discovery research and the preclinical testing phases (Kola and Landis 2004). Today, the majority of drugs in the development refer to novel targets making drug development less predictable and, thus, less successful (Berggren et al. 2012). Biologics showed a higher PoS from Phase I to submission than small molecule drugs (SMOLs; DiMasi et al. 2010). The PoS of drugs that addressed acute diseases was also higher than the PoS of drugs treating chronic diseases (Pammolli et al. 2011). Furthermore, it could be shown that in-licensed drug candidates have a higher PoS for Phase I to submission than self-originated drugs (DiMasi et al. 2010) (Fig. 2.4). Finally, the size of a company may also have an impact on the attrition rates. While large organizations have a mean PoS of 7.86% from Phase I to submission, small organizations have a PoS of 6.07% (Pammolli et al. 2011). In the same context, biotechnology organizations seem to have lower success rates in clinical development than nonbiotechnology companies (Pammolli et al. 2011).

Further reasons for the low PoS of pharmaceutical R&D may be founded in:

- An advanced complexity of drug targets
- The higher proportion of novel drug targets
- The competition in target selection, as half of the drug targets are pursued by two or more pharmaceutical companies (Agarwal 2013)
- The complex process of target validation (Sams-Dodd 2005)

**Table 2.6** Success rates per phase of pharmaceutical R&D

Period	Literature	Phase: PoS
2003	DiMasi et al. (2003)	Probability for entering phase (%) starting with Phase I: Phase I: 100.0 % Phase II: 71.0 % Phase III: 31.4 %
2006	DiMasi JA. J Health Econ. 2006;10:107–42	Probability for entering phase (%) starting with Phase I: Phase I: 100.0 % Phase II: 75.0 % Phase III: 36.2 %
2010	DiMasi et al. (2010)	Probability for submitting a new drug: Phase I to submission (total): 19 % Phase I to submission (biologics): 32 % Phase I to submission (SMOLs): 13 %
2010	Paul et al. (2010)	Probability per phase: Preclinical to registration: 4.1 % Target to hit: 80 % Hit to lead: 75 % Lead optimization: 85 % Total discovery research: 51 % Preclinical testing: 69 % Phase I: 54 % Phase II: 34 % Phase III: 70 % Submission to launch: 91 %
2011	Pammolli et al. (2011)	Average success rates: PoS for acute diseases: 8.77 % PoS for chronic diseases: 6.88 % PoS of small organizations: 6.07 % PoS of large organizations: 7.49 % PoS of biotech: 5.14 % PoS of nonbiotech: 7.86 %
2012	Berggren et al. (2012)	Probability of clinical development (including review and launch): Phase I to launch (total): 8.3 % Phase I to launch (SMOLs): 7 % Phase I to launch (biologics): 12 %
2013	2013 CMR International Pharmaceutical R&D Factbook ( <a href="http://cmr.thomsonreuters.com/pdf/fb-exec-2013.pdf">http://cmr.thomsonreuters.com/pdf/fb-exec-2013.pdf</a> )	Probability per phase: Preclinical: 67 % Phase I: 46 % Phase II: 19 % Phase III: 77 % Registration: 90

*SMOLs* small molecule compounds, *NCEs* new chemical entities, *NBEs* new biological entities, *R&D* research and development, *PoS* probability of success. *CMR* Center for Medicine Research International

Sustainable Development for the Healthcare Industry

Reprogramming the Healthcare Value Chain

Morgon, P.A. (Ed.)

2015, X, 154 p. 14 illus., 8 illus. in color., Hardcover

ISBN: 978-3-319-12525-1