A Case for Small Cap Investing: Biotech

Emerald Small Cap Life Sciences Team
In this paper, we sought to lay out the rationale for investing in small cap biotech. There are two key drivers of stock performance of small cap biotech: clinical data and acquisitions. As clinical data must be analyzed on a case-by-case basis, we have focused our efforts in this paper on factors that will drive M&A in this space. We have also examined the forces that worked to get us to the point we are today.

We have arrived at four principles that we believe frame the discussion around the future of M&A. The discussion begins by taking a deep dive into the desperation being felt by the potential acquirers. Section 1 addresses the patent cliff that big pharma will face in the next 3 years, big pharma’s desire to move into biotech, and the fact that pharma has moved away from innovation while turning its focus to selling and marketing. Cash-rich big pharma will seek to rectify a decade of research and development that from a revenue perspective was mildly successful but from an innovation perspective was nothing short of failure. This will force acquirers to pay a premium for the innovation available at small biotech companies.

In section 2 we examined the life blood of biotech—funding. When one considers that the average length of development is approximately 15 years for a biotech agent, mere examination of recent funding trends would be myopic. NIH funding which supports the idea generation at the academic level more than doubled from 1995 through 2002. We believe that we are just beginning to see the fruits of this research emerge in the public markets. Secondly, although the venture capital market has struggled over the past couple years, the amount invested annually in biotech has remained stable, further supporting a crop of new companies that will come public.

We next looked at the geographic breakdown of the biotech companies and the impact that legislation has had on spurring innovation in the US. Although the entire world benefits from biotech innovation, the biotech industry is largely supported by investors in the United States. As Americans, we are all beneficiaries of this industry. In addition to the life saving therapies created by this industry, the biotech industry also helps grow local economies as 6.7 jobs are created for every biotech job created in a given region.

Finally, we show that since inception, the NASDAQ Biotech Index has tripled the return of the broader NASDAQ index. Despite this outperformance, we have actually seen takeout premiums rising over the past 3 years, as the market is not yet appreciating the scarcity of quality biotech assets and the desperate situation in which the buyers have found themselves. We also present data that indicates the market for biotech drugs will be growing, driven largely by the aging population.

In summary:
1. **Demand is strong from big pharma for the innovation** provided by development stage biotech (Section 1).
2. **Supply has been consistent** in the form of NIH and venture capital funding, which produces new ideas and seeds new companies (Section 2).
3. **Adequate funding of biotechnology research is the key to curing diseases** that end the lives of millions of people per year. Additionally, biotech companies create high quality domestic jobs. (Section 3).
4. Since inception in 1994, **returns from the NASDAQ Biotech Index have tripled that of the broader NASDAQ**. In addition, we present data that indicates that **takeout premiums are rising** (Section 4).
Section 1

Demand side: Pharma recognizes that their strength has shifted from R&D to selling and marketing. This shift of core competency has created holes in the pipeline of big pharma that can only be filled by small biotech companies and by big pharma’s willingness to adopt a research culture a-la biotech.

- Pharmaceutical companies have changed over the past 15 years. **The core competency of pharma is now selling and marketing**, a shift from their innovative roots. Commercializing drugs takes on the form of direct-to-consumer marketing, sales forces educating doctors, obtaining reimbursement from payers, and lobbying. There is no better illustration of this principal than the fact that the 12 largest pharmaceutical companies spent **16% of revenue on R&D and 46% of revenue on SG&A in 2008** (source-company filings and Factset).
  - To further illustrate this point, there were two mega-mergers in big pharma in 2009 (PFE/WYE and MRK/SGP). For both transactions, the **majority of synergies were driven by SG&A savings**. In both cases, the combined entities in 5 years will likely be smaller than the present value of either stand-alone company today due to the patent cliff. **This cliff is not specific to only the companies mentioned above; it is an issue that the entire industry must address. The patent cliff exists because pharma has under-invested in innovative products.**

Pharma research productivity has been abysmal

- R&D expenditures have been growing at 8% annually for the last decade with little to show for these efforts in the way of new classes of drugs or new chemical entities. We argue that this has been because the **majority of big pharma’s R&D efforts have focused on making minor modifications to already approved drugs in hopes of gaining extended patent life** (see the trend line tracking new molecules approved as a percentage of total drug approvals in the chart below).
  - Pharma will have to pay up for the innovative molecules that they chose not to pursue over the last decade.
New drugs approved in the US

Source: FDA website and Jefferies & Co.

- This futility has prompted a debate in the academic literature as to whether or not the IRR of R&D for big pharma is even positive. A recent article pegs the NPV of an average small molecule at $65M with an IRR of 7.5% while the estimated NPV for an average biologic is $1,260M with an IRR of 13%. For reference, the authors calculate the cost of capital for drug development to be 9.5% (Nature Reviews Drug Discovery Volume 8, August 2009).
  - Interestingly, there is no debate around big biotech ROI as the pricing and duration of sales for these biological molecules yield positive returns any way the data is sliced.
- 75% of all 2008 drug revenue is from products launched prior to 2002.

Source: Jefferies and company July 14th 2009 CRO Report
The new frontier for pharma—biologics

<table>
<thead>
<tr>
<th>Complexity</th>
<th>Small molecules (Pharmaceuticals)</th>
<th>Biologics (Biotech)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size of molecule</td>
<td>Small</td>
<td>Large (&gt;1000x bigger)</td>
</tr>
<tr>
<td>Cost to manufacture</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Easy to copy</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Oral-mostly pills</td>
<td>Injection or infusion</td>
</tr>
<tr>
<td>Price</td>
<td>Cheap</td>
<td>Expensive</td>
</tr>
<tr>
<td>Generic pathway</td>
<td>Established 1984</td>
<td>Not yet established</td>
</tr>
</tbody>
</table>

- To combat the spate of upcoming patent expirations, **big pharma has shown interest in becoming involved in biologics** due to the absence of a defined pathway for generic biologics and the difficulties associated with manufacturing generic biologics. We estimate that when a pathway is put in place there will be at most 2 copies of a given biologic drug, the innovator will retain 50% of the market, and pricing will be at a 25% discount. This contrasts favorably with small molecule pharmaceuticals where there are often >10 generic companies selling copies, the innovator loses 80% of sales within weeks, and the price is <20% of the original sales price. The long tail on the sales of branded biologics is the key to the superior IRR calculated for biologics as opposed to pharmaceuticals.
  - Evaluate Pharma predicts that by **2014, the 6 biggest selling drugs in the world will all be biotech molecules**. Additionally, 7 of the top 10 selling molecules will be biologics, up from 5 in 2008 and 1 in 2000.
  - Roche, the 8th largest pharmaceutical company in the world, bought Genentech for $47B in 2009.
  - Following the merger with Schering Plough, Merck announced a **new R&D structure** where they will be working in two groups: one group will be working on traditional pharmaceuticals while the other will be working on cutting edge biotech molecules. This illustrates that big pharma has realized the errors they have made in the past and are trying to become more like biotech.
  - Two pharma giants (GlaxoSmithKline and Sanofi-Aventis) have recently been very open about their desire to partner/acquire smaller biotech companies.
    - Sanofi Aventis’ new CEO Chris Viehbacher has pledged to dedicate 20% of his time, as well as 20% of his senior management’s time, **to exploring partnership opportunities with biotech** in hopes of raising the biotech share of their pipeline from 14% in 2008 to 25% in 2012.
    - GSK has reorganized their R&D program into pods to function more like min-biotech companies and has also begun a CEEDD program (Centre of Excellence for External Drug Discovery).
whose stated goal is to seek out highly innovative and transformative science from outside the organization. They hope to work with small biotech companies to bring the ideas to proof of concept at which point GSK has the option to license for full development. Biotechnology companies brought inside of GSK will function as their own unit so as to preserve the entrepreneurial culture of the small company.

- An increasing amount of total biotech funding (IPOs, Follow-ons, PIPES, Venture, Debt, and partnering) has come from partnerships over the last two years; illustrating the point that pharma has realized they can grow their pipeline through partnership with biotech.

**Conclusion:** We believe that big pharma has under-invested in innovative R&D over the past decade and the group is feeling the effects of these decisions. The source of innovation on which big pharma will have to bid is found in the small cap biotech space.
Section 2:
Supply side: Financial support of the National Institutes of Health (NIH), venture investors, and public equity investors is critical to the success of the biotech industry. We believe there is sufficient sponsorship from these classes of investors to allow the biotech industry to continue to expand.

- NIH
  - Basic science research is done both by scientists at the National Institutes of Health (NIH) and also by researchers at academic institutions who are awarded grants by the NIH.
    - The NIH spends $30B tax dollars on early stage research annually (80-85% of the $35B budget). This research produces academic publications, which are picked up by entrepreneurs who start a company around the science that the NIH sponsored.
    - This investment accelerated in the early 2000s but has been flat recently. The lag between NIH research and IPO is at least 5-10 years, so we should be seeing the benefit of the acceleration from the early 2000’s soon.

![NIH research dollars](chart)

- The Bayh-Dole act of 1980 granted universities ownership of patents arising from federally funded research. As shown below, this piece of legislation has spurred innovation (not only in biotech), as the number of startups and commercial products coming out of the university tech transfer process has grown steadily since the late 1990’s.
Despite this surge in new companies, the number of new biotech companies as counted by Biocentury has been down since the height of the genomics bubble of 2000. Biocentury notes that the number of startups in recent years may be undercounted as companies wish to remain under the radar.
• Venture
  o Overall VC fundraising is down since the bubble of 2000, but has steadily rebounded. 2008 was the first down year since 2002.

![Fundraising by Venture Funds](image)

Source: PricewaterhouseCoopers/National Venture Capital Association MoneyTree Report

  o A look at the data in terms of maturity of companies that were attracting venture capital reveals that through 2008 VC investors were actually increasing their exposure to early stage/seed companies. This effect has been augmented by corporate venture funds.

![VC investment by development stage (overall VC)](image)

Source: PricewaterhouseCoopers/National Venture Capital Association MoneyTree Report

  o Biotech and pharmaceutical companies have begun forming corporate venture funds, intended to look at very early ideas. Often these
arrangements give the parent pharmaceutical company a right of first refusal on the technology. Shown below are publicly disclosed corporate venture funds and the value of the fund. This trend illustrates the dependence pharmaceutical companies have on baby biotech for future innovation.

<table>
<thead>
<tr>
<th>Fund</th>
<th>Value ($-millions)</th>
</tr>
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<tbody>
<tr>
<td>Novartis Ventures</td>
<td>650</td>
</tr>
<tr>
<td>SR One/GlaxoSmithKline</td>
<td>100</td>
</tr>
<tr>
<td>Amgen Ventures</td>
<td>100</td>
</tr>
<tr>
<td>Takeda Research</td>
<td>100</td>
</tr>
<tr>
<td>Biogen-Idec New Ventures</td>
<td>100</td>
</tr>
<tr>
<td>Astellas</td>
<td>67.5</td>
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<tr>
<td>Merck Serono</td>
<td>60</td>
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<tr>
<td>Pfizer Venture Investments</td>
<td>Not disclosed</td>
</tr>
<tr>
<td>J&amp;J Development Corporation</td>
<td>Not disclosed</td>
</tr>
<tr>
<td>Roche</td>
<td>Not disclosed</td>
</tr>
</tbody>
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- **Total amount invested by VC into biotech was down in 2007 and again in 2008**, both in terms of dollars invested and in number of deals.

![Venture deals in biotech](source)

*Source: PricewaterhouseCoopers/National Venture Capital Association MoneyTree Report*

- **However, biotech dollars as a % of total investments was up in 2008 over 2007 levels.** Looking longer term, investment in biotech as a percentage of total investment from a VC standpoint has been relatively flat since the run-up in 2001/2002.
o Additionally, the outlook from VC investors seems to forecast more of the same.

o Shown below is a rough breakdown of all sources of funding to biotech over the years. Funding through the first three quarters of 2009 has already surpassed the depressed figure from 2008.
Conclusion—we believe that federal government investment in basic science research is yielding results, tech transfer from the universities to entrepreneurs is alive and well, and that venture investors are still interested in putting dollars to work in biotech. We believe that both the rate of company formation and funding are growing at the same rate that they have since 2002.
Section 3:

Biotechnology is among the most innovative fields and advances will improve human health and curtail health care costs. The fact that 2/3 of the biotech industry is in the United States underscores the importance of supporting the sector from a job creation standpoint in addition to the promise of medical revolution it provides.

- Geographically, where is innovation coming from?
  - In the past, Europe was the leader in pharmaceutical/biotech innovation. Price controls and diminishing profitability due to the public payer system in Europe has diminished European innovation, while the US has surpassed the rest of the world in new molecular entities approved.

![Graph showing new chemical entities approved by geography](image)

*Source: Grabowski, H and Wang, R. Trends March/April 2006, 452-460*

- Heavy investment in biopharma R&D by the US has allowed the US to become the country where most new drugs are launched first. This results in improved health care for patients in the United States.

![Graph showing first-launch country of new chemical entities](image)

*Source: Grabowski, H and Wang, R. Trends March/April 2006, 452-460*
We argue that there are several factors including public support of research, favorable technology transfer from universities, good reimbursement for medicine, and the strength of the public and private equity markets in the US. The appetite of both public and private investors for US-led biotech innovation is illustrated below.

Source: Grabowski, H and Wang, R. Trends March/April 2006, 452-460

Clearly investment in cutting edge US biotechnology research is essential to spur innovation for the entire world. As a result of the domestic exposure to biotech, **patients in the US have been the initial beneficiary of the most novel treatments.**

Additionally, thousands of high quality jobs in the biotechnology arena have been created in the United States over the past two decades. In 2006, there were 627,600 jobs in biotechnology. The Milken Institute found that biotech jobs have an enormous ripple effect throughout the economy. It projects **that for every job in biotech, an additional 6.7 jobs are created in other sectors of the economy.** The Milken Institute estimates that total employment in the biopharmaceutical industry will increase to over 3.6 million by 2014 (*Patient Capital* by Michaela Platzer).

- **Conclusion:** Future innovations from biotech companies hold the cure to some of the world’s deadliest and most painful diseases like cancer, heart disease, and Alzheimer’s. Support from US investors in this industry is critical to the livelihood of the industry. In addition to medical advances, the industry also creates high quality jobs in the US.
Section 4:
Since inception in 1994, performance of the NASDAQ Biotech Index (NBI) has tripled that of the broader NASDAQ index. Higher takeout premiums of publicly traded biotech companies have been paid over the past 3-4 years, and we believe this trend will continue. Finally, secular tailwinds portend further growth of the biotech industry.

- The number of publicly traded biotech companies acquired annually has been relatively stable over the past 6 years, but the premium for which the technology has been acquired has grown substantially. The rising premium implies that investors are underestimating the price an acquirer will pay for novel technology.

Source: Credit Suisse and SEC filings
• A key driver of demand for biotech molecules is the aging population.

![Drug plan costs by age group](image)

Source: 2009 Drug Trend Report Vol.11; Medco Health Solutions

• There are drivers in addition to the aging population. Shown below is Medco Health Solutions’ estimate of future drug consumption in the US. They project the dollar value of drugs consumed per person will grow at 4-6% in 2010 and 5-7% in 2011. The utilization category is driven by both the aging population and by population growth/growth of number of insured individuals. Price and mix accounts for both price increases and for introduction of new drugs which results in a mix shift from generic drugs to more expensive branded drugs. Most importantly, the growth of specialty biotech drugs is far outpacing the overall drug growth. In 2008, specialty biotech utilization was up 4.3% while overall drug utilization declined 1.1%. According to Bioscrip, the 2006 US spend on specialty molecules (mostly biotech) was $54B. This figure is expected to grow to $99B by 2010.

<table>
<thead>
<tr>
<th></th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
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<tbody>
<tr>
<td>Utilization increase</td>
<td>0% to 1%</td>
<td>0% to 1%</td>
<td>1% to 2%</td>
</tr>
<tr>
<td>Price and mix increase</td>
<td>3% to 4%</td>
<td>4% to 5%</td>
<td>4% to 5%</td>
</tr>
<tr>
<td>Annual total</td>
<td>3% to 5%</td>
<td>4% to 6%</td>
<td>5% to 7%</td>
</tr>
</tbody>
</table>

Source: 2009 Drug Trend Report Vol.11; Medco Health Solutions

• The best estimates available on biotech molecules are from the Express Scripts Annual Drug Report shown below. This chart shows that specialty drugs are increasing as a percentage of total drug spend with an expected penetration of 20% of total spend in 2012. Since this chart measures percentage of drug spend on biologics, these estimates actually represent growth above that of overall drug spend. Importantly, this chart under-reports biologic usage as a percentage of
total drug spend as it only represents drugs covered by pharmacy benefits. A high percentage of biotech molecules are not covered under pharmacy benefits.

Source: 2008 Express Scripts Drug Trend Report

- Conclusion: Biotech stocks have performed well relative to the broader tech index. Despite strong stock performance, the premium at which biotech companies have been acquired has been increasing, indicating that investors underestimated either the value of the asset or the desperate position from which the acquirer negotiated. Further, the drug industry is growing at 4-7% and the biotech growth is poised to significantly outpace this growth.
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Mr. Rosengart is a Biotech and Life Sciences Consultant for Emerald Research. He is President and CEO of HK & Associates, an investment and consulting firm, specializing in financial and strategic advice to small and medium-sized companies with an emphasis on life sciences. Mr. Rosengart is the founder of LigoTech, Inc., a privately held DNA / RNA and macromolecule bioseparations company, employing 14 individuals. For three years, he served as Chairman of its Board of Directors, President and CEO and is currently a Member of the Board of Directors. He raised $5 million in two equity rounds of capital. During his tenure, Mr. Rosengart consummated several licensing transactions, acquired Affinity Biotechnology and successfully integrated the acquisition into LigoTech and launched a number of products. Mr. Rosengart is also co-founder of SunPharm Corporation, an anti-cancer drug development-stage company. He is active in a number of civic and professional organizations and holds a B.S. in Chemical Engineering and an MBA from Rutgers University.

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