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Restructuring the Pharmaceutical Industry

Global Corporate Advisory Americas
(1-212-282-3669)

Tim Wang, CFA
Timxin.wang@mizuhocbus.com

<Summary>

☐ Pressured by the tough environment, the global pharmaceutical industry has been going through a transformation over the last decade. In this report we examine how the industry has evolved and point to some successful strategies for the future.

☐ First the industry has relentlessly taken the cost out of the system by internal restructuring or through mergers. Pfizer is leading the industry in terms of cost cutting. We believe Pfizer serves as the low-cost benchmark for the industry. Some big pharma still have some way to go to shrink their expenses.

☐ Another important strategic decision for pharma is how they allocation capital. In recent years, several big pharma have aggressively used free cash flow to repurchase company shares. Such buybacks have boosted share prices of these companies in the short run but its long-term impact is uncertain. Going forward, the amount of buyback is likely to decline. Companies will again shift resources to business development deals.

☐ Big pharma have also sharpened their R&D and commercial focus. The current landscape calls for companies to have true leadership in innovation and commercial excellence. Many pharma have narrowed their business focuses and pooled assets to create category leaders. By mapping out each company's therapeutic focuses, we found many pharma are drawn to similar therapeutic. This herd mentality could lead to lower return on investment in hot spaces, and to create better return opportunities in neglected areas.

☐ Pharma companies should utilize either an innovation leadership strategy whereby the organization is intensely focused on scientific innovation or adopt a specialty pharma mindset by going after neglected diseases. As a part of the new innovation fabric, big pharma have switched to an open innovation system that is built on networks. With its FIPNet model, Lilly is the pioneer in this. Pharma should separate R from D and externalize early research. Pharma should be actively engaged in the creation of new ventures from academia. Pharma should also learn from Celgene for aggressively capturing external innovations early.

☐ We regard the current biopharma M&A environment as challenging. Valuation for biotech assets is generally expensive. This argues for going after innovations before the PoC inflection point. Big pharma are indeed doing more early-stage deals. However, Good opportunities do exist in some neglected areas.

EXECUTIVE SUMMARY

- The pharmaceutical industry is going through a period of significant changes. We are witnessing significant M&A deal activity and aggressive tactics. In this report, we review how the pharma industry has evolved to the current state and where they are headed. We also try to infer some good practices for the industry.
- Over the last decade, a significant amount of cost has been taken out of the pharmaceutical industry. Pharma companies either cut cost on a stand-alone basis or more aggressively through mergers. The pharma industry has pursued savings through all expense lines – COGS, SG&A and R&D. Pfizer is leading the industry in terms of downsizing its cost structure. Probably its cost structure can serve as a low-end benchmark of the industry. In comparison to Pfizer, other big pharma firms have some way to go in terms of cost-cutting potential. Big pharma has also been shedding non-core, adjacent businesses to concentrate on the main pharma business. This focused pharma strategy has also played out for conglomerates such as Abbott and Baxter.
- Another important decision for the industry is how it allocates capital. It is a tricky act to balance shareholder return with reinvestment in the business. With a ratio of around 50%, dividend payout has been relatively stable for the industry. Over the recent period, some major pharma companies such as Pfizer, BMS and AZ, have been aggressively buying back shares. But with shares becoming expensive and the increasing need for reinvesting in the business, some companies are significantly curtailing share buybacks. Going forward, we will see more free cash flow going to business developments and internal pipelines.
- Pharma R&D has also been considerably redesigned. The current environment calls for focused leadership in narrowly defined diseases. Therefore even big pharma cannot afford to spread its R&D too thin. By looking at overlaps in prioritized TAs, we found big pharma firms are often drawn to the same areas because of their similar investment criteria. This crowding will lower the investment return for the participants. We believe pharma companies should take a hard look at their chosen TAs to see if they have the resources to become a leader. If the answer is no, they should shift the focus to less crowded areas.
- We believe there are several types of successful competitive strategies. For most innovative pharma, they should adopt an intense innovation-driven business model, in which science is put at the center of organization. It helps if these companies have visionary scientists at the helm who truly understand science and are not afraid to make long-term, risky bets. On the other end of the spectrum, the specialty pharma model based on neglected therapeutic areas such as GI, dermatology, women's health, etc. will continue to do well. Big pharma can learn from leading specialty pharma companies such as Valeant and Actavis.
- M&A will always serve as a critical lever to achieve strategic goals. One good deal can boost a company significantly. There were indeed quite a number of very successful deals over recent years. But acquiring premium biotech asset requires internal expertise as well as luck. In addition, the run-up in biotech valuation has made attractive assets prohibitively expensive. Therefore, M&A cannot be counted on as an escape route for pharma companies. We view the current M&A environment as challenging. But there are some good opportunities in neglected areas. For specialty pharma firms, M&A has been bread-and-butter in their strategy. Their motivation can be more financial-driven than strategic-driven. Therefore, they have more leeway to make M&A deals work.
- Another hot topic in pharma R&D is the open innovation model adopted by big pharma. Eli Lilly is the pioneer in adopting its FIPNet model. We believe pharma should separate R and D by allocating resources for early discovery research from external sources. Pharma can also utilize external capital to develop its pipeline. Through these endeavors, pharma can spread the risk and cost while tapping into a broader market for innovation. Pharma should be more engaged in actively creating new innovations from academic labs and young biotechs. The old game of waiting for PoC before jumping in has become too expensive. Celgene is a good example of aggressively capturing early innovations.
- Overall, we found the pharma industry had successfully weathered the patent cliff. Some companies are poised for growth. However, pharma business needs to be reconfigured to position for the future. There are a number of best breed examples for the industry to reference. If the industry can successfully adapt, the next ten years should be better than the last ten years.

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I. Introduction

The global pharmaceutical industry is facing pressure from multiple fronts, including patent expiries, poor R&D productivity, payer pushbacks, tough regulatory oversight, etc. But pharmaceutical is not a declining industry. According to IMS Health, the global pharmaceutical market was worth $962bn in 2012 and is expected to grow at 5.3% CAGR to reach $1.25 trillion in 2017. Therefore as a whole the market has decent growth prospects. Pharmaceutical companies have responded to the business environment by cutting costs, adopting a more flexible and focused R&D structure, and repositioning their businesses to high growth areas such as specialty drugs and emerging markets. In this paper, we review how pharma companies have been restructuring their businesses to cope with the challenges, and identify some promising strategies going forward.

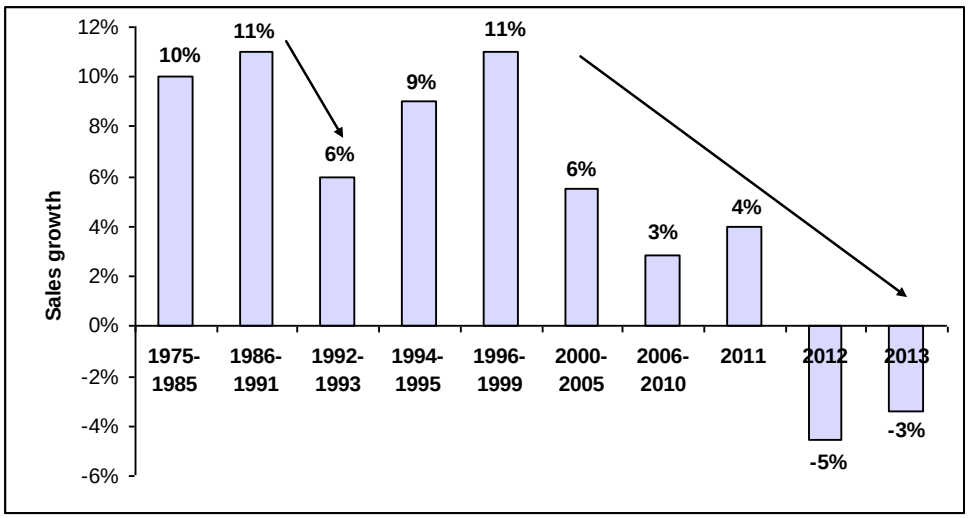
II. Overview of Pharmaceutical Industry Restructuring

The pharmaceutical industry is fundamentally driven by top-line growth, which is fueled by product innovation. The same holds true for any individual pharma company. For a turnaround situation (e.g., the successful turnaround of Schering-Plough), the priority is to get the topline growing again. A pharma company with a growing topline is in a very healthy position. Conversely, falling revenues will expose the bloated cost structure and lead to painful belt-tightening. However, top-line growth is often not within the immediate control of management. The in-line portfolio is more or less fixed, and it takes years of investment and a lot of luck to get a good pipeline. Therefore, pharma executives often resort to cost-cutting to alleviate the hit to earnings from a declining topline. If the topline pressure is too great to be managed with internal cost-cutting alone, big pharma firms sometimes pursue mergers to better absorb the hit. We have seen this old pharma playbook played out in recent years just as in the early 1990s.

A. The Shallow Restructuring in the Early 1990s

As shown in Figure 1, the US pharmaceutical industry faced slowing sales growth in the 1992-1993 period. During that time, many US pharma firms undertook cost-cutting efforts. Another consequence of that tough period was the ensuing pharma mergers. As shown in Table 1, several pharmaceutical companies merged in the mid. 1990s to cope with the top-line pressure. However the soft revenue patch was short-lived as big pharma recovered to see robust growth for the next ten years (see Figure 1). This golden age of the pharmaceutical industry was driven by the overwhelming success of the blockbuster model, with products targeting mass-market indications generating huge sales that often surpassed the most optimistic projections. We have witnessed a more drastic decline in sales in recent years and the industry has taken more draconian cuts to absorb it. The question remains whether the pharma industry can embark on another golden era following these tough times. If so, specialty medicine is widely expected to be the primary driver for big pharma's growth.

Figure 1 Historical Sales Growth Trend of US-based Big Pharma



Source: Compiled by MHBK/IRD based on public company reports. Note: U.S. pharma industry includes Pfizer, Merck, Eli Lilly, Bristol-Myers Squibb, J&J and their pre-merger predecessors

B. Pharma Restructuring over the Last Decade

The hardship in the early 1990s was merely a blip compared to the sales decline and patent cliff over the last decade. The patent cliff combined with low R&D output has significantly depressed the pharmaceutical industry's growth profile. Sales have declined for the leading pharma companies for the last two years and the decline will persist in 2014.

In anticipation of the slowdown, big pharma started trimming costs in 2003. Initially big pharma firms approached cost-cutting at a very measured pace. For example, Schering-Plough, which was the worst hit pharma in 2003 due to the loss of patent exclusivity for Claritin, only trimmed its cost base slightly. As late as 2006, Pfizer was resisting cuts to its massive US sales force for fear of unilateral disarmament when in fact the old feet-on-the-street sales model was widely recognized as outdated. However, bad R&D news kept pouring in (see Table 23 and Table 24 in Appendix). The failure of torcetrapib and Exubera from Pfizer in 2006-2007 finally drove home the message that the old model was not justifiable. Subsequently big pharma started trimming its sales force in earnest. Big pharma also aggressively attacked manufacturing costs by closing sites and wringing out savings from procurements. However, until recently, big pharma CEOs had mostly spared R&D from cost-cutting for fear of killing the goose that lays the golden eggs.

In 2008, with the bad R&D news accumulating and the dreaded patent cliff drawing closer, it became clear to several big pharma CEOs that drastic action was needed. Hence, in early 2009, two mega mergers (Pfizer/Wyeth, Merck/Schering-Plough) took place that forever changed the industry line-up. Historically on average big pharma mergers led to ~25% reduction in target company's expenses (see Table 1). Both Pfizer and Merck exceeded this average by announcing synergies above 30% of target expense within two years of the mergers. Subsequently, these two companies have continuously cut the expense from the combined company.

Overall, big pharma reduced its headcount substantially between 2006 and 2013 (see Table 2). This headcount reduction is the most drastic for Pfizer and Merck. Basically these two companies eliminated the total headcounts from their acquired companies.

Big pharma M&As are becoming very active. As this report was being published, Pfizer had approached AstraZeneca for a takeover. Valeant had just made a hostile take-over bid to acquire Allergan for around $47bn. In its proposed deal, Valeant indicated its plan to cut 37% of combined expenses (30% of 2014 projected expenses), which amounts to 70% of the target company's expenses. This level of merger synergy is almost unprecedented in the pharma industry. The $2.7bn synergy is composed of $1.8bn cut in SG&A costs and $900mn cut in R&D expense. Allergan spent $2.2bn on SG&A and $977mn on R&D in 2013. So basically Valeant plans to cut 80-90% of Allergan's operating expense. Valeant plans to use tax inversion to lower Allergan's effective tax rate from 28% currently to a level closer to its own tax rate, which is less than 5%. The combined company is expected to start with a tax rate in the high-single digit range. With such enormous synergy and huge tax benefits, perhaps no big pharma can compete with a better offer.

Table 1 Historical Cost Synergies Associated with Big Pharma Mergers

Acquirer/Target	Announce. Date	Close. Date	Savings (US$ in MM)	Combined Sales	% Target Sales	Combined Expenses	% Target Expenses	Employee Reduction
Pfizer/AstraZeneca (Proposed)	Apr-14	TBD						
Valeant/Allergan (Proposed)	Apr-14	TBD	2,700	24%	48%	37%	70%	20%
Actavis/Forest Labs	Feb-14	TBD	1,000	8%	30%	9%	32%	
Valeant/Bausch+Lomb	May-13	Aug-13	850		26%		33%	
Takeda/Nycomed	May-11	Sep-11	300					
Sanofi-Aventis/Genzyme	Feb-11	Apr-11	700	2%	17%	2%	18%	
Teva/Cephalon	May-11	3Q11	500	3%	17%	4%	25%	
Valeant / Biovail	Jun-10	Sep-10	350	20%	43%	33%	56%	
Merck/Schering-Plough	Mar-09	Nov-09	5,000	11%	24%	15%	31%	~30%
Pfizer/Wyeth	Jan-09	Oct-09	6,000	8%	26%	13%	36%	~20%
Roche/Genentech	Jul-08	Mar-09	750-850	2%	7%	3%	12%	na
Schering-Plough / Organon Biosciences	Mar-07	End '07	500	3%	11%	4%	13%	na
UCB/Schwarz	Sep-06	End '06	375	9%	32%	10%	30%	na
Merck KGaA/Serono	Sep-06	Early '07	125	1%	5%	1%	6%	na
Bayer/Schering AG	Mar-06	Jun-06	840	2%	13%	2%	15%	na
Sanofi-Synthelabo/Aventis	Apr-04	Jul-04	2,000	6%	10%	9%	13%	na
Pfizer/Pharmacia	Jul-02	Apr-03	4,200	8%	28%	13%	39%	na
Bristol-Myers Squibb/DuPont Pharma	Jun-01	Oct-01	600	3%	38%	4%	41%	70%
Glaxo Wellcome/SmithKline	Jan-00	Dec-00	1,700	6%	13%	9%	17%	na
Pharmacia/Monsanto	Dec-99	Mar-00	600	4%	7%	4%	8%	na
Pfizer/Warner-Lambert	Nov-99	Jun-00	1,600	6%	12%	7%	15%	na
Hoechst/Rhone Poulenc (formed Aventis)	Dec-98	Nov-99	1,200	7%	15%	8%	17%	na
Astra/Zeneca	Dec-98	Apr-99	1,100	7%	15%	9%	20%	13%
Sanofi/Synthelabo	Dec-98	May-99	350	6%	17%	7%	21%	na
Ciba-Geigy/Sandoz (formed Novartis)	Mar-96	Dec-96	1,520	7%	na	8%	na	12%
Pharmacia/Upjohn	Aug-95	Nov-95	500	7%	na	9%	na	12%
Glaxo/Wellcome	Jan-95	May-95	1,250	12%	35%	18%	51%	12%
American Home*/American Cyanamid	Aug-94	Dec-94	650	5%	14%	6%	16%	10%
Roche/Syntex	May-94	Nov-94	825	5%	39%	6%	49%	11%
Hoechst/Marion Merrell Dow	Feb-95	Jul-95	750	9%	25%	11%	30%	18%
Bristol-Myers/Squibb	Jul-89	Oct-89	500	6%	19%	7%	25%	10%
SmithKline/Beecham	Mar-89	Jul-89	400	6%	na	na	na	na
Mean				7%	22%	10%	27%	19%
Median				6%	17%	8%	25%	12%

Source: Compiled by MHBK/IRD based on public company reports. Note 1: expense represents the total expense (COGS, SG&A and R&D). Note 2: The percentage of headcount reduction is based on announcements within two years of merger. Sometimes companies announce significant further cut in headcounts several years after merger, which is not captured in the table above.

Table 2 Headcount Reduction by Big Pharma

	Year End 2005	Year End 2013	Goal	% Reduction
Pfizer	98,704	77,700		-49%
Wyeth	53,000			
Merck	63,000	76,000	64800	-43%
Schering-Plough	~31500			
Organon	~20000			
Eli Lilly	44,500	37,925		-15%
Bristol-Myers Squibb	43,000	24,000		-44%
AstraZeneca	64,000	51,500		-20%
GSK	100,019	99,451		-1%
Sanofi	96,400	112,128		16%
Roche	65,000	85,050		31%
Novartis	47,325	135,696		187%

Source: Compiled by MHBK/IRD based on public company reports. Note: the substantial increases in headcounts for Novartis, Roche and Sanofi were due to large acquisitions.

C. Where do Big Pharma Stand Currently on the Cost Curve

The structure of pharmaceutical industry's P&L is a reflection of the industry's evolution. As the industry's fundamentals worsened, the operating margin first declined (Table 3). Gross margins were hit hard by the patent expiries of high-margin blockbuster drugs. To compensate for the gross margin erosion, big pharma cut SG&A and R&D expenses. So overtime the operating margin recovered to pre-crisis level.

What is the optimal margin structure for the industry? There shouldn't be a fixed target for each expense line. The size of each expense line should be dictated by the condition of the industry and specific situation of each company. Gross margin is heavily influenced by product mix and is a constant tug-of-war between margin erosions due to big patent expiries and savings from manufacturing expenses. SG&A expense has declined substantially in recent years for good reasons. In the developed market, payer's influenced has been rising whereas doctors' influence has been waning, which justifies a smaller sales force. On the R&D side, the situation is mixed. A company with a large and attractive pipeline should invest a bigger sum in pipeline than a similar sized company with a poor pipeline. A company with traditionally poor R&D productivity should cut internal R&D spending and buy innovations from outside. Therefore there are no hard and fast rules on how much each company should spend on R&D. As shown in Table 3, Pharma industry used to spend much less on R&D in the 1980s. But with advent of the genomic revolution and high throughput screening, the R&D expense has grown significantly. However as the R&D productivity fell, the massive spending in R&D hasn't proven to be the solution. So big pharma have been focusing their R&D in therapeutic areas where they give the highest priority. Big pharma's R&D budget cannot be spread too thin. So this sharpening of focus has led to some reduction in R&D spending.

We believe of the major pharma companies, Pfizer is the trend-setter in terms of cost-cutting. Pfizer was the pharma company that has had the most drastic cut to all expense lines. After several rounds of cost cutting, Pfizer has indicated it is at the late inning of cost cutting, i.e., its cost structure has mostly bottomed. Therefore, Pfizer's cost structure probably can be considered low-end benchmark for the industry.

Table 3 Margin Trends for U.S. Pharma Industry Compared to Pfizer

Margin Analysis	1975	1985	1990	1995	2000	2005	2006	2007	2008	2009	2010	2011	2012	2013
Gross Margin%	56.1%	60.7%	68.6%	72.0%	77.7%	75.8%	75.8%	75.1%	75.1%	75.1%	72.9%	73.0%	73.0%	72.2%
SG&A% of Sales	33.4%	35.6%	37.5%	36.7%	35.4%	33.4%	33.1%	32.9%	31.6%	30.5%	29.0%	29.5%	29.0%	28.9%
R&D% of Sales	4.7%	7.6%	9.3%	10.7%	13.2%	14.8%	16.0%	16.0%	15.6%	15.8%	15.2%	14.4%	14.9%	15.1%
Operating Margin	18.0%	17.5%	21.9%	24.7%	29.1%	27.7%	26.7%	26.3%	27.8%	28.8%	28.6%	29.1%	29.1%	28.2%
Pfizer Margins														
Gross Margin%				78.4%	82.9%	83.8%	85.0%	83.6%	83.8%	83.2%	78.4%	79.7%	81.3%	82.1%
SG&A% of Sales				38.5%	38.2%	32.8%	31.7%	31.4%	29.2%	29.5%	28.8%	28.7%	27.6%	27.5%
R&D% of Sales				14.4%	15.1%	14.4%	15.3%	15.6%	15.6%	15.7%	14.5%	12.9%	12.4%	12.7%
Operating Margin				25.5%	29.6%	36.5%	37.9%	36.6%	39.0%	38.0%	35.2%	38.1%	41.3%	41.9%

Source: Compiled by MHBK/IRD based on public company reports. Note: this industry composite includes U.S. based big pharma companies Pfizer, Merck, J&J, Eli Lilly and J&J (with their pre-merger predecessors).

1. Backdrop of Revenue Growth

Discussion of cost structure has to begin with the backdrop of revenue growth. As shown in Table 4, different pharma companies have fared very differently going through the patent expirations in recent years. Some companies only experienced modest softness in sales going through the 2012 patent cliff, whereas others will experience sales declines three years in a row. Companies that had a modest sales hit can rely on continuous productivity improvement rather than drastic cuts in spending.

Table 4 Revenue Growth Trend of Major Pharma Companies

Sales growth	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014E
AZN	14%	12%	11%	12%	7%	4%	1%	1%	-17%	-8%	-10%
SWX:NOVN	9%	9%	18%	11%	9%	6%	14%	1%	-3%	2%	3%
Alcon	15%	12%	12%	14%	12%	3%	10%				
LSE:GSK	-5%	8%	7%	-2%	7%	16%	0%	-4%	-3%	0%	-3%
ENXTPA:SAN	95%	81%	3%	-1%	-1%	8%	9%	3%	3%	-7%	-6%
SWX:ROG	0%	19%	18%	11%	-1%	7%	-4%	-10%	8%	2%	1%
Total EU Pharma Sales	**17%**	**22%**	**11%**	**11%**	**6%**	**3%**	**5%**	**2%**	**-5%**	**-1%**	**-2%**
BMY	5%	-1%	-17%	-4%	13%	6%	4%	9%	-17%	-7%	-12%
JNJ	13%	7%	6%	15%	4%	-3%	-1%	6%	3%	6%	10%
LLY	10%	6%	7%	19%	9%	7%	6%	5%	-7%	2%	-13%
MRK	2%	-4%	3%	7%	-1%	-3%	12%	4%	-2%	-7%	-9%
Schering-Plough	3%	20%	2%	20%	46%						
PFE	6%	-2%	-6%	0%	0%	-15%	8%	0%	-10%	-13%	-15%
Wyeth	10%	8%	9%	10%	2%						
Total US Pharma Sales	**8%**	**3%**	**0%**	**8%**	**6%**	**-5%**	**6%**	**4%**	**-5%**	**-3%**	**-5%**
Total Global Pharma Sales	**11%**	**11%**	**5%**	**10%**	**6%**	**-1%**	**5%**	**3%**	**-5%**	**-2%**	**-3%**

Source: Compiled by MHBK/IRD based on data from Capital IQ

2. R&D Expense

Big pharma CEOs are often loath to cut R&D expense as they want to invest for the long-term success of the company. On average, big pharma has kept its R&D spending relatively flat in recent years (see Table 5).

However, some big pharma firms have significantly cut R&D expenses post big mergers. Following the big mergers in 2009, as shown in Table5, Merck and Pfizer initially chose different paths in R&D spending. Pfizer dramatically cut R&D spending from $11bn premerger ($7.6bn from Pfizer and $3.4bn from Wyeth) to $6.55bn in 2013, which is even lower than Pfizer's standalone R&D spending. In contrast, Merck CEO defended the R&D spending after the merger in 2009. However, after some disappointments in major late-stage compounds, last October Merck announced a cost cutting program of $2.5bn to be realized before year 2015. Half of the savings will come from R&D. With this cut, Merck's R&D/sales ratio will decline from 17-18% of sales to about 15%. Although Pfizer's big cut in R&D spending didn't have a notable impact on its near-term pipeline, it is likely to have dealt a big blow to the early-mid stage portfolio. Pfizer's recent bid for AstraZeneca to get AZ's attractive pipeline can be considered a form of "catch-up" spending in R&D.

Comparing Table 7 and Table 8 suggests big pharma firms' new molecular entity (NME) portfolios have stayed relatively flat over the last seven years. However the NMEs are distributed very unevenly. We have seen substantially intra-company variability from 2007 to 2014. Mega pharma companies (Pfizer, GSK, Sanofi, Merck), especially those that have gone through mergers, have seen their NMEs decline substantially. But mid-sized biopharma companies (e.g., AZ, Lilly, and BMY) or more innovation-focused biopharma companies (Roche and Novartis) have seen their NME numbers rise (see Figure 2). So at this time pharma industry's R&D is feast or famine depending on which company it is.

The huge drop in NME number is especially pronounced for Pfizer. In 2007 Pfizer combined with Wyeth had 138 NMEs in various stages of clinical development. Currently, Pfizer only has 63. Therefore Pfizer has shrunk its pipeline by over half. It is questionable if a big pharma can sustain long-term on this portfolio without significant downsizing or major acquisitions. The proposed AZ merger will address this problem. The rationale for this business model is that if mega pharma such as Pfizer cannot do productive in-house research, it should just buy from outside.

However, mid-cap pharma or more focused pharma companies have seen their NME pipeline booming. Mid-cap pharma companies have often resisted cutting to R&D expenditures. For example, Eli Lilly has opted to keep its R&D expense relatively flat through its patent expiries (which the company calls year YZ). Lilly management pointed to some R&D underinvestment following the Prozac patent expiry in 2001, which contributed to some weakness later on in its pipeline. Lilly is spending over 24% of sales on R&D, which is the highest in the peer group (see Table 7). Lilly has dramatically replenished its mid-late stage pipeline in recent years. Currently Lilly has 33 compounds in phase II/III/registration, which is markedly higher than 16 in 2007 and only 7 in late 2004. Of the big pharma peers, Eli Lilly has dealt with its cost structure most lightly. Its headcount only declined 15% from 2005-2013 (see Table 2), with substantial numbers shed through divestitures to CROs and attritions. For 2014, facing the patent expiries of two blockbuster drugs, Lilly is finally projecting a substantial decrease in R&D spending (down 15-20%).The poor R&D productivity at some of the bigger pharma companies is sometimes blamed on disruptions from mergers and layoffs. Lilly has maintained its independence, which has contributed to better R&D productivity. Besides Lilly, BMS is also a heavy spender on R&D. However this could be a virtuous cycle as BMS is viewed as having one of the best pipelines in the industry. BMS spent ~23% of sales on R&D in 2013 (see Table 7).

Table 5 R&D Growth Trend of Major Pharma Companies

R&D growth	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014E
AZN	15%	-3%	15%	28%	-2%	-13%	-3%	10%	-5%	0%	
NVS	11%	8%	19%	21%	7%	7%	11%	5%	-1%	6%	
Alcon	12%	8%	21%	10%	10%	6%	13%				
GSK	1%	8%	10%	-6%	8%	13%	-3%	5%	-11%	-1%	
Sanofi	82%	69%	10%	2%	1%	1%	-2%	5%	2%	-3%	Slight increase
Roche	8%	10%	28%	14%	5%	10%	-5%	-11%	5%	7%	
Total EU Pharma R&D Expense	**21%**	**16%**	**16%**	**15%**	**6%**	**0%**	**1%**	**6%**	**-4%**	**3%**	
US											
BMY	12%	10%	10%	2%	6%	4%	4%	5%	2%	1%	
JNJ	14%	18%	13%	8%	-1%	-8%	-2%	10%	2%	7%	
LLY	19%	8%	3%	11%	10%	13%	13%	3%	5%	5%	(20%) - (15%)
MRK	23%	-5%	4%	15%	3%	0%	1%	-6%	2%	-10%	Below 2013
Schering-Plough	4%	14%	26%	34%	21%						
PFE	-5%	-3%	0%	2%	-1%	-13%	0%	-15%	-16%	-2%	(3%) - 5%
Wyeth	11%	18%	13%	5%	3%						
Total U.S. Pharma R&D expense	**8%**	**6%**	**8%**	**9%**	**4%**	**-4%**	**2%**	**-3%**	**-2%**	**0%**	
Total Global Pharma R&D expense	**14%**	**10%**	**12%**	**12%**	**5%**	**-2%**	**1%**	**2%**	**-3%**	**1%**	

Source: Compiled by MHBK/IRD based on data from Capital IQ

Table 6 R&D as % of Sales for Major Pharma Companies

R&D % Sales	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
AZN	16.2%	14.1%	14.7%	16.8%	15.4%	12.9%	12.3%	13.4%	15.3%	16.7%
SWX:NOVN	15.2%	15.0%	15.2%	16.5%	16.2%	16.4%	15.8%	15.7%	16.0%	16.5%
Alcon	10.0%	9.7%	10.5%	10.1%	9.8%	10.1%	10.4%			
LSE:GSK	14.5%	14.5%	14.9%	14.2%	14.4%	13.9%	13.5%	14.7%	13.6%	13.4%
ENXTPA:SAN	15.2%	14.2%	15.0%	15.5%	15.9%	14.8%	13.4%	13.7%	13.6%	14.3%
SWX:ROG	16.6%	15.3%	16.8%	17.2%	18.2%	18.7%	18.5%	18.3%	17.9%	18.7%
Total EU Pharma R&D % Sales	**15.3%**	**14.5%**	**15.2%**	**15.8%**	**15.9%**	**15.4%**	**14.7%**	**15.3%**	**15.4%**	**16.0%**
BMY	12.4%	13.7%	18.1%	19.2%	17.9%	17.5%	17.6%	17.0%	20.9%	22.7%
JNJ	11.3%	12.5%	13.4%	12.6%	11.9%	11.3%	11.1%	11.6%	11.4%	11.5%
LLY	20.3%	20.7%	19.9%	18.7%	18.9%	19.8%	21.2%	20.7%	23.4%	23.9%
MRK	17.5%	17.4%	17.5%	18.8%	19.6%	20.5%	17.9%	16.1%	16.7%	16.2%
Schering-Plough	17.7%	16.8%	20.7%	23.1%	19.1%	19.0%				
PFE	14.5%	14.4%	15.3%	15.6%	15.6%	15.7%	14.5%	13.1%	12.3%	12.7%
Wyeth	13.3%	14.6%	15.2%	14.5%	14.6%	15.0%				
Total US Pharma R&D % Sales	**14.3%**	**14.8%**	**16.0%**	**16.0%**	**15.6%**	**15.8%**	**15.2%**	**14.5%**	**14.9%**	**15.1%**
Total Global Pharma R&D % Sales	**14.7%**	**14.7%**	**15.6%**	**15.9%**	**15.7%**	**15.6%**	**15.0%**	**14.9%**	**15.2%**	**15.6%**

Source: Compiled by MHBK/IRD based on data from Capital IQ

Table 7 The Number of NMEs in Big Pharma's Pipeline, 2014

2014	Phase I	Phase II	Phase I + II	Phase III	Filed	Total NMEs in clinic	Time of Company Update
BMY	15	7	22	6	1	29	2014 company website
PFE + Wyeth	31	19	50	9	4	63	November 2013 update
LLY	24	22	46	8	3	57	2014 company website
MRK + SGP*	30	12	42	14	7	63	2014 company website
Roche	32	28	60	8	1	69	2014 company website
AZN	32	28	60	8	3	71	May 2014 Investor update
NVS	22	23	45	9	1	73	1Q14 result, Nov. 2012 R&D Day
GSK	26	28	54	5	0	59	Feb 2014 update
Sanofi-Aventis	23	14	37	11	1	49	Feb. 2014 update
Sector			416	78	21	515	

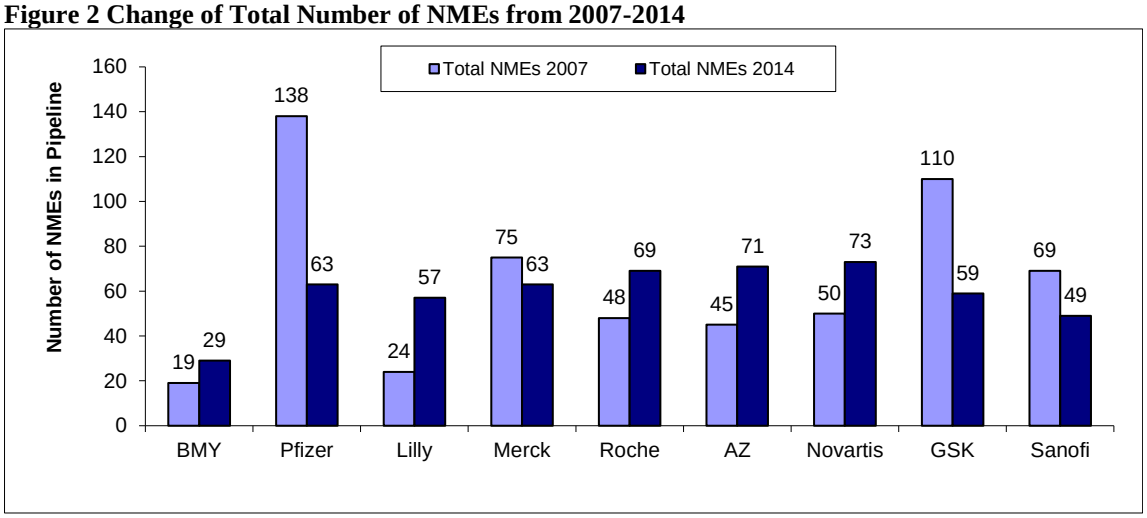
Source: Compiled by MHBK/IRD based on public company reports. Note 1: Big pharma have different policies in disclosing their NME portfolios. Sometimes we estimated the number based on either most recent updates or our estimate. This is most relevant for GSK, Novartis and Merck. Note 2: we only counted novel vaccines as NMEs. Note *: Merck (MRK) didn't disclose phase I NME number, we estimated based on industry average adjusted for its size.

Table 8 The Number of NMEs in Big Pharma's Pipeline, 2007

2007	Phase I	Phase II	Phase I + II	Phase III	Filed	Total NMEs in clinic	Time of Company Update
BMY			13	6	0	19	Feb 2007
PFE	51	38	89	6	4	99	Nov 2006
WYE	18	13	31	2	6	39	Oct 2006
LLY	8	11	19	5	0	24	Dec 2006
MRK	28	21	49	5	3	57	Dec 2006
SGP	6	8	14	3	1	18	Feb 2007
Roche	25	18	43	3	2	48	Feb 2007
AZN	22	18	40	5	0	45	Early 2007
NVS	20	20	40	7	3	50	Feb 2006
GSK	38	50	88	13	9	110	Feb 2007
Sanofi-Aventis	24	29	53	14	2	69	Feb 2007
Sector			479	69	30	578	

Source: Compiled by MHBK/IRD based on public company reports. Note: we estimated Schering-Plough (SGP) had 6 phase I compounds in 2007.

Figure 2 Change of Total Number of NMEs from 2007-2014



Source: Compiled by MHBK/IRD based on public company reports. Note: data used in this chart are based on numbers in the two tables above and therefore are subject to the same limitations.

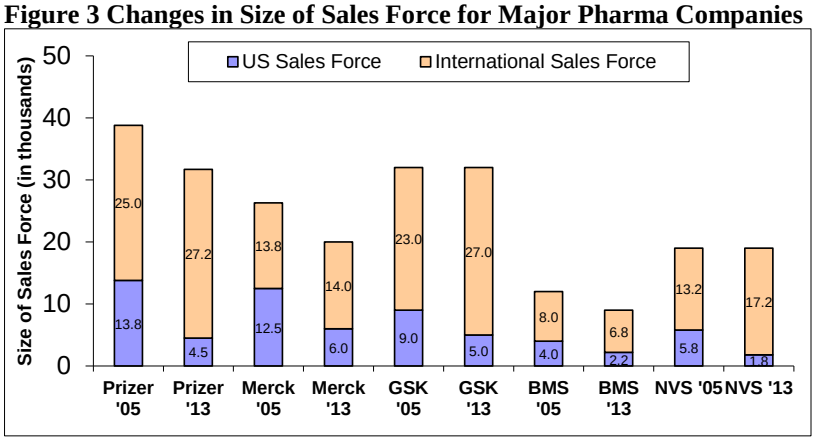
3. SG&A Expense

In the U.S. and EU markets, the importance of payers has been steadily on the rise, while the benefits from influencing physicians via sales reps have been on the decline. Therefore, large pharma has shifted to a key account management model, which relies on contracting to compete for market share. At the same time, big pharma has substantially curtailed the size of its sales force. The sales force targeting the primary care market was especially hit hard in this retrenchment from primary care to specialty care medicines.

Starting in 2006, big pharma started to meaningfully cut back its sales force in developed markets and the trend has continued to today. Comparing the data in 2005 to today (see Figure 3) shows big pharma has reduced the size of its U.S. sales force by half or more. In the case of Pfizer, in 2005 Pfizer and Wyeth had a combined U.S. sales force of 13,800 people. Today it is only 4,500, which represents a decline of 2/3. Pfizer has indicated its cost-cutting has entered into the equivalent of the 9th inning in baseball terminology, suggesting after years of deep cuts its cost structure is near optimization. We believe the reduction to the primary care sales force probably has peaked. Some pharma companies have actually been adding back sales staff on the specialty care side. BMS has added ~700 reps in oncology and other specialty care areas over recent years. Table 9 compares sales rep productivity of several pharma companies. Companies such as Roche and Novartis, which have mostly a specialty care portfolio in the U.S., generate a lot more revenues per sales rep than big pharma peers. For the traditional big pharma companies, both BMS and Pfizer have around $4mn sales per rep in the U.S., suggesting they are perhaps leading the pack in terms of restructuring their US sales force. Merck and GSK have less revenue per rep in the U.S. Merck is going through a new restructuring program that will pare back its SG&A cost further.

While the U.S. sales force has gone through a sharp reduction, most big pharma companies have grown their international sales force. The net result is the size of big pharma's global sales force has held flat or only declined modestly. Big pharma substantially ramped up its sales force in emerging markets. Big pharma now each employ thousands of sales reps in China. For example, AstraZeneca has increased its sales force in China from a couple of hundred in 2002 to 4,500 currently. In the process, it has seen its sales ramp up over this ten year period in direct proportion to increase in selling efforts. Similar to AstraZeneca, Merck currently has 4,000 reps in China.

Figure 3 Changes in Size of Sales Force for Major Pharma Companies



Source: Compiled by MHBK/IRD based on public company reports

Table 9 Sales Force Productivity (2013 Rx Sales /Rep)

$mn Rx Sales / Rep	U.S.	International	Global
Pfizer	4.1	1.1	1.6
Merck	2.5		
GSK	2.2	0.8	1.0
BMS	3.8	1.2	1.8
Novartis	5.7	1.3	1.7
Roche	8.1	2.9	3.9

Source: Compiled by MHBK/IRD based on public company reports

4. Manufacturing Expense

Big pharma realized early on that there was significant room to cut manufacturing expense through consolidation of plants and procurement. Although transferring products across plants and closing plants require some heavy lifting, manufacturing is actually the low-hanging fruit for cost-cutting as the impact on the top line is minimal. Therefore pharma companies often cut manufacturing expense ahead of R&D expense and concurrently with sales and marketing expense. Pfizer is again a trend-setter in terms of cutting manufacturing expense. It is on track to reduce the number of manufacturing sites by half from 96 before the Wyeth merger to 50.

Despite the substantial cut in manufacturing expense, the beneficial effect on gross margins is more than offset by margin erosion from the loss of revenues of high-margin blockbuster drugs. The result is a declining gross margin trend across big pharma (see Table 11).

Table 10 Reduction in Manufacturing Sites by Big Pharma

Company	Number of Manufacturing Sites in 2005	Number of manufacturing sites currently
PFE	96 at merger in 2009	56 (6 more targeted for exit)
MRK	95 at merger in 2009	68
BMY	38	12
LLY	25	22
AZN	30	22
GSK	82	87

Source: Compiled by MHBK/IRD based on public company reports. Note that for Merck, the animal health business accounts for a large number of manufacturing sites (as many as 30).

Table 11 Evolution of Big Pharma Gross Margins

Gross Margins	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
AZN	75.9%	78.0%	79.0%	79.7%	80.8%	83.0%	81.6%	81.8%	81.2%	80.0%
NVS	75.4%	75.0%	73.2%	72.8%	73.3%	72.9%	72.6%	68.7%	67.9%	66.8%
Alcon	72.4%	75.3%	75.6%	75.5%	76.6%	75.2%	76.7%			
GSK	78.2%	78.0%	78.4%	77.1%	76.3%	75.0%	72.9%	72.3%	71.3%	69.7%
Sanofi	71.8%	74.8%	74.3%	74.1%	74.5%	74.3%	72.8%	70.3%	69.1%	67.0%
Roche	75.2%	74.9%	69.8%	71.6%	71.6%	71.9%	73.4%	73.7%	74.9%	74.6%
Total EU Pharma Gross Margins	**76.9%**	**77.6%**	**76.4%**	**77.4%**	**77.9%**	**76.8%**	**76.2%**	**75.6%**	**74.4%**	**73.2%**
BMY	70.4%	70.2%	67.6%	69.6%	71.4%	73.3%	73.5%	74.0%	75.5%	70.4%
JNJ	71.5%	72.3%	71.8%	70.9%	71.0%	70.4%	69.5%	68.8%	68.4%	68.7%
LLY	76.6%	76.3%	77.4%	77.2%	78.8%	80.6%	81.1%	79.1%	78.8%	78.8%
MRK	78.4%	77.4%	76.7%	76.6%	77.1%	73.0%	65.3%	66.0%	65.6%	63.7%
Schering-Plough	64.4%	67.8%	66.5%	67.3%	65.3%	65.4%				
PFE	85.7%	83.8%	85.0%	83.6%	83.8%	83.2%	78.4%	79.7%	81.3%	82.1%
Wyeth	71.5%	71.8%	73.2%	72.9%	73.7%	74.3%				
Total US Pharma Gross Margins	**76.4%**	**75.8%**	**75.8%**	**75.1%**	**75.1%**	**75.1%**	**72.9%**	**73.0%**	**73.0%**	**72.2%**
Total Global Pharma Gross Margins	**76.6%**	**76.6%**	**76.1%**	**76.2%**	**76.5%**	**76.0%**	**74.6%**	**74.3%**	**73.7%**	**72.8%**

Source: Compiled by MHBK/IRD based on data from Capital IQ

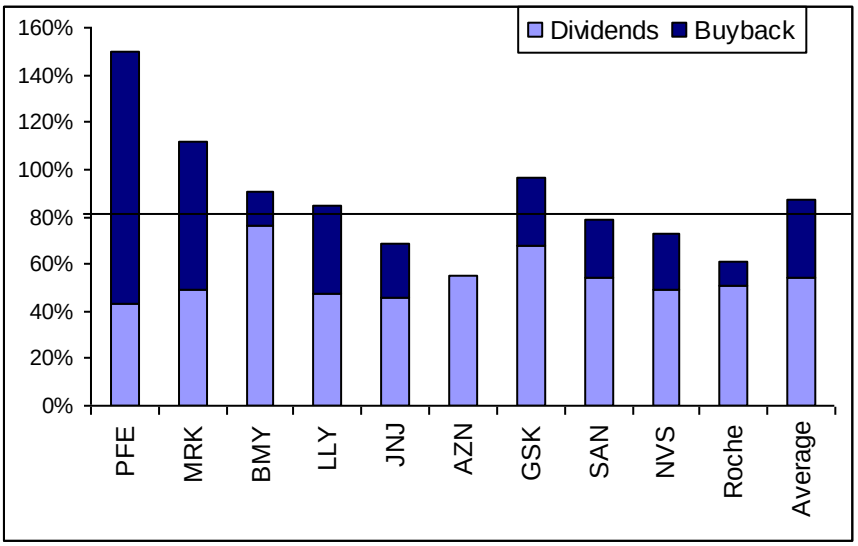
III.Capital Allocations by Big Pharma

Capital allocation is a very important decision for big pharma. It is the progressive capital allocation decisions in recent years that propelled some big pharma's stock price appreciation. The simple corporate finance tenet indicates if a pharma can find projects with returns above its hurdle rate, it should reinvest in its business. Otherwise it should return the cash to shareholders. Quality and quantity of pipeline varies greatly among pharma, thus necessitating various levels of internal investment. In addition, it seems pharma's ability to make good acquisitions also various significantly. Although there is huge uncertainty in the drug business, the outcome of acquisitions in our view cannot be explained simply by luck. Some companies such as Pfizer have consistently made bad biotech acquisitions in the past. But some other companies have done better (more on this topic in the next section). To its credit, Pfizer took an honest look at itself in the mirror and decided it is better to return cash to shareholders than continuing on the path of high-risk acquisitions. Overall big pharma have adopted aggressive capital allocation policies to return cash to shareholders. Pfizer is again a poster boy for aggressively returning cash flow to shareholders in recent years. Besides Pfizer, other companies including Merck, BMS, J&J, Eli Lilly, AZ and GSK have also been aggressive in returning cash.

1. Dividends payout

Dividend is considered sacrosanct in the pharma industry and no big pharma has cut dividends even if they face harsh times. Historically, big pharma pays out ~50% of net income as dividends and the variability is small across pharma (see Figure 4). The payout ratio varies depending on the ebb and flow of profit (see Figure 5), while the actual dividends are held steady or growing slightly. As the short-term earnings took a hit from patent expiries, the ratio has gone up for several companies such as BMS and Lilly.

Figure 4 Total Cash Return to Shareholders % Net Income in 2013

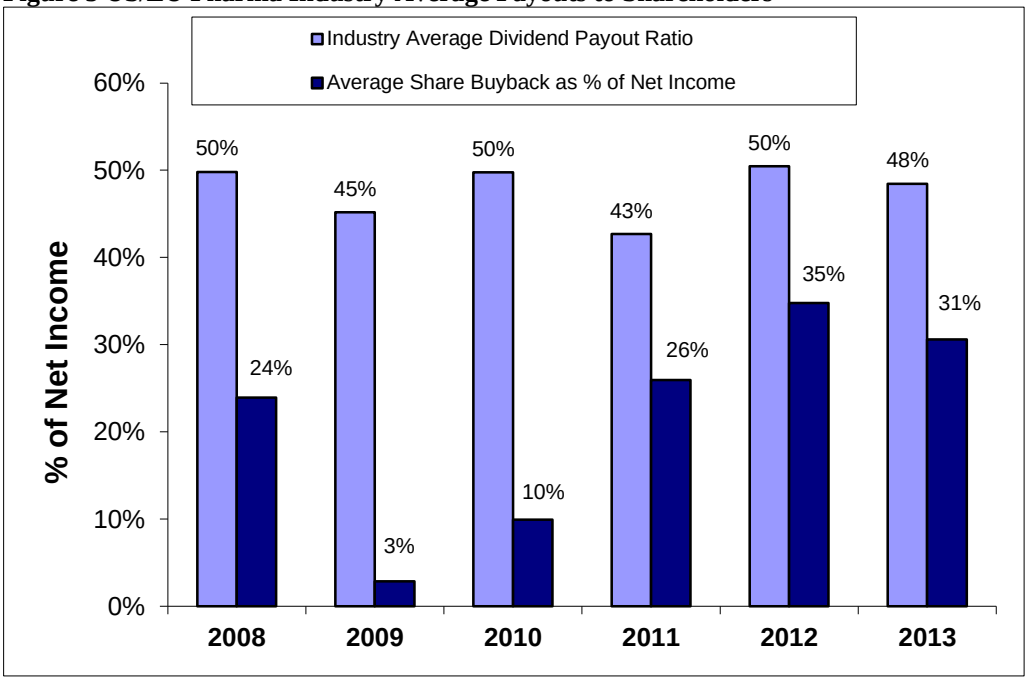


Source: Compiled by MHBK/IRD based on public company reports.

2. Share buybacks

Pharma have great flexibility in terms of their share repurchase decisions. In recent years, overall big pharma have significantly dialed up their share repurchases as a means to return cash to shareholders (see Figure 5). Big pharma differ widely in how much buybacks they conduct (Figure 4).

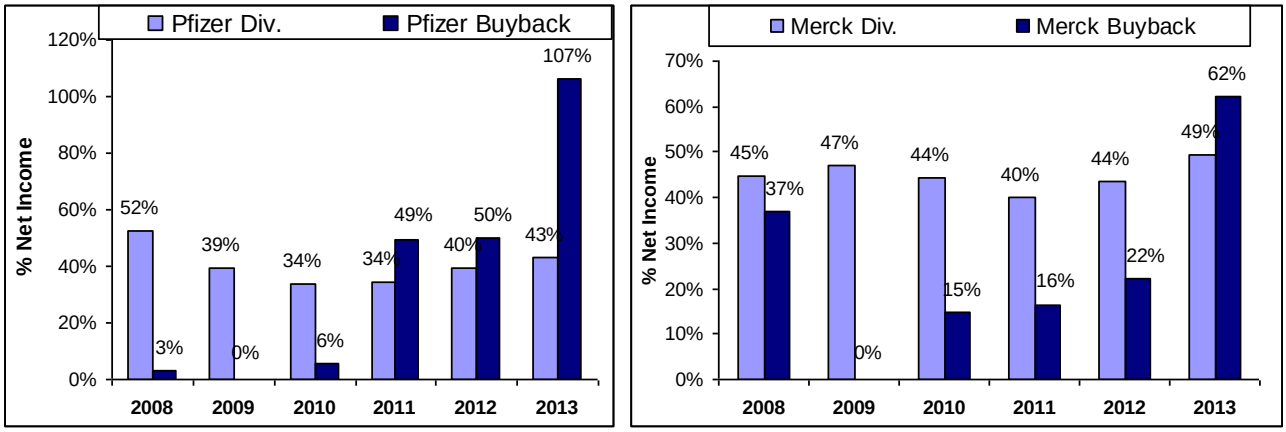
Figure 5 US/EU Pharma Industry Average Payouts to Shareholders



Source: Compiled by MHBK/IRD based on data from Capital IQ

If a company sees few opportunities to reinvest in its business, it should pursue share buybacks aggressively. Pfizer is the poster boy for big share buybacks. As shown in Figure 6, Pfizer stepped up share repurchases over the last three years as it returned almost 90% of net income to shareholders. Pfizer has found the valuation of biotech companies often excessive and therefore it is challenging to find suitable acquisition targets. Instead of paying out big acquisition premiums to enrich other companies' shareholders, Pfizer would rather buy back its own shares to enrich its own shareholders. Therefore, Pfizer has been pursuing share buybacks with a vengeance. In contrast, Merck has done much less share repurchasing than Pfizer. However, in May 2013, in a change of course, Merck announced a new $15bn share repurchase program, half of which will be completed within 12 months. In over a month (as of June 30, 2013), Merck repurchased $5bn worth of company stock. We believe much of the step-up could be due to shareholder pressure and peer pressure from Pfizer. However, after the $7.5bn repurchase in the first year, the remaining $7.5bn is likely to be completed over a longer period. This is because Merck now recognizes a higher urgency to do business development deals to support its top-line.

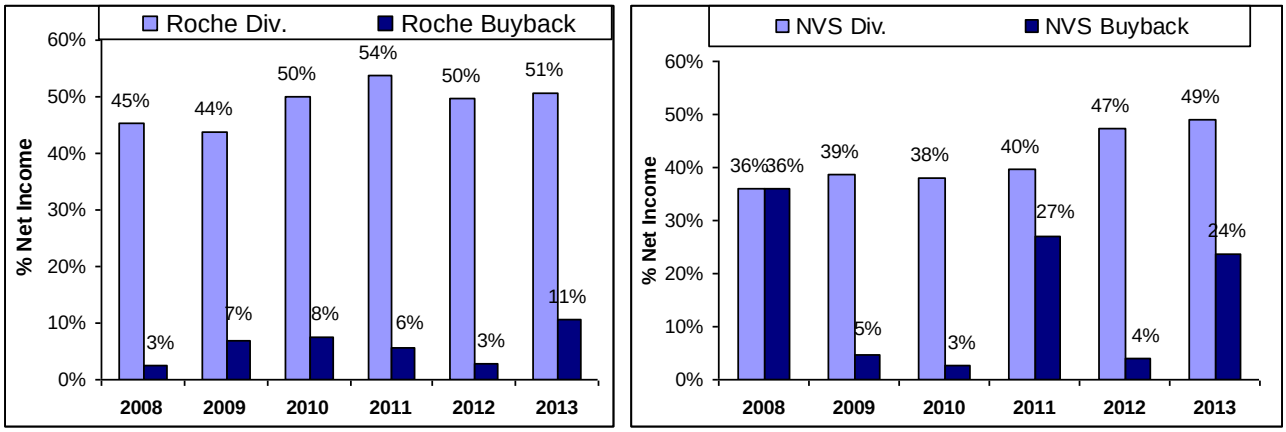
Figure 6 Trend of Cash Flow Return to Shareholders by Pfizer and Merck



Source: Compiled by MHBK/IRD based on data from Capital IQ. Note: the spike in Pfizer's 2013 share buyback was due to the one-time proceeds from selling ancillary businesses

Share buyback is often a trade-off with investment in the internal pipeline or external business development deals. Companies with rich pipelines such as Roche and Novartis do little share buybacks (see Figure 7). We believe this is a virtuous cycle and should be the first option if there is indeed a very attractive internal pipeline.

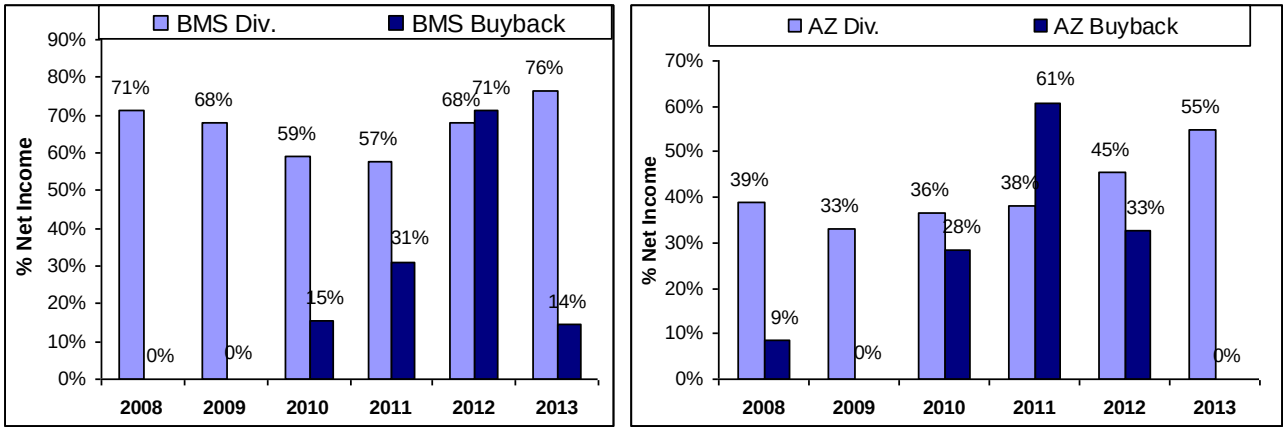
Figure 7 Trend of Cash Flow Return to Shareholders by Roche and Novartis



Source: Compiled by MHBK/IRD based on data from Capital IQ

For companies pressured by near-term patent expiries, often times they tried to do substantial share repurchases to boost stock price. Examples include AstraZeneca and BMS (see Figure 8). However, they cannot dodge the need to boost revenues and therefore they often come around to curtail share buybacks in favor of M&A. Both AZ and BMS have suspended their share repurchase programs despite aggressive buybacks over the last two years. When the new CEO joined AZ in the middle of 2012, AZ suspended share repurchase. Instead of buybacks, it is using the cash to do licensing deals or make acquisitions. In 3Q2013 earnings call, BMS announced suspension of share repurchase. The sharp jump in BMS share over the last year may be one of the reasons why the company is not buying back more shares at a higher price level.

Figure 8 Trend of Cash Flow Return to Shareholders by BMS and AstraZeneca



Source: Compiled by MHBK/IRD based on data from Capital IQ

3. Capital Allocation Policies

Big pharma have made various comments on their capital allocation policies (see Table 12). We can divide the large pharma universe broadly into the three camps as discussed previously. We note this classification is not so rigid. For example, Merck's priority is probably transitioning from share buyback to business development. Also companies can pursue multiple priorities at the same time. For example, BMS is investing in its rich pipeline and at the same time pursuing external product acquisitions.

Table 12 Summary of Publicly Stated Capital Allocation Policies

Company	Public Comments on Capital Allocation Policies
Priority is given to returing cash to shareholders	
Pfizer	Pfizer will maintain its dividends. Share repurchase is the option to beat. Pfizer repurchased $8.2bn in shares in 2012 and $9bn in 2011. In 2013 with the windfall of cash from selling its nutritional business and the IPO of Zoetis, Pfizer is expected to do share repurchases in the mid-teen billions range. Pfizer has said that currently biotech assets are priced for perfection, but that it will keep looking. Returning cash to shareholders is a good option.
Merck	Returning cash to shareholders is high priority in the near term. Merck announced a $15bn share repurchase program in May 2013, half of which will be completed within 12 months. $5bn had been completed by Q2. Maintain or grow dividends. Since the new R&D head took office, M&A/licensing has gone up in priority. Merck can rely on its strong balance sheet for M&A.
GSK	The first priority is to increase dividends. The second is to look at buybacks and bolt-on acquisitions. GSK has a steady £1-2bn per year buyback program. Recently given the abundant internal R&D pipeline, GSK has said the hurdle for bolt-on acquisition has gone up. Not interested in large M&A.
Priority is to do acquisitions or licensing deals	
BMS	Progressive dividend policy (maintain or increase dividends each year). Business development is high priority. In 3Q13 call, BMS announced temporary suspension of share buyback activities.
AZ	Reinvest up to 50% of post-tax, pre-R&D on-market cashflows to drive future growth and value. For the other 50%, maintain progressive dividend policy, and use the remainder for acquisitions or share buybacks. AZ suspended share buyback in October 2012 after new management came in.
Priority is invest in own pipeline	
Roche	Has not set a target. Increase dividends each year. Limited share buybacks. Invests in pipeline.
Novartis	Steady growth in dividends.
Eli Lilly	Maintain dividends at current level. Then first priority is to invest in own pipeline. Second is to supplement with business development deals. And third is to return money to shareholders through share buybacks or other means. Not interested in big mergers.
Sanofi	Maintain or steadily grow dividends. Good level of buybacks.

Source: Compiled by MHBK/IRD based on public company reports

IV. Pharmaceutical Industry Competitive Strategies

A. Big Pharma's Sharpened TA Focus Creates Room for Deals

1. Current Pharmaceutical Industry Requires A Focused Strategy

From the R&D standpoint, there is a wide perception that medicines for easily druggable targets have already been invented. To discover new medicines, pharma companies have to dig deeper into more complex diseases. Concurrent with the explosion of genomics tools and other enabling technologies, the task of understanding a disease is also getting more complicated. To succeed competitively, it is important for big pharma to have innovation leadership in the chosen disease. For example, it is no longer tenable to say you are focused on cancer. It may not be sufficient to say you focus on hematological cancer or solid tumors. Increasingly, companies have to choose which type of cancer they are focused on (for example lung cancer or breast cancer). This increasing fragmentation presents both challenges and opportunities. The opportunity is for a relatively small company to dominate in a small niche. The challenge is for big pharma to compete and win in a broad array of fragmented markets.

From the marketing standpoint, it is beneficial to have a portfolio of drugs with different mechanisms of actions to target a single disease. This way, companies can increase the productivity of sales calls (a single doctor visit can promote multiple drugs) and pursue FDC (fixed dosed combinations). One prominent example is in diabetes. As shown in Table 13, big pharma increasingly is amassing a portfolio of oral and injectable drugs for diabetes. In doing so, pharma companies can be more effective in marketing to endocrinologists and primary care doctors. Highlighted in Table 15 are the alliances in diabetes forged by big pharma companies. For example, Merck has achieved great success with just one drug in diabetes. But with multiple DPP-4 inhibitors entering the market, the growth of the Januvia franchise has screeched to a halt. Recognizing the benefit of a portfolio approach, Merck recently licensed a SGLT-2 inhibitor Ertugliflozin from Pfizer and also entered into a JV to develop long-acting insulin with Samsung. Eli Lilly is a primary beneficiary in its alliance with Boehinger Ingelheim, through which it acquired 2 oral diabetes drugs. AZ and BMS have pooled their diabetes resources together to create a category leader. The AZ/BMS alliance also acquired Amylin to fill the hole in the GLP-1 class. Then AZ bought out BMS's interest in the alliance in late 2013.

Table 13 Comparison of Diabetes Portfolios of Big Pharma

Administration	Target	Lilly	Merck	Novo Nordisk	AZ	Sanofi	GSK	J&J	Takeda
Oral	**DPP-4**	Trajenta	Junuvia		Onglyza				Nesina
	SGLT-2	Empagliflozin	Ertugliflozin		Forxiga			Invokana	
Injectable	**GLP-1**	Dulaglutide		Victoza	Byetta / Bydureon	Lyxumia	Albiglutide		
	Insulin	√	√	√		√			

Source: Compiled by MHBK/IRD based on public company reports. Note: checkmark for insulin indicates the company either have commercial insulin or have insulin in clinical development.

2. TA Focus of Big Pharma – A Roadmap for Asset Swapping

As shown in Table 14, although pharma companies have a commercial presence in many areas through their legacy businesses, for R&D, they are typically focused on just a few TAs. Table 14 also serves as a roadmap for pharma asset swapping. For example recently Novartis signed a huge deal with GSK, in which GSK sold its oncology business to Novartis for $14.5bn, acquired Novartis's vaccine business for $5.25bn and pooled their consumer healthcare businesses into a JV with Novartis owning a minority stake. Novartis also sold its animal health business to Eli Lilly for $5.4bn.

Several observations can be drawn from Table 14:

- Big pharma has sharply focused its targeted therapeutic areas (TAs). For example, in a reorganization announced in October 2013, Merck announced it will focus on four TAs – vaccine, oncology, diabetes and acute care.
- Many pharma companies are simultaneously attracted to the high growth areas such as diabetes, oncology, inflammation and HCV. This makes the field super-competitive and valuation of biotech assets very expensive. Pharma companies are also attracted to areas where science is on the cusp of a breakthrough and being translated into medicine. One such example is fibrosis in the specialty medicine area.
- Big pharma companies are shunning TAs that are viewed as being largely satisfied with existing therapies or very risky to develop new drugs. Examples for each include GI and CNS respectively. AZ has exited the GI field as it is hard to innovate beyond proton pump inhibitors. Both AZ and GSK have exited the internal CNS research area.
- There is "spatial" as well as "temporal" positioning for TA focus. Spatial focus is simply where the companies want to place their bets at a given time. Temporal focus means a company may decide to invest very differently for late-stage assets and discovery research efforts. For example, mid-late stage HCV pipeline is viewed as full and many companies are operating at full-throttle to develop them. But industry thinks the current pipeline will largely satisfy the unmet medical need and there is no need for early R&D efforts in HCV. The reverse is true for HBV where there are few late-stage assets but a number of companies are pursuing early-stage programs actively.
- For ancillary businesses, following Pfizer's successful IPO of its animal health business Zoetis, there is increasing pressure for other pharma companies to consider such divestiture. Some pharma appreciate the stable ancillary business (e.g., Eli Lilly wants to keep the animal health business). But that may not be the case for other big pharma companies (e.g., Merck, Novartis, and GSK). Eli Lilly just acquired Novartis Animal Health for $5.4bn.
- Different pharma have different appetite for platform technologies. Most big pharma companies have by now built biologic capabilities through acquisitions. Different companies have different appetite for investing in futuristic platform technologies. Companies such as Merck, which was burned by prior platform deals such as Sirna, have decided to eschew platform acquisitions. In contrast, AstraZeneca has inked multiple platform deals recently for ADC technology (Spirogen and ADC Therapeutics), cancer immunotherapy technology (Amplimmune) and mRNA therapeutics (with Moderna).

Table 14 Comparison of Therapeutic Focus of Big Pharma

Therapeutic Areas	2012 Sales ($bn)	% growth	Pfizer	Merck	Eli Lilly	Abbvie	BMS	Amgen	J&J	AZ	GSK	Sanofi	Novartis	Roche
Primary Care														
Diabetes	22	7.1%		Focus	Focus				√	Focus	√	√		
CV Metabolism	34.9	-16.9%	√	√	√		√ (HF)	√	√	Focus	√	√	√	↓
Lipid regulators	16.9	-20.6%												
Anti-hypertensives	13.6	-3.0%												
Anti-platelet	4.4	-45.7%												
Obesity														
Vaccine			√ (Focus)	Focus						√	√	√		
Respiratory	22.1	1.9%								Focus	√		√	
Pain	18.2	1.6%	√											
Gastro Intestinal	10	-4.7%												
Genital Urinary														
Women's health						√								
Hormonal contraception	5.5	5.1%												
Antibacterial	7.9	-14.8%								√				√
CNS	46.1	-6.7%	√	√ (AD)	√	√		√	√	Virtual	Virtual		√	↑
Mental health	23.5	-21.0%												
ADHD	10.4	13.1%												
Nervous System Disorders	7.2	3.7%												
Other CNS	5	4.0%												
Osteoporosis				√	√			Focus						
Kidney disease					√	√		√		√				
Dermatology						√		√	√				√	
Specialty Care														
Oncology	25.9	7.8%	√ (Focus)	Focus	Focus	√	Focus	Focus	Focus	Focus		√	√	↑
Inflamation	14.8	17.9%	√		√	Focus	Focus	√	Focus	Focus	√	√	√	↑
Multiple Sclerosis	8.9	17.8%				√						√	√	
Orphan Drugs			√								√	√		
HIV	11.7	12.1%					√		√		√			
Other anti-viral (HCV, HBV)	4.5	20.1%		√		Focus	√ (HBV)		Focus					↓
Other Focus														
Biologics			√ (WYE)	Build	√ (IMCL)	√	√ (MEDX)	√	√	√ (MEDI)		√ (REGN)		√ (DNA)
Biosimilars			√					√					√	
Platform technology				No				√	√	√			√	√
Acute Care				Focus									√	
Ophthalmology													√	
Generics													√	
Diagnostics									√				√	√
Animal health			IPO	√	√							√		
Consumer health			Sold	√					√		√	√		
Agnostic of Core TAs				√						√				

Source: Compiled by MHBK/IRD based on public company reports. Note: Market size and growth rate are according to data from IMS Health. Checkmarks indicate the company has strong presence in certain TAs. The word "Focus" is used to denote the TAs that the company put as the highest priories. For Roche, the arrows indicate where the company is increasing or decreasing its investment for its core TAs.

1. Pharma-Pharma Deal Making Created Huge Value in Industry

Recognizing the benefits of category leadership, big pharma companies have come together to pool resources or swap assets to create category leaders. There have been many pharma-pharma deals (see Table 15). In doing such deals, pharma companies are able to eschew paying high premiums to acquire biotech companies, but at the same time acquire desirable assets and sell subscale assets. This approach also avoids the business disruptions and unwanted assets that often come with big pharma mergers.

Table 15 Pharma-Pharma Deals

Partner I	Partner II	Upfront payments ($mn)	Deal	Year
Bayer	Merck	$14,200 for Consumer; $1,000 for sGC	Bayer acquired Merck Consumer Care for $14.2bn. Entered into collaboration of sGC modulators for $1bn upfront payment.	2014
Novartis	Eli Lilly	$5,400	Sold animal health business to Eli Lilly Elanco.	2014
Novartis	GSK	$14.5bn for oncology; $5.25bn for vaccine.	Acquired GSK oncology business, sold Vaccine business to GSK. Pooled consumer healthcare business with GSK's to create a category leader, retaining a minority stake in the JV with a put option to exit.	2014
Eli Lilly	Pfizer	$200	Collaborate to develop anti-nerve growth factor pain drug tanezumab	2013
AstraZeneca	BMS	$2,700	AZ acquired BMS's stake in the diabetes alliance	2013
Servier	Amgen	$50	Amgen gains U.S. rights to heart failure drug ivabradine and a phase II compound also for CHF. Servier gains EU rights to omecamtiv mecarbil for heart failure.	2013
Merck	Pfizer	$60	Merck and Pfizer will collaborate on SGLT2 inhibitor Ertugliflozin and fixed dose combos with Januvia. Ertugliflozin will enter into phase III in 2013. Profit split 60-40.	2013
Lundbeck	Otsuka	$150	Otsuka further expanded alliance with Lundbeck by co-developing Lu AE58054 for Alzheimer's disease.	2013
Otsuka	Lundbeck	$200	Global collaboration including injectable Abilify and OPC-34712 from Otsuka and three compounds from Lundbeck.	2011
Otsuka	Kyowa Hakko Kirin	¥3.0 billion; ¥8.2 billion at approval	Otsuka sub-licensed Saxagliptin to KHK. Strategic alliance to develop KHK's oncology portfolio in Japan and Asia.	2012
BMS	Astra Zeneca	$100	Entered into an alliance to co-develop BMS's DPPIV inhibitor and SGLT-2 inhibitor; jointly acquired Amylin; merged their U.S. commercial operation in diabetes in January 2013.	2007 2012
Amgen	Astra Zeneca	$50	Jointly develop and commercialize five inflammatory disease treatments in Amgen's portfolio.	2012
Boehringer Ingelheim	Eli Lilly	€ 300	Entered into an alliance to co-develop and market four mid-late stage diabetes assets, including BI's DPPIV and SGLT2 inhibitors, and two insulin products from Lilly (dropped later on)	2011
GSK	Pfizer / Shionogi		Pooled HIV franchise under ViiV Healthcare. GSK owns 76.5%, Pfizer owns 13.5% and Shinogi owns 10%.	2009
Amgen	Takeda	$300	Licensed rights of 13 clinical candidates in Japan, global co-development right to TKI motesanib	2008
Lundbeck	Takeda	$40	Alliance to develop several compounds in Lundbeck's pipeline for depression and anxiety	2007
BMS	Pfizer	$250	Co-development and marketing of Factor Xa inhibitor Eliquis	2007
Bayer	J&J	$290 upfront & milestone	Co-development and marketing of Factor Xa inhibitor Xarelto	2005

Source: Compiled by MHBK/IRD based on public company reports

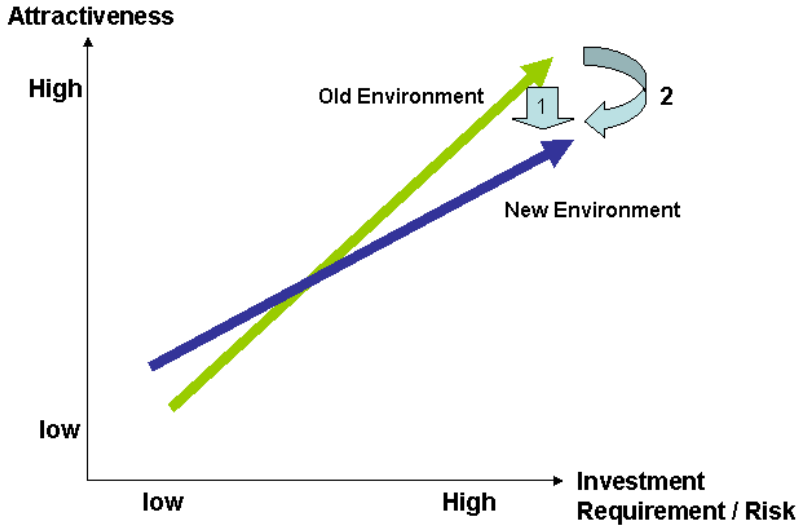
2. Focus is Also Important for Specialty Pharma Companies

Focusing on a specific therapeutic area is also important for specialty pharma companies. It is equally desirable to have a portfolio of products targeting the same disease for a specialty pharma company as for a big pharma. However, the focus needs to be relaxed given the shortage of products in the specialty pharma industry. A good example is Forest Labs' line call strategy. In lieu of having sales reps detailing 1-2 big products, Forest Labs has its reps detail 3-5 mid-sized products in a given therapeutic category. Specifically, instead of detailing the blockbuster Lexapro in the past, Forest Labs has its psychiatric sales force detailing Viibryd, FETZIMA, Saphris and the to-be-approved Caprazine. Each product may have sales potential of $200-500mn, but they collectively add up to the scale of a blockbuster like Lexapro (peak sales of >$2bn in the U.S.). This approach preserves the economics of the blockbuster model, minimizes the impact of one particular patent expiry, optimizes the efficiency of reps and increases their relevance for the targeted physicians.

B. Successful Biopharma Business Strategies

How should pharma companies position themselves in today's ultra-competitive environment? Perhaps it is helpful to look at the following diagram (see Figure 9), in which we graphed the perceived attractiveness (defined as market potential if we can view this in isolation) of the market vs. the required investment and accompanied risk. For investment projects, the more attractive the end market is, the more investment is likely required. And oftentimes, not always, such large investment is accompanied by high risk. In recent years, perhaps the curve has moved two ways. Firstly, the curve shifted downwardly. For the same attractive projects, pharma companies have to invest in a lot more than before. There are many examples ranging from ever larger clinical trials to satisfy the FDA to the ever increasing price of biotech assets. Secondly, perhaps the curve has rotated clock-wise. As the investment for top projects increases, pharma companies have to move aggressively up the curve. One example is the industry's mad rush to develop checkpoint inhibitors for cancer. Speed is critical for such hotly pursued projects. To compete, companies are forced to make aggressive investment often in a parallel fashion rather than in a sequential fashion. In doing so, they have to curtail investment in projects with a lower level of attractiveness. For example, because pharma companies want to focus on areas such as diabetes, oncology, and specialty drugs, they have cut their investment in areas such as GI, CNS, etc. If the industry as a whole allocates capital this way, it could lower the return on hotly contested areas but raise return in the less attractive markets. Some specialty pharma companies have emerged as the beneficiary by focusing on these neglected therapeutic areas. Valeant is a prime example for its focus on Dermatology, Ophthalmology, etc. (more on Valeant's successful strategy in the following section).

Figure 9 Innovation Payoff Diagram



Note: Illustrated by MHBK/IRD

How can companies compete in such an environment?

1. The model applicable for most biopharma firms is to be the innovative leader in the attractive therapeutic areas. Companies need to move faster and invest more aggressively than competitors to capture the emerging breakthroughs in innovation. Examples include the ongoing race in cancer immunotherapy and the almost finished race in HCV.

Pros of this strategy include:

- Biopharma is fundamentally an innovation driven business. Payers will pay for true medical innovation, not incremental benefits.
- Attractive therapeutic areas are poorly served by existing therapies and could have huge potential.

Cons of this strategy:

- Most biopharma companies are attracted to the same areas for the same reasons (fast-growing categories, large unmet medical needs, diseases where biology is on the cusp of breakthroughs, etc.). Therefore, competition is fierce. These days, first movers only enjoy a few months of lead time instead of a few years as in the past. And valuation for acquisitions is very high (think of Gilead's $11bn acquisition of Pharmasset in 2011).
- Sometimes drug development for attractive diseases with large unmet medical needs entails high risk (think of Alzheimer's Disease or the failed deals in the past as illustrated in Table 16).

Table 16 Notable Failed In-licensing Deals in the Recent Past

Acquirer / licenser	Target / licensee	Ann. Date	Deal Details ($mm)	Upfront ($mm)	Equity ($mm)	Stage
Bristol-Myers Squibb	Inhibitex	Jan-12	$2,500mn acquisition		$2,500	Phase II
Abbott	Reata	Dec-11	$400mn licensing fee for second-generation oral antioxidant inflammation modulators (AIMs).	$400		II
Abbott	Reata	Sep-10	$450mn near-term payments for OUS licensing rights to bardoxolone and a minority investment in the company , $350 in dev. and reg. MS, plus royalties.	$450		II
J&J*	Elan	Jul-09	Acquired all Elan's AD immunotherapy program including half of Elan's share in Bapineuzumab.		$1,000	III

Source: Compiled by MHBK/IRD based on public company reports. *Note: Despite the failure of Bapineuzumab, J&J's loss is offset as its investment in Elan was made at a low valuation ($9.32 per share)

For a company to succeed in this approach, it helps if it has an intensely R&D-driven culture. Historically, many successful R&D organizations had this science-focused mindset. Often these companies were led by visionary scientists rather than commercial or finance people. In these organizations, commercial people work for the scientists, rather than the other way around. Following are some prominent examples of scientist CEOs that have had a huge impact on pharmaceutical innovation[1]:

- Janssen Pharma was responsible for developing 70 drugs between 1955 and 1993, including fentanyl for pain, haloperidol for schizophrenia and many other drugs for CNS. Although the company was acquired by Johnson & Johnson in 1961, founder Paul Janssen was granted full autonomy for running its business.
- Merck under CEO Roy Vagelos from 1985-1994 produced many breakthrough therapies including Timoptic for glaucoma, Vasotec and Prinivil for hypertension and heart failure, Mevacor and Zocor for hypercholesterolemia and Proscar for benign prostate hyperplasia. These drugs became the mainstay revenue generators for Merck for more than a decade.
- Before its acquisition by Roche in 2009, Genentech under the leadership of Art Levinson invented many of the most important drugs in cancer, including Herceptin, Avastin, Rituxan, etc. Genentech almost single-handedly ushered in the era of antibody-based drugs for cancer.
- Regeneron under the leadership of Leonard Schleifer and George Yancopoulos has invented breakthrough technologies in antibody engineering. Regeneron has also invented important commercial drugs such as Eylea and compounds in development such as PCSK9 inhibitors. It is a mini-Genentech with its culture intensely focused on innovation.

Currently, most big pharma CEOs have commercial, legal or finance backgrounds. Thus it is very important for these organizations to have strong heads of R&D. Unfortunately, due to the recent disappointments in R&D, the R&D function may not be highly regarded within certain pharma companies. R&D organization has become a source for cost-cutting. In addition, R&D has also endured distractions from pharma mergers. However, the risk to the industry may be a narrower, more "near-term gratification" pipeline portfolio that doesn't have enough breadth and depth.

[1] Discussion on this section was partly referenced from "What Can Biopharma Learn From Apple" by Markus Thunecke, Ph.D. published in In Vivo in January 2014

2. Strategy #2 is to avoid the high-stake, high reward game in inventing cutting-edge medicines by focusing on neglected areas. This is essentially a specialty pharma model. Many specialty pharma companies have benefited from this strategy. Valeant is a prime example for its focus on neglected disease areas such as Dermatology, Ophthalmology, etc. Valeant has declared its goal of reaching $150bn in market cap. Combining this strategy with savvy deal making (more on this in the following section) and an aggressive tax-reduction strategy, specialty pharma companies have delivered much higher shareholder returns than big pharma in recent years. Salix is another example of focusing on an unpopular disease – Gastrointestinal disease - and it has carved out a nice niche for itself.

3. Another way to benefit from the industry dynamics is to acquire assets deprioritized by big pharma. There is a lot of churning in big pharma firms' pipeline. Often big pharma invests a lot of money in a project, only for it to be jettisoned at a later date. Assets from big pharma have the advantage of going through more rigorous development than assets from cash-strapped small biotech. Venture capitalists have seized the opportunity to establish companies with assets spun off from big pharma companies. For example, a number of Pfizer's acquisitions were later spun off to form venture-backed companies, and several such companies went public (see Table 17). A number of serial entrepreneurs have successfully created enormous wealth by licensing and developing compounds from big pharma or smaller companies (see Table 18). Finally, as we noted earlier (see Table 15), pharma-pharma deal-making has created a lot of value in the industry. Instead of competing with each other, big pharma with complementary strengths can join forces to create category leaders.

Table 17 Pfizer's Biotech Acquisitions and Spin-Offs

Company Acquired	Acquisition Date	Acquisition price ($mn)	Company Spun off	Spun-off time	Current valuation if public ($mn)	Disease Area
Esperion	2003	$1,300	**Esperion***	2008	$230	Atherosclerosis
Idun Pharma	2005	$300	**Conatus**	2010	$87	Liver fibrosis
Vicuron	2005	$1,900	**Durata Therapeutics**	2010	$417	Antibiotics

Source: Compiled by MHBK/IRD based on public company reports and Capital IQ. Note: * One program of the original Esperion (ApoA1 Milano) was licensed by The Medicines Company

Table 18 Successful New Ventures by Serial Entrepreneurs

5/15/2014 Company name	Ticker	Year Founded	Market Cap $mn	Price ($USD)	52-wk	52-wk	% 52-wk High	Source of the compounds	CEO founder	CEO's former company
Clovis Oncology, Inc.	CLVS	2009	$1,733	58.52	93.33	32.32	63%	Avila, Pfizer	Patrick J. Mahaffy	Pharmion
Tesaro, Inc.	TSRO	2010	$976	26.53	51.95	22.15	51%	Schering-Plough, Merck, Amgen	Lonnie Moulder	MGI Pharma
Puma Biotechnology, Inc.	PBYI	2010	$2,031	63.22	143.65	31.73	44%	Pfizer	Alan Auerbach	Cougar
TG Therapeutics, Inc.	TGTX	2012	$170	4.58	8.02	2.97	57%	GTC Biotherapeutics; Rhizen Pharmaceuticals	Michael S. Weiss	Keryx
Kadmon		2009						Exelixis, Surface Logix	Sam Waksal	ImClone
Blueprint Meidinces		2011							Alexis Borisy	CombinatoRx

Source: Compiled by MHBK/IRD based on public company reports and Capital IQ

C. Winning M&A Strategies in the Pharmaceutical Industry

Today's business environment is characterized by:

- Innovation has become much more competitive and requires significant expertise, large investment and fast speed.
- Return on R&D investment has been dropping.
- Greater payer say in reimbursement. Demand for value and payers' bargaining power will become ever more intense.

Big pharma companies have taken many actions to streamline their business and position for the future. However these internal actions alone may not be enough to transform the industry into a model best positioned for the future. Thus M&A may be the key to effect transformation for the industry. In this section, we review the experience of some successful acquirers in the past.

1. Biopharma Firms' Successful Acquisition of Biotech Companies

Successful acquisitions can go a long way in curing big pharma's pipeline woes. Table 17 lists the ten most successful M&A deals (for the acquirer) in recent years by our assessment. We can perhaps learn a number of lessons from this list.

- Some deals helped the acquirer tremendously. Without the deal, the alternative would have been much worse. For example, BMS's acquisition of Medarex can be considered perhaps the most successful deal in recent industry history as it gave BMS a portfolio of cancer immunotherapy drugs such as Yervoy, PD-1 etc. Without the Medarex deal, it would have been hard for BMS to survive, let alone thrive as an independent company. Pfizer's acquisition of Wyeth was a huge boost for Pfizer as it helped stabilize Pfizer's topline with Wyeth's vaccine business and gave it the ability to dramatically cut costs in the combined company.
- Some deals were transformative as they gave the acquirers key technologies such as antibodies or exposure to attractive therapeutic areas. Eli Lilly's acquisition of ImClone helped it transition from small molecules to biologics. Sanofi's acquisition of Genzyme made Sanofi a leader in the coveted orphan disease area.
- The asset's price is only secondary as long as the acquired asset proves to have stellar clinical data. Examples include Pharmasset, Cougar Biotech, Proteolix and Calistoga. In each case, the acquisition occurred before the phase3 data became available. Although the valuation seemed high at the time of the deal announcement, clinical data turned out to be excellent. Therefore acquirers earned high returns on their investments. In the biopharma business, clinical data is paramount while price is secondary.
- While picking up good clinical assets is always beneficial, additional optionality is important. One good example is Abraxis. At the time of the acquisition Abraxane was only approved for breast cancer. Following the acquisition, Abraxane demonstrated efficacies in phase 3 trials in lung cancer, melanoma and pancreatic cancer, thus greatly expanding its market potential. Celgene is likely to reap multifold return on its initial investment.
- Never avoid purely financial-driven deals. Companies should be more agnostic in what they are focused on. Sometimes, the strategic intent may be simply to get bigger. Companies shouldn't shun deals that only offer good financial rather than strategic value. One example is Warner Chilcott's acquisition of Procter & Gamble's pharmaceutical business. Many pharma companies didn't show interest in P&G's pharma business due to the lack of synergy and short life cycle of its main products. But the specialty pharma company Warner Chilcott didn't refrain from these shortcomings. Warner Chilcott received significant financial return on this acquisition.
- Biotech seems to be better than big pharma in making acquisitions. Perhaps this is due to having similar mentality to the biotech target.

How easy is it to make smart acquisitions? We think it is certainly getting harder. Making smart deals requires good internal scientific expertise, streamlined decision making and a deal-savvy management team. In addition, there have to be good opportunities in the environment for the

picking. It is often said that in today's environment, there are very few companies with decent phase II data and novel technology that are still independent. Also the sheer jump in valuation has priced many target companies out of the market. The robust IPO and secondary offering markets have provided biotech an attractive alternative to seeking deals with big pharma. So it will be exceedingly hard to replicate the success of BMS and others. Just like the R&D process, making good acquisitions requires scientific insight and some luck. We believe future deals are more likely to be done at full price with lower upside for the acquirer.

Table 19 Top Ten Successful M&A Deals for Large Biopharma Companies

Aquirer	Target	Ann. Date	Value ($mm)	Premium 1 Day	Premium 1 Month	Target Sales ($mm)	EV/Sales
Gilead	Pharmasset	21-Nov-2011	$11,000	89%	74%		
Sanofi Aventis	Genzyme	16-Feb-2011	$20,100		48%	4,049	5.0
Gilead	Calistoga	22-Feb-2011	$375+$225				
Celgene	Abraxis	30-Jun-2010	$2,900	17%	62%	359	8.1
Onyx	Proteolix	12-Oct-2009	$276+$535				
Warner Chilcott	P&G Pharma Business	24-Aug-2009	$3,100			2,300	1.3
Bristol-Myers Squibb	Medarex	22-Jul-2009	$2,100	90%	93%	52	
Johnson & Johnson	Cougar Biotech	21-May-2009	$1,000	16%	19%		
Pfizer	Wyeth	26-Jan-2009	$67,900	29%	33%	22,800	3.0
Eli Lilly	ImClone	31-Jul-2008	$6,585	51%	73%	591	11.1

Source: Compiled by MHBK/IRD based on public company reports and Capital IQ. Note: we compiled the top-ten list based on our assessments of biopharma acquisitions with value over $500mn since 2008.

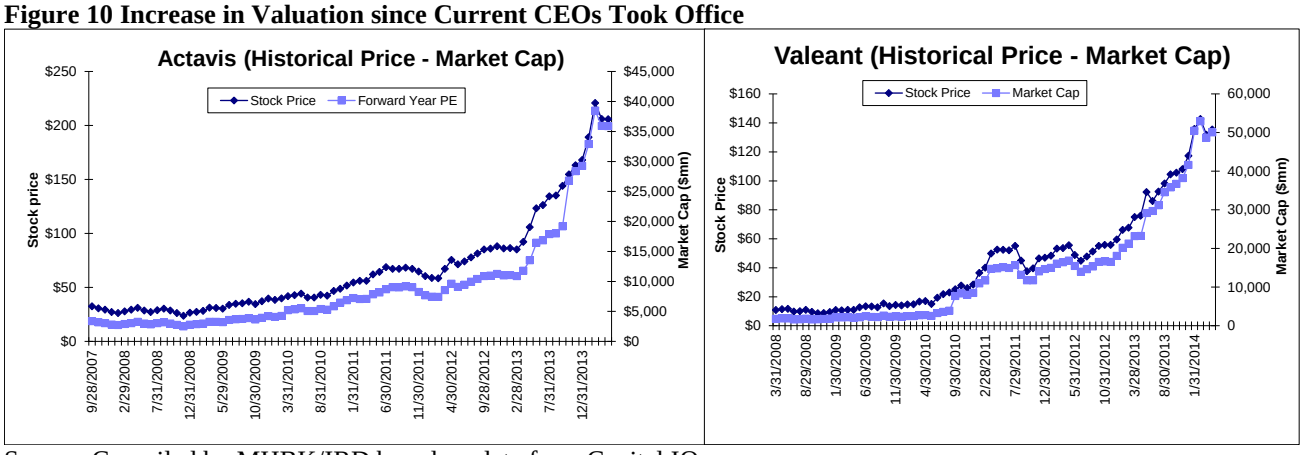
2. The Very Successful Specialty Pharma Serial Acquirers

Another group of companies that have done tremendously well are specialty pharma companies that have adopted aggressive M&A strategies. Both Valeant and Actavis have been deal machines that continuously gobble up smaller rivals. They have been very successful (see Figure 9) and can probably serve as textbook examples of how to build big, profitable corporations through acquisitions. The two companies have some similarities in that both are run by strong, visionary CEOs and have superior execution as the foundation of their business. Michael Pearson was appointed CEO of Valeant in February 2008. A former star at McKinsey, Mr. Pearson went on a non-stop shopping spree to make over 100 licensing and acquisition deals worth $19bn in total. Since his appointment, Valeant's stock price has risen more than 25 times (with dividends reinvested) and its market cap has gone from $2bn in 2008 to over $45bn currently. It has announced a goal of becoming a top 5 pharma company in value terms by the end of 2016. To achieve that goal, Valeant has to leapfrog Merck which had 2013 sales of $44bn (in comparison, Valeant is expected to have sales of $8.2-8.6bn in 2014). Valeant needs to acquire large rivals with market cap in the tens of billions range. There aren't so many such companies around (see Figure 11). Recently Valeant teamed up with activist investor Pershing Square Capital to make a hostile takeover bid to acquire Allergan. Its proposed $2.7bn synergy for the deal would equate stripping out 85% of Allergan's operating expense. Such a drastic cut promised at the outset is perhaps unprecedented.

As shown in Table 20, Valeant has a unique configuration compared to big pharma/ big biotech. Its operation bears no resemblance to any other pharma company. No innovative brand company can survive by investing only 2-3% of sales in R&D. No big pharma enjoys the <5% tax rate like Valeant. In recent years, specialty pharma companies have aggressively used tax inversion to dramatically lower their tax rate. The low tax rate gave specialty pharma companies such as Valeant an advantage in competing with U.S.-domiciled pharma companies.

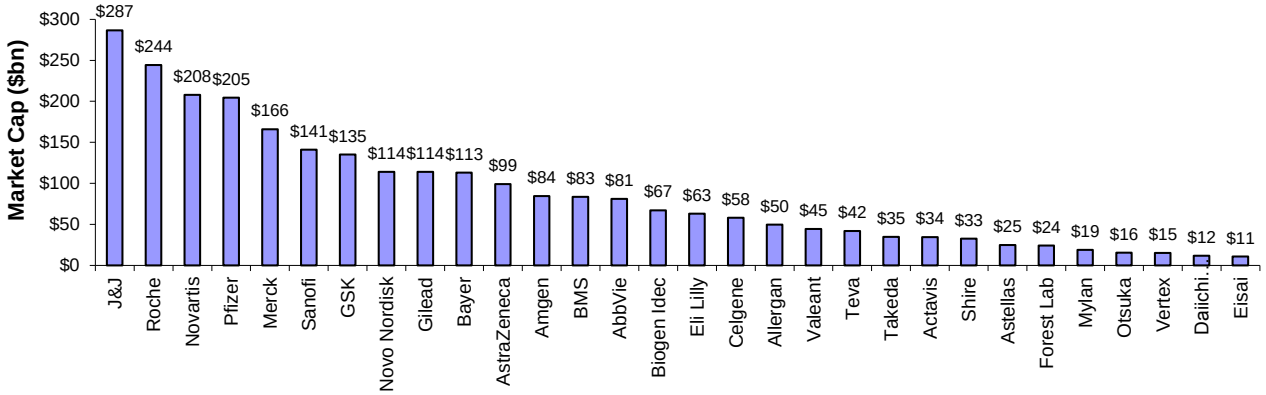
We believe although it is generally impossible for big pharma to adopt Valeant's approach, it can nonetheless learn from it. Certain parts of Valeant's approach such as decentralized decision making, nimble and flexible business practices, and low cost are useful for reference purposes to other big pharma companies. But it would be detrimental to innovation if all pharma companies adopt such an approach. Mainstream pharma companies have to innovate in order to survive. The industry cannot only rely on outside to buy innovation, as eventually someone has to innovate. The industry cannot just be traders and marketers.

Figure 10 Increase in Valuation since Current CEOs Took Office



Source: Compiled by MHBK/IRD based on data from Capital IQ

Figure 11 Ranking of World's Largest Pharma Companies By Market Cap



Source: Compiled by MHBK/IRD based on data from Capital IQ. Note: Actavis's valuation appears low in this ranking because its merger with Forest Labs hasn't been completed

Table 20 Differences Between Valeant and Big Pharma

Strategy	Valeant	Big Pharma
R&D	Not enamored by science, more focused on D instead of R.	Focused on science / innovation.
Organization	Decentralized	Centralized
Cost structure	Lean organization.	Downsized, but still substantial organization overhead. But with it, pharma have full-fledged capabilities.
Therapeutic Focus	Niche areas neglected by big pharma. Stay away from primary care.	High growth areas with potential breakthroughs. Legacy strengths of the company.
Geographic Focus	Markets neglected by big pharma.	High growth, big markets (e.g., BRIC countries).
People's career progression	Perform or out. Not afraid of high turnover.	Long-term, steady career progression.
Deal mentality	Financial-driven. Sensitive to price. Opportunistic. Fast decision-making.	Strategically driven. Less sensitive to price if the strategic fit is great. Slow decision-making.
Financial metrics		
R&D % Sales	2-3%	15%
Tax rate	<5%	20-30%

Source: Compiled by MHBK/IRD based on data from Capital IQ

In a similar fashion to Valeant, Paul Bisaro took over the CEO position at Actavis' predecessor company Watson in August 2007. During his tenure, the company's share price has jumped seven times. The market cap has gone from $3bn to $55bn. Through a number of deals, he has transformed a domestic, also-run generic drug company into a global pharma company with strong presence in both generics and brand pharma (see Table 21). Among the series of deals, the acquisition of Actavis was the most significant as it cemented the company's global position in generics and added key executives to the company. The recent acquisition of Forest Labs has again transformed the company into a top-tier generic/brand hybrid pharma company. With the acquisition of Forest Labs, Actavis has forever changed from being viewed as a potential prey in the overall industry consolidation to a predator. With this deal, pressure will be on other specialty pharma companies such as Mylan and Endo Pharma to further increase in scale or to sell out to bigger companies.

Table 21 Acquisitions by Actavis (Previously Watson) Since Mr. Bisaro Took Office

Acquirer	Target	Announce Date	Deal Value (mn)	Revenues prior yr ($mm)	EV / Sales	EV/EBITDA prior year	Country
Actavis	Silom Medical	31-Mar-2014					Tailand
Actavis	Forest Labs	18-Feb-2014	$25,000	$3,371	7.4		U.S.
Actavis	Warner Chilcott	20-May-2013	$8,500	$2,400	3.5		Ireland
Watson	Actavis	25-Apr-2012	€ 4,500	€ 1,900	2.4	14.6	Europe
Watson	Ascent	24-Jan-2012	AU$375	AU150	2.5		Australia
Watson	Specifar	24-May-2011	€ 400	€ 85	4.7		Greece
Watson	Arrow	17-Jun-2009	$1,750	$647	2.7	11.1	U.K.

Source: Compiled by MHBK/IRD based on public data reports

Recently, the U.S. economy has improved, firms' business foundation has strengthened, and CEOs have become more confident about their businesses. So companies are more ready to do transactions. This is in stark contrast with the environment during the financial crisis when most companies were hunkering down for survival. However, with the improving stock market, biotech valuation has sky-rocketed. Now may be a bad time to attempt M&A in the pharma industry. Acquirers may have to make rosier forecasts and higher assumption for the clinical success rate of pipeline candidates to justify such a price. Inundated with cash infusions from the public market, sellers are sitting pretty to wait for their clinical data to come in, rather than rushing to the exit before the critical clinical inflection point. So we believe the M&A environment for big biopharma is challenging. But some good opportunities still exist, especially in neglected disease areas.

D. New Innovation Model by Big Pharma

Big pharma companies recognize that with the explosion of information, solutions for diseases are getting ever more complex. It is impossible to generate all the innovations in-house. Therefore, they have changed their R&D model from a closed, linear model to a networked model (see Figure 12).

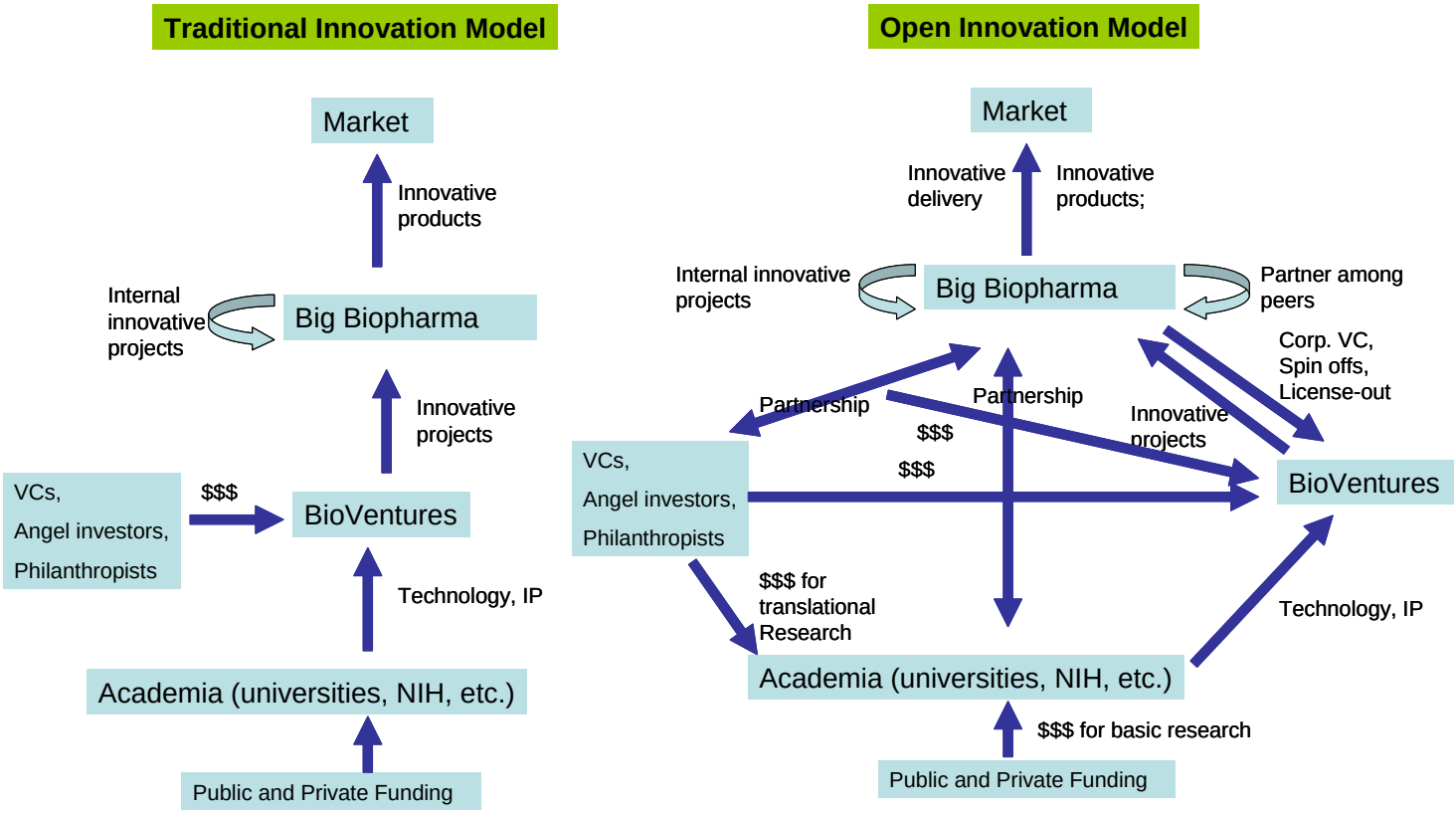
The goal of the new network-based innovation model is to capture innovation early and spread out cost and risk. Such an approach makes good sense because:

1. With the fast-moving scientific developments and increasing complexity in understanding diseases, it is unlikely for innovation to occur only within the confines of one company's R&D centers. Pharma more often play a facilitator role in shepherding drugs to market than inventing drugs de novo.
2. As discussed earlier, assets post the PoC stage are very expensive. At that stage, the assets are typically sold via auctions and it is a contest of who has a deeper pocketbook and the resolve to win. In a bull market, public investors often drive up stock price of biotech companies with good data to stratospheric levels, and thus price many assets out of the market. If pharma can access innovation in its infancy, it won't be subject to the vicissitude of public or VC investors.
3. Pharma's early discovery has not been productive. Pharma should separate discovery research from development (i.e., R from D). Pharma should outsource research by tapping into external expertise. Meanwhile, pharma should retain the development and commercialization functions in-house. We believe shrinking spending on in-house research is a better solution for reducing R&D spending than an across-the-board cut to R&D.
4. Clinical development has become increasingly costly. Pharma companies need P&L sparing capital to support their clinical programs. Therefore, venture capital and private equity firms have frequently joined forces with big pharma. Big pharma companies have gained through these relationships. For example, Lilly's decision to partner its phase III Alzheimer's programs with private equity firms and CROs has saved the company hundreds of millions of dollars with no cost as the programs ultimately failed.

To carry out this network-based innovation model, pharma companies have taken the following measures:

1. Establish innovation hubs in hotspots such as Boston, San Francisco, New York, San Diego and London. Many big pharma companies have also established Asian innovation centers, often in Shanghai, China.
2. Forged collaboration with leading academic centers. Pfizer is a prominent example. Launched in 2010, Pfizer's Centers for Therapeutic Innovation (CTI) allows Pfizer researchers to work side by side with scientists from leading academic labs to discover new targets and do translational research. Pfizer provides access to Pfizer compound libraries, proprietary screening methods, antibody development technologies, and other resources. Pfizer also offer equity interest to academic researchers and their institutions. CTI now has more than 23 academic institutions in its network, with a portfolio of 25 projects across a variety of disease areas.
3. Big pharma companies often have their own in-house venture funds to help them scout for innovation. It is also important to have access to external venture funds. Big pharma often partners with external venture funds. In April 2013, GSK entered into a $495mn alliance with San Diego-based Avalon Ventures. Avalon will invest $30 million and GSK will invest $465 million to launch 10 or so startups over the next three years. We believe partnership with external venture funds is especially important for small biopharma companies as innovations don't proactively go to their door step.
4. Pharma companies have found innovative ways to engage with bioventures. It is no longer a one-way street whereby pharma licenses from bioventure companies. Pharma companies also actively spin off assets to form bioventures. In addition to outright acquisitions, pharma companies have also been active in signing option-based deals with venture companies.

Figure 12 Changes in Innovation Model in Biopharma Industry



Note: Illustrated by MHBK/IRD

Eli Lilly is the pioneer in this open innovation model and its approach can almost serve as a textbook for its peers. Eli Lilly first articulated its strategy of transitioning from a FIPCo (fully integrated pharmaceutical company) to a FIPNet (fully integrated pharmaceutical network) in 2008. Since then, Eli Lilly has fully put this concept to work through creating various structures[2] such as its deals with CRO, the Chorus program, and having outside capital to participate in the development of its clinical programs. The result is Lilly was able to spread the risk and cost of its R&D and at the same time effectively tap into external innovation. Especially noteworthy, the Chorus program was set up as an independent organization at Lilly that uses a fully outsourced model to advance compounds from phase I to the PoC data. The program is considered very successful[3].

For biopharma companies, Celgene is a good example for tapping into innovation early. In good times, a smart company should aggressively sow the seeds for future success. This is indeed what Celgene has been doing. There are a finite number of cutting-edge innovations at a certain point. Celgene has signed deals with many truly cutting-edge companies in oncology (see Table 22), and thereby removing competitors' access to them. Although the financial outlay may seem steep given the early-stage nature of the assets, true medical innovation is almost priceless. As we discussed in the M&A section, what is critical for biopharma deals is not the price but the innovation itself (as demonstrated by the ultimate clinical data). With the right strategy, it is hard for us not to envision Celgene continuing its upward trajectory.

Table 22 Celgene's Early-Stage Oncology Deals

Date	Partner	Technology	Upfront ($mn)	Deal Description
4/1/2014	Forma Therapeutics	Protein-protein interaction	$225	For 3.5 years Celgene will have an exclusive option to license international rights to Forma programs after Phase I testing. Two extensions with two years each. Option to acquire Forma.
12/2/2013	OncoMed	Cancer stem cell	$177	Celgene invests in OncoMed's Demcizumab and up to five additional preclinical programs; OncoMed leads early clinical trials and retains co-development, co-commercialization and profit-sharing rights.
7/29/2013	Acetylon	Cancer epigenetics (HDAC inhibitors)	$100	Option to acquire Acetylon. Main asset is HDAC6 inhibitor for multiple myeloma.
3/21/2013	Bluebird Bio	CAR-T adoptive T cell therapy / Gene therapy	Not disclosed	Licensed ex vivo lentivirus gene delivery technology for CAR-T therapy from Bluebird. Potential payment up to $225mn per program.
4/26/2012	Epizyme	Cancer epigenetics (HMT inhibitors)	$90	Celgene received an exclusive license outside the U.S. to some of Epizyme's programs for three years.
4/15/2010	Agios	Cancer metabolism	$130 including an equity investment	Agios will lead discovery and early translational development. Celgene has an exclusive option to license any resulting clinical candidates at the end of Phase I.

Source: Compiled by MHBK/IRD based on public data reports

[2] http://fnih.org/sites/all/files/documents/Andrew_Dahlem.pdf
[3] http://www.choruspharma.com/pharma.focus.pdf

E. Conclusion

In the section above, we discussed various aspects of competitive strategies in the pharma industry. The current environment demands companies have a focused strategy. Many big pharma companies have taken this to heart by pooling resources to form category leaders, which makes good sense.

By looking at overlaps of focus in therapeutic areas, we found many big pharma companies are drawn to similar TAs for similar reasons. This crowding will lower investment returns in these hotly pursued areas. Meanwhile the neglected diseases will have higher prospective returns as big pharma companies shift their resources to higher-priority areas. In our view, companies need to take a hard look at the market and decide whether they have the wherewithal to become a leader in a competitive area (e.g., oncology). It not, they should shift focus to less competitive areas.

We looked at some companies successful in the past and found several models for success. Applicable to most biopharma companies is the innovation leadership model. Biopharma companies are ultimately in the innovation business. It is an innovate-or-die business. The bar to becoming the innovation leader in a given TA has become ever higher. To succeed, we believe companies need to put R&D as the forefront of their enterprise. Historically, successful pharma companies have been often run by visionary scientists rather than by executives with a commercial, legal, or other background. Absent a change at the top, big pharma companies should have a strong head of R&D who enjoys autonomy in decision-making. Unfortunately in recent years, for good or for bad, R&D has become a source of cost-cutting. In addition, the impact on R&D organizations from pharma mergers has been immeasurable. Although the short-term impact has been minimal and the financial logic was often overwhelming, the long-term impact of big cuts to R&D is hard to quantify. We note it is companies that haven't gone through mergers or big cuts in R&D that have the best pipelines in the industry (e.g., Novartis, BMS, Roche, Eli Lilly, etc.). Meanwhile the current size of Pfizer's pipeline is lower than its pre-merger level. The risk to the industry is having pipelines built for the purpose of short-term gratification but lacking breadth and depth.

Another successful strategy adopted by specialty pharma companies is to focus on niche areas that are neglected by big pharma. Combined with an aggressive M&A strategy, specialty pharma companies such as Valeant and Actavis have achieved unparalleled returns in the industry. Although there is inherent incompatibility between the specialty pharma model and the innovative pharma model, we believe biopharma can still learn a lot by assimilating some practices of aggressive specialty pharma leaders.

M&A is a critical element of big pharma's success. Depending on the company, 25-50% of big pharma's portfolio can come from external sources. Looking at the deals over the last six years, indeed there have been many favorable deals for the acquirers. But the current environment is rich in valuation. After years of picking by big pharma and a sharp run-up in biotech valuations, worthwhile M&A has become a very expensive endeavor. We believe it is unlikely for acquirers to walk away with investments that have a big upside as in some past deals. Maybe that is why biopharma companies are shifting to early-stage deals. However, some good opportunities do exist in some neglected areas.

Mindful of the high cost of catching innovation late, big pharma companies are competing aggressively to tap into innovation at an earlier stage. As an extension of the R&D strategy, biopharma companies have formed innovation hubs in the hotspots of biomedical research. They have formed alliances with VCs, academia and among themselves to actively create innovation. So pharma innovation has changed from the linear model in the past to a network-based model at present. Eli Lilly is leading the industry for its FIPNet model, which we believe serves as a good template for its peers. In our view, pharma companies should separate R from D and rely extensively on external sources for discovery research. Pharma firms' involvement in venture creation is good for the ecosystem. Given their tremendous in-house expertise, they could help select and catalyze the best innovation coming out of academic labs and young biotechs. They should be flexible in deal terms and not afraid to step in at an early stage. Big pharma can regard this as an extension of its in-house early R&D organization. For biopharma companies, Celgene is a good example of tapping into innovation early.

Appendix

Table 23 Notable Late-stage Development Failures from Big Pharma (2004-2008)

	2004	2005	2006	2007	2008
Pfizer		Daxas (roflumilast, COPD) Oporia (lasofoxifene, osteoporosis) *Bextra (Arthritis)* Endotecarin (cancer) Capravirine (HIV)	Torcetrapib (Atherosclerosis) Indiplon (Insomnia) Asenapine (Shizophrenia)	Exubera (Inhaled insulin)	Tremelimumab (melanoma), CP-945598 (obesity)
Merck	*Vioxx (Arthritis)*	Pargluva(Diabetes)		Gaboxadol (Insomnia) Arcoxia (Arthritis)	Taranabant (obesity)
Bristol-Myers Squibb		Pargluva(Diabetes) E2F decoy (vein graft failure)			
Eli Lilly			Arxxant (diabetes complications)		AIR Inhaled Insulin
Astra Zeneca	Exanta (oral anti-coagulant) Iressa (Cancer)		NXY-059 (Stroke) Galida (Diabetes)	AG-1067 (Atherosclerosis)	Recentin/AZ 2171 (NSCLC)
Novartis		PTK 787 (Cancer)		Zelnorm (IBS) Galvus (diabetes, U.S.)	
Roche					
Sanofi-Aventis				Acomplia (obesity),	Amibegron (depression)
GlaxoSmithKline				gepirone ER (depression)	

Source: Compiled by MHBK/IRD based on public company reports

Table 24 Notable Late-stage Development Failures from Big Pharma (2009-2014)

	2009	2010	2011	2012	2013	2014
Pfizer	Axitinib (adv. Pancreatic cancer), Sutent (Colon cancer) esreboxetine (fibromyalgia), PD 332,334 (GAD)	Dimebon (Alzheimer's); Figitumumab (lung cancer); Sutent (breast, liver, lung, prostate cancer); Tanezumab (OA), Thelin agonist (PAH)	Neratinib (breast cancer)	Bapineuzumab (ApoE4 Alzeimer's disease)	inotuzumab (NHL)	
Merck	Rolofylline (CHF)	Vicriviroc (HIV); Acadesine (Ischemia-Reperfusion Injury)	telcagepant (Migraine)	vernakalant (AF); Ridaforolimus (Sarcoma); Tredaptive (Atherosclerosis)	Preladenant (PD)	
Bristol-Myers Squibb				Brivanib, INX-189 (HCV), γ secretase inhibitor (AD)		
Eli Lilly	Dirucotide (RRMS)	Semagacestat (Alzheimer's disease), Tasisulam (melanoma), Teplizumab (T1DM)	Arxxant (DR); Sollpura (liprotamase panreatic enzyme replacement)	pomaglumetad (mGluR2/3) for Schizophrenia, tabalumab (RA), Solanezumab (AD)	Enzastaurin (DLBCL); BACE inhibitor (AD); Edivoxetine (depression)	
Astra Zeneca	Zactima (lung cancer)	Recentin (Colon cancer), Motavizumab (RSV vaccine), Zibotentan (CRPC), Certriad	TC-5214 (depression)	fostamatinib (RA)		
Novartis	QAB 149 (COPD)		elinogrel (anti-platelet) Agomelatine (depression), SMC021 (osteoarthritis)	Tekturna (hypertension),	Dovetinib (kidney cancer)	
Roche	Avastin (Adjuvant CRC); Tarceva (NSCLC maintenance)	Avastin (breast, prostate, gastric, colon adjuvant); Ocrelizumab (RA); Taspoglutide (Diabetes)		Dalcetrapib (atherosclerosis)	Aleglitazar (T2DM with ACS)	bitopertin (Schizophrenia); onartuzumab (MetMab, NSCLC)
Sanofi-Aventis	Ciltyri (insomnia); Idrabiotaparinux (DVT, PE, AF); Xaliproden (neuropathy); Larotaxel (cancer) Satavaptan (hyponatremia); Saredutant (depression); AVE5530 (cholesterol); TroVax (cancer vaccine)	NV1FGF (Critical limb ischemia)	iniparib (triple-negative breast cancer); Prochymal (GvHD)	Over 2011-2012, under the new leadership of Zerhouni, Sanofi substantially pruned its late-stage portfolio by discontinuing 10 phase III programs.	Otamixaban (Factor Xa inhibitor), Lemtrada (MS in U.S.), Fedratinib (Myelofibrosis)	
GlaxoSmithKline	Rezonic (nausea); Mepolizumab (HES)	Simplirix (Herpes vaccine)	Almorexant (insomnia), otelixizumab (T1DM)	Migalastat (Fabry Disease)	vercirnon (Crohn's disease); drisapersen (DMD)	darapladib (ACS, CHD); MAGE-A3 (melanoma, lung cancer)
Abbvie				Bardoxolone (CKD)		

Source: Compiled by MHBK/IRD based on public company reports

Abbreviations	
ABT	Abbott
AMGN	Amgen
AZN/AZ	Astra-Zeneca
BLA	Biologic License Application
BMY/BMS	Bristol-Myers Squibb
CMS	Centers for Medicare & Medicaid Services
CNS	Central nervous system disease
COGS	Cost of goods sold
CRO	Contract Research Organization
FOB / Biosimilars	Follow-on Biologics. Generic copy of branded biologic drugs.
GI	Gastrointestinal disease
GILD	Gilead Sciences
GSK	GlaxoSmithKline
IPO	Initial Public Offering
JNJ	Johnson & Johnson
LLY	Eli Lilly
M&A	Merger and Acquisition
MRK	Merck
NDA	New Drug Applications
NME/NCE	New Molecular/Chemical Entities
NVS / NOVN	Novartis
P&L	Profit and loss statement
PFE	Pfizer
PoC	Proof of Concept
R&D	Research (discovery research) and Development
ROG	Roche
SAN	Sanofi-Aventis
SG&A	Selling, General and Administrative Expenses
SGP	Schering-Plough
Specialty Medicine	Drugs that treat diseases which are not suffered by the general public and are prescribed by specialty doctors rather than by primary care physicians (PCPs). Disease conditions include inflammation, Multiple Sclerosis, Cancer, Blood cell deficiency, Growth deficiency, Hepatitis C and others.
TAs	Therapeutic Areas
WYE	Wyeth

CONTACTS

Global Corporate Advisory (Americas)
Industry Research Division
Mizuho Bank, Ltd.

1251 Avenue of the Americas
New York, NY 10020

Team Head
Ryohei Oikawa
Deputy General Manager
(212) 282-3298
Ryohei.oikawa@mizuhocbus.com

Pharmaceutical, Biotechnology & Healthcare
Tim Wang, CFA
Senior Vice President
(212) 282-3669
timxin.wang@mizuhocbus.com

Edited / issued by Industry Research Division Mizuho Bank, Ltd.
Address: 1-5-5 Otemachi Chiyoda-ku Tokyo
Tel: (03)5222-5075

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