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Does R&D pay?

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Pharmaceutical R&D is notoriously risky, lengthy and costly; moreover, it does not always produce products of blockbuster status. The conventional route of fully discovering, developing and marketing a new chemical entity is followed by the large pharmaceutical companies, whereas other organizations in the pharmaceutical sector – such as generic or specialty companies and biotechnology companies – only operate over portions of the full R&D process. Here, we compare the ten-year financial performance of these three subsectors through their price/earnings ratios and their return on capital metrics to understand which of these strategic alternatives offered the best return to investors.

Introduction

Among the myriad problems facing the pharmaceutical industry, one statistic that is little dwelt upon is the proportion of approved products that return their R&D investment. Beyond the sequential and increasingly high hurdles of preclinical and clinical safety and efficacy, only a small proportion of even the successful outputs from development actually command sufficient commercial payback to refuel the R&D engine. In fact, a 2008 study reported that seven out of ten drugs launched in the past five years fell into this unsuccessful category (see 'Pre-launch planning: priming your pharmaceutical brand for profit and success' at http://www.pharmaprelaunchroi.com/index.asp) [1].

A recent analysis of the estimated average internal rate of return on R&D investment for a typical small-molecule compound gave a figure of approximately 7.5%, leading to a negative present value of USD $65 million [2]. This analysis challenges the precept that R&D delivers positive value to the pharmaceutical industry and leads to the central question of whether new chemical entity research is actually self-sustaining. We have attempted to answer this question by looking at the share price/earnings ratio for companies with very different attitudes to R&D. We have chosen three types of company: mature biotechs, generic or specialty pharma and large pharma. Large pharma companies not only have substantial investments in R&D, especially in new chemical and biological entity research, but also have substantial commercial and marketing power; generics and specialty pharma, though different in the execution of their business strategy, have a much lower risk commitment to R&D as a proportion of their sales (see 'A blurring of the lines? Is 'innovator' or 'generic' becoming harder to discern?' at http://scientific.thomsonreuters.com/m/ppt/phtl/13.blurringlines.ppt), and the money they do spend is predominantly on reformulations, abbreviated New Drug Applications and regulatory submissions (hence, they are grouped together in our analysis). Biotech companies are mostly devoted to R&D for future promise and upside. Out of necessity, our analysis focused on companies with histories of positive earnings – particularly mature, listed biotech companies. This makes the biotech portion of our analysis heavily selective, compared with the broader biotech sector, but still allows useful comparative insights between the three subsectors.

Why price/earnings ratio?

Price/earnings ratio (P/E) is one of the most commonly used and simplest metrics for looking at respective valuations of company shares. Although too basic when looking at individual companies (the valuations of which are affected by a myriad of quantitative and qualitative business issues), when comparing companies between sectors, the P/E can give a useful indication of sentiment regarding such sectors. Simply put, a low P/E suggests the companies are out of fashion and more cheaply valued, and a higher P/E suggests the companies are more popular and, hence, more

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1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2009.11.002

expensive. Generally speaking, high P/E ratios are found in high technology or growth stocks, reflecting the expectation that the investment of today will pay out as earnings in the future.

A substantial body of thought suggests that low P/E shares, as a cohort, offer better longer term opportunities for investment return than higher P/E shares [3]. For lower P/E-rated shares, much of the bad news is already 'priced in', so subsequent negative developments have a limited impact on share price, whereas even small positive news has a disproportionately positive effect. By contrast, the highest P/E-rated shares are often priced for perfection, so even a small glitch in a company's development can have a disproportionate and negative effect on share price.

Thus, our reason for examining P/E within the three sectors described is to ascertain (i) whether there is a difference in sentiment toward each of them, (ii) whether there is an expectation that R&D investment will pay out as a future earnings reward and (iii) whether a sector-wide pricing discrepancy indicates a contrarian investment opportunity, potentially going against current financial sector dictums.

Results of analysis

We considered P/E for large pharma, generic or specialty pharma and mature biotech, with annualized ratios from 1999 to 2008 and current P/E for 2009 (Table 1; Fig. 1).

The analysis showed some interesting results. First, mature biotechs had by far the highest P/E over the 11-year period, ranging from a high of 75× (2001) to a low of 19× (2009), substantially higher than both of the other groups. Second, specialty pharma/generics generally had a higher P/E than large pharma; the difference ranged from 40% greater to equal ratios in 2009, and there were only two years where large pharma had a higher P/E. Finally, P/E for each of the subsectors has generally trended downwards over the 11 years, except for mature biotech in 2001 (when biotech valuations were part of a bubble).

These results indicate that over the period examined, the sectors ranking in terms of investment popularity rank from biotech to specialty/generics to large pharma. This is largely consistent with anecdotal industry findings, whereby biotechs are valued highly based on future promise rather than current earnings. (In fact, these results are significantly skewed downward when considering the broader biotech subsector because most biotechs are never profitable and many fail to ever reach a public listing, introducing survivorship bias.) Furthermore, industry perception suggests that specialty pharma/generics compared with large pharma are more attractive as investment opportunities. This might be because generic or specialty pharma are considered more nimble and adaptable, more able to shift the performance dial without blockbuster hits and less exposed to the risk of early-stage research and discovery. This is reflected by specialty pharma/generics generally maintaining higher P/E ratings than large pharma.

These results also suggest some interesting implications for private-stage investors (e.g. venture capitalists and angels) in biotech and specialty/generics. Because public market valuations are higher than large pharma, this suggests (i) retail and institutional investor support from healthcare investors, enabling partial exits via initial public offerings; and (ii) potential pressure for large pharma to consider biotech and specialty/generics as acquisition targets, to import the future opportunity and 'allure' of such companies into large pharma pipelines. This second point is particularly relevant to large pharma because looming patent expirations cause increasing pressure to replace and build future pipelines, often through acquisitions.

Reflection on recent events

We considered whether the analysis above is reflected in events that are happening or have happened in the industry over the past few months. There are several examples of a shift by large pharma away from the standard pattern to discover new medicines based on new molecules (new chemical entities or new biological entities), with the new molecule either coming from in-house discovery, or licensed from external sources and then developed and commercialized internally.

TABLE 1

Companies used for analysis[a]

Large pharma sector	Generic/specialty pharma sector	Mature biotech sector
Johnson & Johnson	Teva Pharmac. (ADR)	Amgen
Pfizer, Inc.	Allergan, Inc.	Gilead Sciences
Novartis AG ADR	Forest Labs.	Celgene Corp.
GlaxoSmithKline ADR	Hospira, Inc.	Genzyme Corp.
Sanofi-Aventis	Mylan, Inc.	Biogen Idec, Inc.
Abbott Labs.	Watson Pharmac.	Cephalon, Inc.
Wyeth	Perrigo Co.	United Therapeutics
Merck & Co.	Endo Pharmac. Hldgs.	Cubist Pharm, Inc.
Bristol-Myers Squibb	Biovail Corp.	
Schering-Plough	King Pharmac.	
Lilly (Eli)	Sepracor, Inc.	
Novo Nordisk ADR	Valeant Pharmaceuticals	
	Medicis Pharmaceuticals	
	Par Pharmaceutical	

[a] The data were compiled using a well-established and NASDAQ-listed US stock research service called Value Line (NASDAQ: VALU). The data-service used considers the largest 1800 or so US listed companies. The analysis is limited to companies for which these data are available.

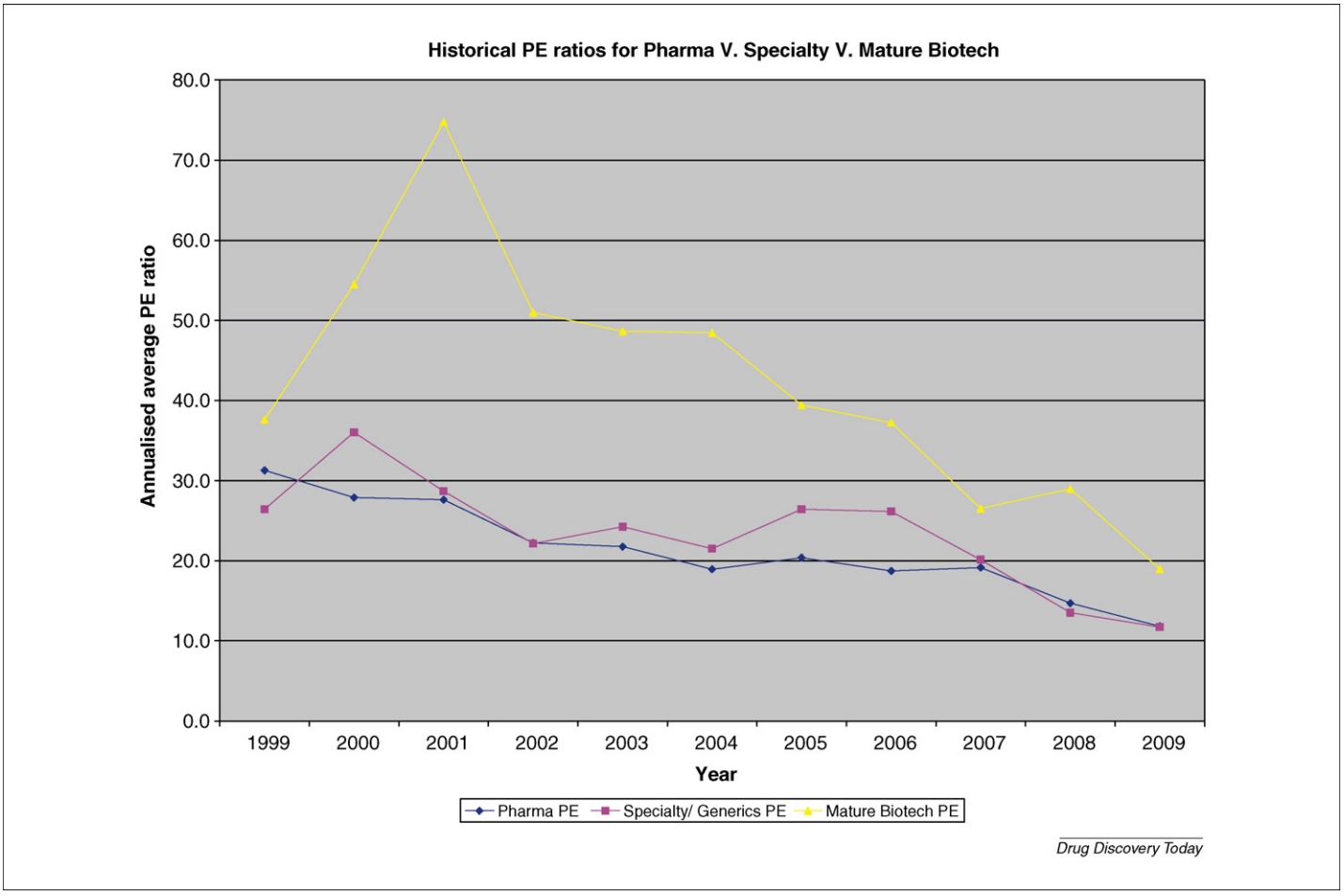

FIGURE 1

Historical P/E ratios for Large Pharma vs Generics/Specialty Pharma vs Mature Biotech.

Such examples include the recent $3.6 billion tie-up between GSK and privately held specialty dermatology company Stiefel. The *Wall Street Journal* reported this as a move away from high-priced blockbusters toward more steady and, in their words, 'boring' products like acne creams. Analysts viewed the Stiefel deal as directed toward low-growth revenue.

The deal was the largest undertaken by GSK's new CEO, Andrew Witty, since his appointment a year ago and followed shortly after the announcement of a tie-up between GSK and Pfizer to pool R&D efforts in HIV. At the time of the announcement, one of the goals of the venture was to develop new fixed-dose combination therapies (FDCs), using existing and novel medicines. GSK is well aware of the commercial attractiveness of FDCs in the treatment of HIV, having marketed Combivir™ and Trizivir™ for many years. Combivir™ is a combination of zidovudine and lamivudine, and Trizivir™ includes abacavir in addition to these two agents. It is also worth noting that GSK's biggest product is currently the FDC of salmeterol xinafoate and fluticasone propionate (Advair™/Seretide™) for the treatment of asthma and chronic obstructive pulmonary disease, which is expected to have sold $7.9 billion in 2008 (see 'Glaxo says Advair sales to top 4 bln pounds in 2008' at http://uk.reuters.com/article/UK_SMALLCAPSRPT/idUKL215105120080521). The attractiveness of new presentations of existing drugs is an area that we have remarked upon recently as a low-risk but commercially rewarding avenue for R&D [4].

In July last year, GSK made the decision to enter into the branded generics marketplace with the acquisition of South Africa's Aspen Pharmacare Holdings. GSK already had an R&D collaboration with Indian Generics Company Ranbaxy, which was bought by Daiichi Sankyo Co. Ltd. in 2008. This year, Pfizer took a further step to enter into the generics market with a set of collaborations with Indian generics maker Aurobindo (see 'Pfizer grabs rights to sell more generics' at http://blogs.wsj.com/health/2009/03/03/pfizer-grabs-rights-to-sell-more-generics/). Novartis bought Eon/Hexal in 2006 and Sanofi-Aventis' merger with Zentiva was approved in 2009. Other large pharma companies already have a presence in the generics sector; in the case of Novartis, their generic division is Sandoz.

One reason for the new era of cooperation between large pharma and generics companies is the shortening timetable for the loss of patent protection for a substantial proportion of branded products in the coming three or four years. A tsunami of new generic products is ahead of us, particularly in the years 2011 and 2012 (Table 2), by which time more than $100 billion in sales will have been lost since 2008 (see 'Drug lifecycle management could be the answer to the $100 billion question' at http://www.pharmafocus.com/cda/focusH/1,2109,21-0-0-SEP_2008-focus_news_detail-0-492155,00.html). Accommodations between large pharma and generics companies have taken place in some cases to effect managed transition to generic versions of patent-expired or -expiring products, or

TABLE 2

Earliest dates for the loss of patent protection for brand name drugs

2010	2011	2012	2013	2014
Imiquimod	Naratriptan	Dolasetron	Entacapone	Sirolimus
Tamsulosin	Pantoprazole	Rasagiline	Decitabine	Zanamivir
Nateglinide	Ranolazine	Escitalopram	Zolmitriptan	Mesalamine, e.r.
Atorvastatin	Famciclovir	Rosiglitazone	Riluzole	Temozolomide
Felbamate	Zafirlukast	Quetiapine	Ritonavir	Moxifloxacin
Losartan	Azelastine	Tiagabine	Alosetron	Nelfinavir
Lamivudine	Tinidazole	Irbesartan	Memantine	Loteprednol etabonate
Meropenem	Letrozole	Modafanil	Dutasteride	Lopinavir
Anastrozole	Zileuton	Fluvastatin	Tegaserod	Risedronate
Miglustat	Levofloxacin	Clopidogrel	Rabeprazole	Amprenavir
Trospium	Capecitabine	Temsirolimus	Efavirenz	Telmisartan
Eprosartan	Pioglitazone	Abacavir	Emedastine	Lubiprostone
Salmeterol and fluticasone	Latanoprost	Raloxifene	Duloxetine	Eszopiclone
Docetaxel	Pramipexole	Alitretinoin		Sevelamer
Gemcitabine	Candesartan	Montelukast		Glatiramer acetate
Apraclonidine	Olanzapine	Tigecycline		Esomeprazole
Donepezil	Azacitidine	Rivastigmine		Sertaconazole
Cidofovir	Tazarotene	Ziprasidone		Nepafenac
	Clofarabine	Ibandronate		Colesevelam
		Valsartan		
		Levocetirizine		
		Tolterodine		
		Dofetilide		
		Sildenafil		
		Arformoterol		
		Indinavir		
		Rizatriptan		

'authorized generics' (see 'Assessment of authorized generics in the US' at http://www.phrma.org/files/IMS%20Authorized%20Generics%20Report_6-22-06.pdf). With increasing regularity, brand name drug companies are signing deals for an authorized generic version shortly before or just as the patent is due to expire. Examples of this practice include Cipro™ (ciprofloxacin) from Bayer to Barr, Duragesic™ (fentanyl) from JnJ to Sandoz and Cutivate™ (fluticasone) from GSK to Taro. Some large pharma companies have set up generics divisions specifically to accommodate authorized generic products: Johnson and Johnson (Patriot) and Pfizer (Greenstone), for example. Other arrangements involve spinning out separate companies; for example, Abbot set up Hospira, a new, independent global hospital products company in 2005.

These examples indicate a more pluralistic strategy from large pharma companies toward generics. It is interesting in this regard that the publicly declared corporate strategy from Andrew Witty includes a focus on 'return on investment' as one of its four mantras (http://www.gsk.com/mission-strategy/products-value.htm). We wondered, therefore, whether an analysis of return on capital would give different results to the P/E analysis or, indeed, whether a consideration of both metrics together would be the most useful approach.

An alternative view – looking at return on capital

Return on capital (ROC) is commonly used in business by managers to assess the efficiency with which assets are being allocated. This suggests companies with higher ROC are better allocators of capital because they achieve a greater return for every dollar of capital deployed. Investors focused on company fundamentals as part of their investment process also use ROC as a way to determine efficiency of operations and quality. (When considered alone, this can be a more useful measure than similar ratios, such as return on equity, because it includes the equity and debt portion of a company's balance sheet.)

Once again, we performed the analysis by looking at annualized ratios back to 1999 for each of the subsectors and current ROC for 2009 (Fig. 2). The results indicated that large pharma had by far the highest ROC of the groups. This ranged from a peak of 34% (2000) to a low of 19% (2007) and, in 2009, is currently just more than 21%. For most of the period, specialty/generics had a higher ROC than mature biotechs, except in the first two and the past two years of the analysis. However, bearing in mind that the broader biotech sector would have a negative ROC because most companies are loss making, this indicates that specialty/generics companies have a higher ROC than biotech. The range of ROC for specialty/generics

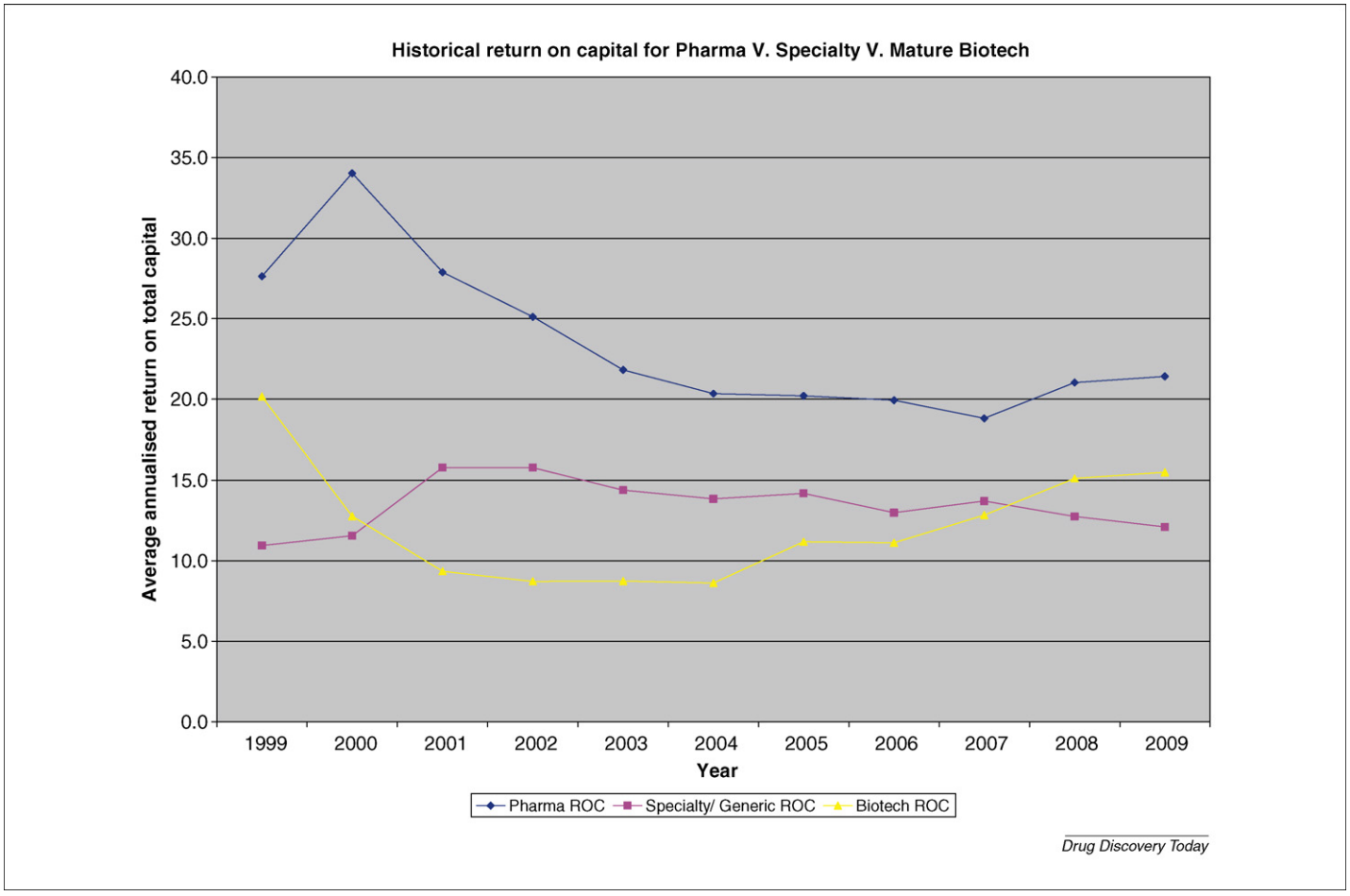

FIGURE 2

Historical ROC for Large Pharma vs Generics/Specialty Pharma vs Mature Biotech.

was narrower than for large pharma, ranging from 11% (1999) to 16% (2001) and, in 2009, is currently just more than 12%.

From an operating basis, these results suggest that large pharma – with the highest ROCs – are the most efficient businesses, followed by specialty/generics, with biotech in last place. Biotech's low ROCs are readily explained because the sector is largely built on the future promise of the science and potential benefits for human healthcare, rather than current business performance. Large pharma outperform specialty/generics on ROCs because they have a long history of substantial earnings with blockbusters and considerable advantages of scale. However, it will be interesting to see how this changes over the next five years to 2014, as many blockbuster drugs come off patent.

Concluding remarks

When considering both P/E and ROC together, we can draw several conclusions for investors and managers. For public market investors (particularly those with a value and contrarian inclination), the best opportunity seems to be among the large pharma, which offers the cheapest valuations with the most efficient use of capital (i.e. getting the most 'bang for your buck'). Biotech investors clearly have the highest risk game, given that so much is dependent on the validation of science and clinical trials. Most companies never make it to positive earnings, but valuations are based on future promise and potential, rather than business performance today. The opportunity for spectacular – though unpredictable – gains will, no doubt, always attract a certain profile of investor. Finally, generics or specialty pharma seem to offer an interesting compromise for certain investors. These offer an interesting mix between fairly consistent ROCs and higher historical P/E ratings, and they might make interesting acquisition targets for large pharma looking to boost revenues short term or protect themselves from portfolio genericization over the next few years.

References

1 Grabowski, H.G. and Vernon, J.M. (1994) Returns to R&D on new drug introductions in the 1980s. *J. Health Econ.* 13, 383–406

2 David, E. *et al.* (2009) Pharmaceutical R&D: the road to positive returns. *Nat. Rev. Drug Discov.* 8, 609–610

3 Dremen, D. (1998) *Contrarian Investment for the Next Generation.* Simon Schuster

4 Cavalla, D. (2009) APT pharmaceutical R&D: the right active in the right presentation for the right therapeutic use. *Nat. Rev. Drug Discov.* 8, 849–853