

A Season of Turbulence

Independent consultant Emile Bellott looks at the changing biotech landscape in light of the global financial crisis and considers the likely implications for the global pharmaceutical/biotech industry

THE STORY SO FAR

By late 2008, it was abundantly clear that the deepening economic recession would not leave the biotech sector untouched. In fact, the capital structure of the smaller pharmaceutical and biotech enterprises and their symbiotic relationship with the sources of private equity investment has left them vulnerable to the same forces that decimated the home mortgage industry. In contrast, during the previous decade, the biotech and pharmaceutical industries had existed in a relatively stable environment of increasing sales, improving profit picture, and abundant access to risk capital.

Access to capital had been excellent throughout 2007, as the major worldwide financial markets reached new highs. Venture capital financing continued its decade-long upward trend to US\$8 billion invested in biotech (1). However, during the first half of 2008, storm clouds were on the horizon. VC investment trend began the year at about the same rate as 2007 but began to decline as the year progressed. VC funding was down by 17 per cent in the third quarter (2) and overall investment in biotech was down by 54 per cent in the first nine months of 2008 (3).

The large pharma and biotech companies entered 2008 with \$105 billion in cash

and equivalents, prepared for continued robust M&A activity, licensing deals, and aggressive pipeline development.

Late in 2008, the situation had changed dramatically. Not without early harbingers, it was clear that the capital position of industry as a whole, and biotech in particular, had deteriorated. Stock market indices told the story: biotech shares, which had outperformed the markets during the first half of 2008, dropped precipitously in October. Large cap biotech stocks were down 10 per cent from 1st January to 31st October; medium cap biotechs down 28 per cent and small cap biotechs down 39 per cent. This is compared to 25 per cent and 30 per cent for the NASDAQ and DJIA indices, respectively (4). This decrease in share prices not only made the public companies more attractive acquisition targets, but also reflected a lower valuation on the assets of all the smaller firms, private as well as public.

In summary, the crisis in worldwide capital markets has adversely affected the biotech/pharmaceuticals sector, by limiting access to capital (see 'The situation on the ground'). This problem is all the more urgent for emerging biotech companies, which are net cash flow negative.

Distortion of the forces normally at work in the financial industry pushed the

biotech sector, as well as other industries, beyond a tipping point. This article looks at the effects of the present capital market crisis and worldwide recession on the pharma/biotech landscape. It discusses some examples of the forces at work within the global pharma/biotech ecosystem and near-term outcomes of the present situation.

THE NEW MILLENNIUM – EMERGENCE OF THE EXTENDED VIRTUAL PIPELINE

A continuing theme in the biotech/pharmaceutical sector has been innovation of the business model to respond to market demand for novel disease treatments within the context of forces shaping the competitive world stage. These forces have been discussed in terms of factors in the competitive landscape, such as: Capital Markets and Sources; Markets; Competitive Rivalry and Government (5).

In response to the demands by investors for continuous revenue growth, the large product marketing players in the pharma/biotech industry have mainly emphasised the development of blockbuster drugs and well-chosen, highly profitable niche drugs. It has become clear in recent decades that the industry pipeline-output of approved new drug products has failed to keep pace with growth expectations. The industry has turned to M&A, partnering and licensing as strategic tools to augment its trajectory. This has been effective by expanding the development pipeline and by bringing on new sources of revenue and marketing channels (6).

Early-stage licensing, partnering and M&A deals have become accepted parts of the overall industry business model. The trend has been for the larger players to place greater reliance on external R&D, increasingly with a global reach.

Emerging companies and research universities now constitute a ‘farm team’ system for the major industry players. This approach capitalises on fresh sources of innovation, new discoveries, and star players, which are not already present, within a fully integrated biotech/pharmaceutical company. Over the past five years, all the major pharmaceutical and biotech companies have built up their external sourcing activity such that externally-initiated programmes now represent as much as 30 to 50 per cent of the pipeline in many major companies.

‘Outsourcing’ of R&D is strategic as it utilises an additional knowledge-base and new discoveries that are not present within established enterprises.

The virtual pipeline business model also tacitly transfers the risk of R&D further upstream to the small innovators and their funding sources, or, ultimately, to the government, in sponsored research programmes at universities and research institutes.

BUSINESS GOVERNMENT AND THE INTERNATIONAL ECONOMY

Most market analysts anticipate that the demand for healthcare and pharmaceutical drugs will continue to grow – due to relative ageing of the population; increased penetration of developing markets; and general increase in the worldwide population. In preceding decades, the drug industry has been consistently profitable, with sales steadily increasing at about seven per cent per year and long-term return on equity exceeding 2.1 per cent (7). Approximately 80 per cent of drug industry sales are attributable to the developed world (US,

EU and Japan). In these regions, the per capita expenditure on pharmaceutical drugs consumed averages 1.5 to 2 per cent of annual per capita GDP, depending on county. It is generally believed that the growing rate of expenditure on personal healthcare is not sustainable for the long term.

The industry faces the backdrop of continuing low output of new drug approvals (24 first-of-a-kind drugs were approved by the FDA during 2008); impending patent expirations on major blockbuster products; and aggressive generic competition. Industry strategists are seeking opportunities to expand overall pharmaceutical drug demand, through focus on high-revenue and high-growth therapeutic areas; market expansion in underserved regions; and aggressive direct-to-consumer marketing in the developed world. This latter point is also related to recent consolidation of pharmaceutical sales forces, as a cost cutting measure.

All of the major pharmaceutical companies have made significant strategic commitments to the biotech area, either by building up their own capability, or through M&A (for example, Lilly-Imclone; AstraZeneca-Medimmune; Merck-GlycoFi; Merck-Sirna; Roche-Genentech). This move toward biotech is attributed to the higher market growth of biotech drugs; higher revenue potential; 10 per cent lower average cost of drug development; 10 per cent higher success rate in clinical development; and regulatory barriers to generic copies (8).

Total healthcare costs continue to increase at a rate that exceeds per capita GDP growth, provoking increased political

pressure to rein in spending. There remains a question regarding the revenue impact of managed universal healthcare in the US, which represents 40 per cent of worldwide pharmaceutical sales. Political analysts expect that reimbursement rates and therefore gross-margin would decline under universal healthcare plans floated by the newly-elected administration in Washington. Analysts debate whether total revenues might still increase due to inclusion of the present large number of the uninsured in a healthcare system. The lower gross-margin scenario highlights the need to ‘turn back the clock’ on the overall cost of developing a new drug – thus implying a stronger current toward partnering with capital-efficient smaller firms and strategic outsourcing to achieve lower cost (9). Outsourcing, particularly to low-cost providers in emerging markets, opens up additional sales opportunities in those geographic regions as well.

Beyond negotiation for lower drug prices, the new administration’s healthcare agenda proposes allowing the import of less expensive drugs from developing countries; increasing use of cheaper generic forms of drugs; and streamlining regulatory barriers to biogenerics and biosimilars.

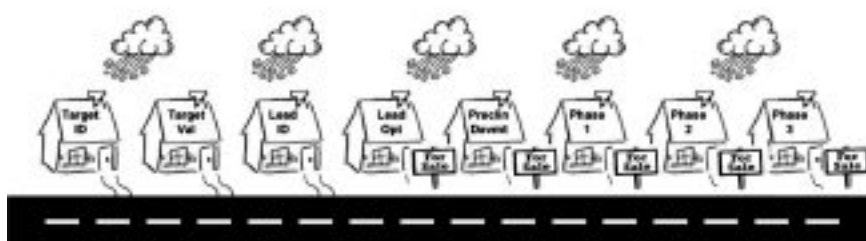
Recognising this potential near-term generic opportunity, industry leader Merck has announced the creation of a new business unit to develop ‘generic’ or follow-on biologics to compete with big-selling biotech products. The Merck plan calls for launch of five new products within the decade. There is a view that regulatory hurdles will be cleared quickly, by a new congress, either as a part of ‘healthcare reform’ or as part of new legislation directed toward the regulatory agencies (10).

SMALL AND MEDIUM BIOTECH COMPANIES

The small and medium biotech/pharma company landscape is comprised of thousands of companies, mostly funded by private investment and formed for the purpose of developing new drugs which capitalise on discoveries in molecular biology and genomics. This development activity is expensive (8). Generally the new company business model anticipates

Figure 1: An abundance of deals

Image: Emile Bellott



years of negative cash flow. Future liquidity through public offering, licensing, or partnering is necessary in order to fund the clinical phases of a programme. Funding by larger partners can provide the expertise, experience and infrastructure in place to carry the programme through to regulatory approval.

During the decade or so that it takes for development and regulatory approval, the emerging companies do not have an ongoing product-derived income stream. In fact, most operate at a net loss. Their operations rely on cash flow provided by venture capitalists, risk-oriented investors, milestone payments from programme partners, and at later stages, cash intake from public offerings of shares or partnering income. As a consequence, they rely on private equity sources for initial and growth funding. Historically, due to the high risk and uncertainty surrounding their ultimate success, biotech companies employ only modest debt financing within their capital structure.

Not surprisingly, the current economic recession and crisis in the financial markets has pushed many of the small and medium biotech companies over a tipping-point. Access to capital has become difficult. Asset values have diminished as many cash-starved firms are seeking licensing and partnering deals for cash to extend their runway, until additional private investment becomes available again on practical terms (11).

As the markets collapsed in recent months, more small companies with minimal asset value are beginning to take more stringent measures, including bankruptcy, workforce cuts, scaling back R&D, shelving programmes, and receding into a 'hibernation' mode, through the anticipated long financial winter (12-14).

Seeking the investor of last resort, biotech companies are lobbying the US government for some form of a bailout. The structure of such a deal is not clear. Loans are unlikely to be repaid in full, but it all leads to questions as to whether the government really has a role in risky investments (15).

CONSTRAINED CAPITAL ENVIRONMENT

In the middle of the financial crisis are the venture capital investors – the traditional sources of risk funds for new technology and life science companies. VC investments in biotech companies reached a peak of US\$8 billion in 2007 and the number of employees and VC firms doubled over two decades (1). The recent numbers tell a different story. In 2008, VC investments in new biotech startups diminished as the global economy inched toward recession. All forms of investment (including VC) raised by biotech firms had decreased by \$9.7 billion or 54 per cent for the first nine months of 2008, compared to the previous year. (3)

VCs are one of the primary sources for at-risk investments in new high-potential startup enterprises. Reflecting the risk profile of the opportunity venture capitalists and their fund investors seek double-digit returns. The success of a few portfolio companies compensates for the many other investments in companies that don't live up to their original forecasted potential. The funds raised by VCs, on the input side, represent the aggregation of many investment sources, each of whom is placing a small portion of their overall capital into this risky sector. Over the past 10 years, VC has experienced an average return on equity of 16 per cent, as compared to 1.2 per cent average return for the 500 companies comprising the S&P500 index.

In the current economic recession and capital crisis, assets and investments are depressed. In particular, the major world market indices have declined by over 30 per cent since the start of 2008. For the VCs, this presents a severe capital sourcing problem for their funds. One private equity manager and funds aggregator intimated, in Q3, that big institutional investors were having difficulty meeting their capital calls for existing and new venture fund commitments. The crux of the matter is that the institutional investors all have guidelines for the deployment of their funds into various sectors, by industry and risk type. In the case of mutual funds, this may relate to the charter of the fund and its expressed investment objectives. In

regulated financial institutions, such as pension funds, insurance reserves, university endowments, charitable foundations, and investment banks, there may be firm percentage limits on capital allocation, defined by law, or by their own governance structures.

In either event, with a greater than 30 per cent decline in the price of publicly traded assets, these institutions suddenly became 'over-allocated' in illiquid investments, representing the higher risk VC and private equity sectors.

The options to deal with this 'technical' problem are severely constrained. With the capital markets still turbulent, and of uncertain momentum, the most straightforward resolution is to limit further investment exposure in the same class of risky vehicles. One Managing Director of a VC recently opined that the major institutional investors, who are subscribers to VC funds (state pension funds, university endowments, insurance companies, and the like) would be faced with the choice of investing or defaulting on their next capital calls. They will need to scrutinise the underlying portfolios and long-term relationships, as well as make difficult choices on where to prune back their exposure.

For the VCs and their portfolio companies, this presents a clear and present capital shortfall, demanding prioritisation of investments. Anecdotally, this has manifested itself in the prioritisation of investment opportunities in existing portfolio companies; in later stage programmes and companies; in publicly traded small firms; and increasing interest in lower risk and potentially tax advantaged sectors, such as energy, green technology, and other industries. These expedients still do not ameliorate the funding shortfall for emerging enterprises.

The increasing emphasis on later stage companies (closer to meeting a valuable milestone) exacerbates the challenging translational problem of early stage startups attempting to cross 'the valley of death' from academic discovery toward a 'fundable' proof of principle demonstration. Major research universities have attempted to address this problem, in order to keep the future

of biotech, by establishing incubators and accelerator funds. But they are cash-poor, as well as instituting spending restraints due to depreciating endowment portfolios and tuition 'payer fatigue'.

Universities – increasingly the wellspring of biotech innovation – are experiencing a capital shortfall of their own. Their endowment portfolios are invested in the same capital markets and hedge funds as the rest of the financial industry. They have experienced the same 30 per cent decrease in asset values, year to date, reflected in major market indices. Recent public announcements across the board in academia reflect caution in new expenditures and measures to control expenses. Major research universities have announced expedients, such as delay of capital expansion programmes; cuts in operating expense budgets of up to 15 per cent; hiring freezes; and salaried pay freezes. The state-funded universities fare no better, in a time of major state budget deficits and curtailment of state-sponsored programmes. There are downstream implications for new academic innovations in the life sciences, including cuts to university research funding selectivity in patent filing and scrutiny of patent maintenance on 'non-productive' IP.

A recent comment heard in an industry meeting, that 'there's always money for an exceptional opportunity' is cold comfort, indeed.

LARGE BIOTECH AND PHARMA COMPANIES

The larger company landscape stands in contrast to that of the emerging companies. Annual worldwide drug sales are estimated at about \$750 billion in 2008. Sales growth is expected to continue, after gaining at about seven per cent per year over the past decade. Biotech drug sales growth has averaged 12 per cent over the same period. The largest pharma and biotech companies operate with a portfolio of profitable drug products. Over time, the industry has enjoyed sustained profitability and positive cash flow from operations. Average corporate debt as a percentage of capitalisation is well below that of industrial companies generally. Although return to shareholders has

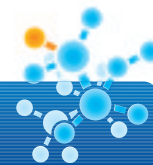
underperformed the market in recent years, at the end of October 2008 stocks of the large players were depressed substantially less than the smaller biotech sector or industry as a whole (4).

As the recession and financial crisis deepens, the large pharmas are poised with an average of six per cent debt capitalisation, and the top nine firms have approximately \$105 billion in cash and equivalents with which to weather the downturn. At least 30 per cent of this horde is estimated to be outside the US and subject to taxation on repatriation (7).

The major issues affecting these enterprises are the longer term prospects for government control over prescription drug pricing; expansion into biotech modalities; and the continued dearth of regulatory approvals of new drugs. To address the latter issue, as described above, the larger industry players are continuing a decade long march toward expansion of external pipeline sources. This fact, and the availability of offshore money, may be an encouragement to investment or partnering with EU-based small biotechs, which as a group are estimated to be closer to profitability than their US counterparts.

Clearly we are seeing acceleration of the deal-making process between larger firms and the emerging players. In a recent industry meeting, one executive of a major pharmaceutical firm observed that the number of transaction opportunities, in recent months, has increased, although the asking-price has not yet moderated. Of these recent enquiries, most were framed in terms of a potential acquisition.

Whether the larger players will do the planned number of deals at a lower price, or do more deals within the same total budget, while the opportunity is present, the executives expressed the view that 'cash and their equivalents' are affected by the same market forces as everyone else. They are watching their cash expenditures carefully. At the end of the day they anticipate M&A business as usual, but at an overall lower negotiated price. On the contrary side, a mid-sized biotech strategy executive predicts that the big players will warm to the opportunities of this rare historic circumstance, and ultimately compete to do more deals in 2009. This approach could result in a pipeline boom and hence more shots on goal for therapeutic programmes ultimately delivering a net higher quality pipeline downstream.



The situation on the ground

Small and medium biotech companies, which rely on a continuous supply of capital are severely constrained and adopting measures for cost containment, including layoffs, acquisitions, and shelving or selling programmes. The biotech industrial landscape is redefining itself in terms of two camps: The 'haves' and the 'have-nots'. The larger players have cash and ongoing product revenues to sustain them; the smaller players have programmes, representing time-sensitive assets, whose marketable value is depressed, and a bleak set of choices for going forward.

- 87 per cent of biotech firms are unprofitable, (as a natural consequence of the business model).
- Industry sources do not expect that IPOs will resume until 2010, at the earliest.
- VC investment in biotech companies, has declined during 2008, versus 2007.

- Large pharma and biotech companies are well-positioned with revenue, cash, low debt, and an appetite for partnering, licensing, and M&A.
- Partnering and M&A activities are heating up, as more companies and programmes are contending for the available investment funds.
- 25 per cent of the small biotech firms have less than 6 months' cash on hand.
- 45 per cent of publicly traded small biotechs have less than one year of cash on hand.
- Small-cap and mid-cap biotech stock indices plunged by over 30 per cent to the end of October 2008. Fully half of this decline was in the month of October, alone.
- It is estimated that 25 per cent of public biotech companies are subject to de-listing due to share prices below \$1 per share. NASDAQ has suspended this rule until 19th January 2009.

CONCLUSION

It is likely that the new year will see a continuation of the consolidation, shakeout and turbulence observed thus far in the biotech and financial sectors. Crisis in the financial sector, capital scarcity and recessionary caution on the part of businesses will exacerbate the ongoing problems amongst small and medium-sized development-stage biotech and pharma companies. The coming year will undoubtedly witness some or all of the following.

The Industry

The industry in general is likely to see a net decrease in the number of small and medium biotech firms, through attrition and acquisition, as well as a continuation and acceleration of the trend toward M&A and partnering, by larger cash-rich companies. The industry will also become a buyer's market – deals at a lower multiple, driven by the large number of depressed assets. Multiple business failures are unfortunately very likely as cash-poor smaller companies are already retrenching and laying-off employees and shelving programmes. Intense lobbying pressure by the industry for financial relief and tax credits is also inevitable as is lobbying in the context of healthcare reform, to stave off drug pricing restraints. Finally, prescription drug price controls in the context of healthcare reform may be delayed until the economy has already begun to recover in order to avoid further potential damage to a fragile business sector.

Private Equity

Institutional investors will remain over-allocated in illiquid investments such as venture funds, as long as their market-based investments are depressed. They will need to be selective in meeting or defaulting on capital calls or making new commitments. Venture funds will be highly selective in their investment strategy – placing emphasis on existing portfolio companies; publicly traded issues; and investment opportunities with possible near term government support and tax advantages. Additionally consolidation is likely within the ranks of the venture capital industry, which has doubled in size over the past two decades.

Large Biotech/Pharma Enterprises

A larger number of potential deals will be seeking acquisition – there will, therefore, be a progression toward more early-stage opportunities as the valuable later-stage opportunities are assimilated. Multiple early programmes will demand support from the larger partner on translational research. More deals will be concluded by the larger companies, within the same budget, resulting in a 'baby-boom' in their pipelines. This will lead to more shots on goal, downstream and a net higher quality pipeline in the out-years, after programme triage. We will also see a corollary pipeline 'baby-bust' within the first few years, as the number of new venture start-ups lags behind the economic recovery. A trend will become evident towards the establishment and operation of accelerator funds for the early-stage opportunities. This is likely to involve large biopharma companies as a general partner, with multiple institutional, private equity, and university limited partners. On a more positive note, there should also be an enhanced opportunity for partnering and M&A with small biotech enterprises outside the US, taking advantage of the offshore portion of large-company cash assets.

References

1. Ernst & Young Global Life Science Report 2008
2. Carroll J, Credit crisis pushes biotechs to the brink, *Fierce Biotech*, 24th November, 2008
3. Olmos D and Waters R, Unprecedented biotech bankruptcies erupt amid finance crisis, *Bloomberg.com*, 21st November 2008
4. Maureen, Biotech reels from one of the worst months on record for the capital markets, *Fierce Biotech*, 5th November, 2008
5. Bellott E, Global Environments: Navigating The Perfect Storm, *European Biopharmaceutical Review*, pp28-35, Autumn 2008
6. Boyle C, Credit Crunch Threatens Investment in Medicines, *Times of London*, 27th October, 2008
7. Flanagan A *et al*, Collateral Damage, *Industry Focus, Boston Consulting Group*, November, 2008
8. DiMasi JA, Measuring Trends in the Development of New Drugs: Time, Costs, Risks and Returns, *Tufts Center for the Study of Drug Development*, 19th March, 2007
9. Tansey B, Biotech firms fear pricing pressure from Obama, *San Francisco Chronicle*, 9th November, 2008
10. Rockoff JD and Winslow R, Merck to Develop Biotech Generics, *Wall Street Journal*, 10th December 2008
11. Carroll J, Credit crisis pushes biotechs to the brink, *Fierce Biotech*, 24th November, 2008
12. Wallack T, Biotech firms cutting back as capital grows scarce, *Boston Globe*, 1st December, 2008
13. McBride R, Buy side experts see major changes afoot in biotechs amid financial crisis, *Xconomy-Boston*, 30th October, 2008
14. Japsen B, Biotech funding down to last drops, *Chicago Tribune*, 23rd November, 2008
15. Pollack A, For Biotech, A Tax Break Spells Hope, *The New York Times*, 10th December, 2008
16. FierceBiotech Biotech reels from one of the worst months on record for the capital markets, *fiercebiotech.com*, 5th November, 2008

About the author



Dr Emile Bellott is a private consultant in drug development, based in the Boston area. Over 25 years of industry

experience, his pharmaceutical activities have focused on drug discovery and development, synthesis and design of small molecule therapeutics, and informatics and structural biology. He has served as VP of Operations, co-founder of two development-stage biotech companies and founder of a life-science software company. His operational experience spans medical devices, pharmaceutical development and chemistry outsourcing. He earned a PhD in Physical Organic Chemistry from Harvard and a MBA from the Harvard Business School.
Email: emile.bellott@gmail.com