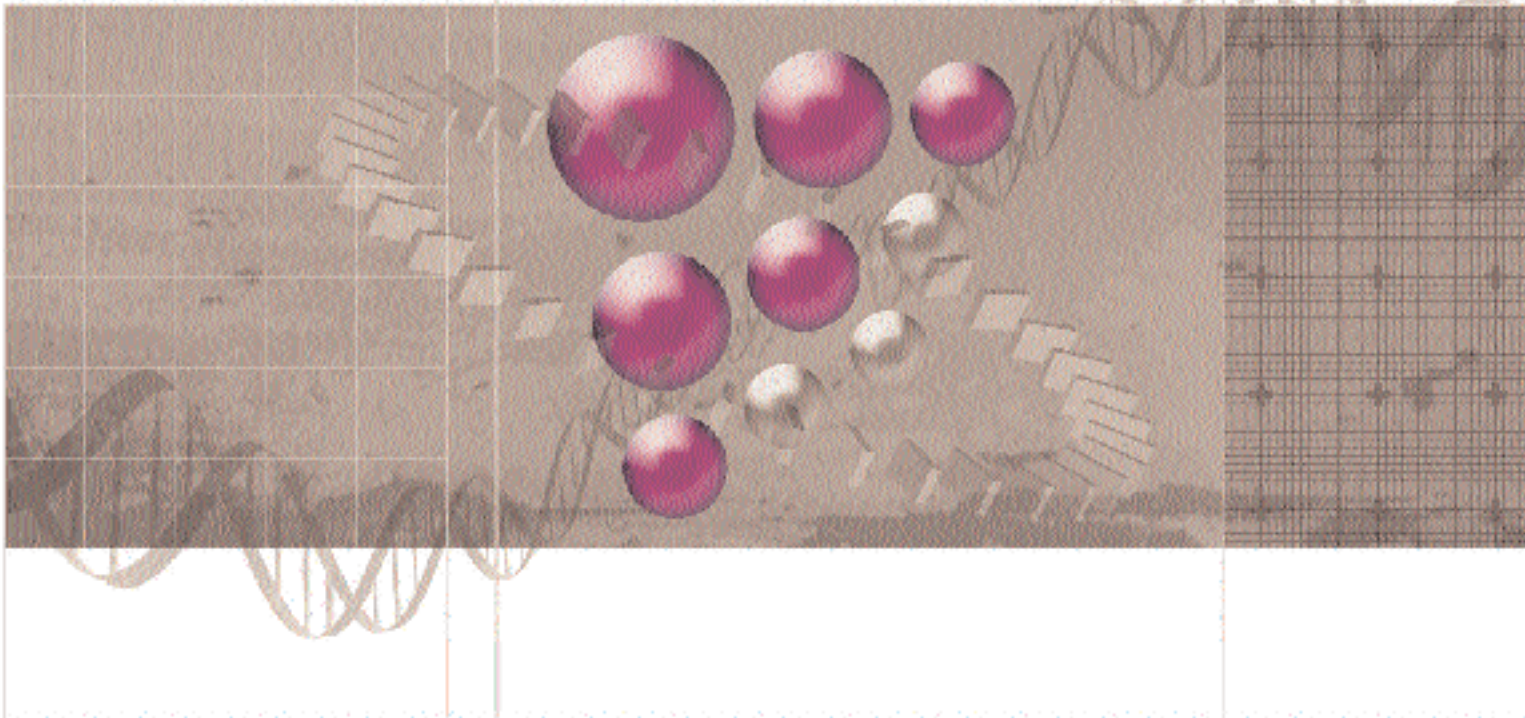




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Biotech Getting Back on Track

After a few years of both public and private biotech companies taking a hit from investors and financiers, it seems the worst may be over. However, barriers to success still remain, ensuring that biotech companies need to stay on their toes.

BY MARK WILLIAMS

After three years of trial-by-illiquidity, biotech industry professionals are almost daring to breathe a sigh of relief. 2003 may be held up as the year that marked recovery. The capital markets rebounded and significantly increased the stock value of biotech companies. Product approvals increased and a number of product launches met with success. Biotech companies showed a desire to take on board more risk, particularly in the in-licensing market. Prominent mergers signalled an upturn in the restricted biotech M&A market, and VC investment reached impressive highs.

But other indicators suggest that celebrations may yet be premature. The US IPO market, for example, opened up in the fourth quarter of 2003 but remains tepid on the back of several dismal aftermarket performances. Also, several 2003 biotech launches appear to have fallen short of expectations. Securing adequate investment continues to remain a major hurdle to the

survival of many biotech companies, and drug regulatory approval delays continue to be a significant barrier to commercialisation. In the face of such adversities, many governments around the globe have committed their support to biotech companies, particularly small to medium-sized entities that struggle to make the journey from research to commercialisation.

Centres of action

North America and Europe have established themselves as recognised hotspots of biotech activity. In the US, Boston, RTP, San Francisco, Los Angeles and San Diego are all major centres. In Canada, there are major clusters of biotech activity, particularly in Ontario, Quebec and British Columbia. In Europe, Ireland, Eastern England, France (particularly Paris and Alsace), the Netherlands, Switzerland, Germany (particularly Munich), Denmark (Medicon Valley), and Sweden (Stockholm/Uppsala) ►►

simply down to human relationships. Scientists need to have a good relationship with people they are taking money from. They need to join up with angels or VCs with whom they can communicate effectively. It may be 7-10 years before a company looks at an IPO, and perhaps 15 years to sale, so the relationship has to work for a long time.

Sometimes the problem is not only finding an investor with whom you can work, but finding an investor at all. In Ms Steinberg's experience, for example, Canadian biotech companies are increasingly finding that they must look to both Canada and the US for venture capital financing. "To be able to secure funding from US VCs, [Canadian biotech companies] must have boards of directors with experience in the US North American market, a sales pipeline to significant markets, established strategic partnerships and innovative proprietary intellectual property," she says. That typically rules out innovative start-ups, and marks the point at which governments have realised that they need to step in with financial assistance or incentives.

In a fairly narrow funding environment, where investors are particular about the opportunities that represent good value, companies that can't meet the requirements have looked to alternative liquidity sources. We're seeing companies monetizing assets, partnering, merging, divesting assets and restructuring, or pursuing such debt strategies as equipment financing, venture loans, subordinated debt, convertible debt and product royalty financing. Until the financing market begins to spread itself more widely across the sector, from early-stage to late, these type of liquidity management strategies will be more the rule than the exception.

Taking the idea public

After the two previous biotech bear markets (1993-1995 and 1998-1999), financing windows opened up at eight months and 13 months, respectively, after stock prices began to rise. In this current biotech bull market, the financing window opened about six months after prices began to rise, according to Prakash Gowd, Biotech Analyst at Canaccord Capital Corporation, says Ms Steinberg. "IPO's tend to follow later, when there is more confidence in the sector, and when valuations rise," says Ms. Steinberg. "We seem to have reached that stage now."

A number of factors have opened the biotech IPO market. Some private companies are at critically low cash levels and want an alternate financing opportunity. Venture capitalists who have patiently supported private companies are now urging them to go public in order to create a liquidity event. Over the last year, valuations of public companies have increased dramatically, and private companies see this as a very attractive time to be able to launch IPO's at a higher valuation than in previous years. Finally, the US industry broke the ice last year, so Europe and Canada are following suit with IPOs of their own.

That's not to say it's all plain sailing. "The biotechnology

industry has been affected by the ImClone scandal, particularly in the wake of the Enron and Worldcom scandals. This has led some investors to stay away from the market and certainly has hurt the IPO market, where generally prices fall on the opening day," says Mr Fersko.

In order to get a biotech away today, that company needs data. Analysts, investment banks and investors all want to know what data the company has in order to evaluate how important it is. When the window opens for biotechs to go public, the first to go through are companies that are further along in clinical programs and have significant statistical data. If the market becomes particularly buoyant, less advanced companies may come in and attempt a float, but it's no longer enough just to have proof of concept. Companies in the current climate really need Phase III clinical trials and Phase II data at least.

Even if they do have advanced data to take to market, public biotech company are still subject to the undulating investor sentiment that drives public investing. The upswings and downswings that these biotech companies go through have nothing to do with their scientific basis, which remains stable throughout. To improve investor sentiment, the industry needs success stories coming out of government approvals, which remind people that biotech companies do develop products that result in hundreds of millions of dollars in revenue. Everyone needs to see the pot of gold at the end of the rainbow.

Combine and conquer

Unlike other sectors, the biotech industry does not seem to enter strong phases of widespread consolidation. That made 2003 particularly significant, says Mr Smith, as several notable acquisitions founded a recovery in M&A. Such deals included Pfizer/Esperion, Genzyme/Sangstat, Roche/Igen, Idec/Biogen, Chiron/PowderJect, and J&J/Scios. "We anticipate additional pharma/biotech acquisitions and biotech/biotech combinations in the coming year. Biotech companies will merge with or acquire other biotech companies to develop the scale required for greater commercial participation; drugs developed in-house generate less cash overall than in-licensed or acquired compounds, due to the cost of capital incurred over long development lead times," says Mr Smith.

So the main reason behind M&A in biotech is the recognition that solid science is not enough to see a company through to sustainability. "The right business model must be put in place," says Ms Steinberg. "Often – particularly for cash-poor early- to medium-stage companies – this involves an alliance or partnership with a larger company. In the case of pharmaceuticals, this most often translates into an alliance, partnership or other deal between biotech and big pharma. In this way, big pharma enhances its product pipeline while small biotech is boosted towards sustainability."

These mergers are dominantly amicable; very rarely do you see ►

a hostile takeover in the biotech industry. They are rare mainly because human capital is so key to the success of a biotech company, and there are no assurances in a hostile situation that integral people won't walk out the door. The value of the company would be completely diminished if they did. Bio patents tend to be tied up in the most complicated technology known – the human body – and can only be properly understood by individuals with years and years of knowledge and experience. Its unlikely that an acquiring firm will be able to bring someone in to replace that person, unless the hostile company happens to be undertaking exactly the same research and development program.

It would appear that competition is hot for the good transaction opportunities out there. While deal prices are nominally the same, licensees are taking on greater risk and complexity. Pharma companies are taking equity positions in biotechs as conditions of deals and biotechs are requiring co-promotion and decision-making to develop internal capabilities. Mr Smith is one professional who expects to see a significant number of more complex, early stage in-licensing deals in the future.

Cash-starved companies are also fuelling the merger market. Unsympathetic market conditions of the last few years have created distressed biotech companies that are being snapped up by more stable rivals. "Companies that have less than a year's worth of cash on their balance sheets need to reduce the number of projects, and oftentimes are prime candidates for acquisition as the only alternative is to go out of business," says Mr Fersko.

But if both companies considering a potential merger are in a healthy financial position, it can be difficult to reach an agreement on valuation, as the margin for variation is so wide. Biotech valuations look at the fundamentals of the company, including validation of science and technology, size and growth of the target market, competition and target market dynamics, development pipeline and news flow, and financials and ability to access capital. In fact, the most important valuation to be made is the predicted future value of a biotech company, as all its revenue tends to be wrapped up in the potential of its people and patents. It's easy to see why one or both parties can leave the negotiation table dissatisfied with the speculative price tag that's been placed on them.

Medicare, re-imports and product liability

The new Medicare bill in the US has divided critics and led to uncertainty about its impact on the biotech industry. Mr Smith describes it as a potential opportunity or threat for biotechs. He explains: "Medical coverage only covers up to \$2250 and then there is a \$2850 gap before coverage picks up again at \$5100. The new Medicare bill also allows employers to drop health care coverage of their retirees who would then be covered by Medicare. That said, the new law does not require statutory rebates or provide for the possibility for supplemental rebates." It could significantly decrease the ability of elderly people to afford expensive biotech treatments.

In Mr Fersko's opinion, the proposed rules are favourable, insofar as they implement payment floors that would restore payments for many biotech products. But, he says, they ignore certain provisions, with the result being that some biotech products would not receive appropriate payment. "BIO is monitoring the situation to ensure that therapeutic classes for drugs and biologics under Medicare's interim regulations are appropriate," he says.

The Parallel Trade or drug reimportation issue poses an additional threat. Large pharma companies such as Merck, GSK, and BMS have stated that they would prevent re-importation by simply including one additional manufacturing step for a Canadian drug that was not FDA approved. Politicians are finding it increasingly difficult to explain why the same drugs in Canada or Mexico are substantially less than in the US. At this time, biologics, while priced highly, are excluded from legislation proposed to authorise reimports.

Increased product liability litigation also continues to be a thorn in the industry's side. "It is feared that if there are not provisions clarifying what the FDA considers to be proper and improper uses of information resulting from the safety reporting system, drug manufacturers would be subject to more product liability lawsuits and a wider array of potentially misleading evidence that could become admissible in product liability litigation," says Mr Fersko.

Positive prospects for 2004

So what trends do the industry professionals believe will define the market in coming months?

"Alliances, partnerships and other deals will all form part of the next year or two. Strategic outsourcing will also be part of the evolution of the biotech business paradigm, along with food and drug safety and related issues and internet pharmacy issues," says Ms Steinberg. Canada will continue to grow as an attractive biotech market – a recent KPMG Report – *'The 2004 Competitive Alternatives Study: The CEO's Guide to International Business Costs'* – ranked Canada as the lowest cost G7 country in which to do business.

Mr Smith anticipates that many of today's current trends will continue into 2003. "Those products addressing unmet needs, critical condition and large markets will fare the best. Superior contracting and pricing strategies will be critical to ensuring optimal reimbursement. While 17 products were approved in 2003, we believe this number will only increase slightly in 2004, although the lifetime value of these product may be as much as 25 percent greater. The M&A market will be robust but may be tempered by several large pharma/pharma combinations. The in-licensing market will remain robust and will continue to include a large number of complex, early stage deals."

It is hoped that steady improvements in drug developments and further industry consolidation or co-operation will bolster the market, putting it on track for good earnings and a sound financing basis over the next couple of years at least. ■

A "Balancing Act" for Brand Name and Generic Drug Makers: Hatch Waxman

BY SEDESH DOOBAY

The high cost of pharmaceutical products in the US is, in part, the result of tensions in drug development between promoting innovation and containing healthcare costs. The Drug Price Competition and Patent Term Restoration act of 1984 (commonly known as the Hatch-Waxman Act) was an attempt by the US Congress to resolve this tension between "pioneering" brand-name drug manufacturers and generic brand drug manufacturers.

I. Pre Hatch Waxman

Prior to passage of Hatch-Waxman, brand-name drug companies were severely burdened by the approval process imposed by the Food and Drug Administration's (FDA) regulations which made the cost of bringing a new drug to market as much as \$800m and take up to fifteen years. The process entails extensive research, pre-clinical and clinical trials, the results of which are submitted to the FDA in a New Drug Application's (NDA). The process limited a pioneer drug company from fully utilising the monopoly created by its patents because no marketing or sales activity could occur until FDA approval, by which time most of the patent term was lost. Even after the expiration of the patent term, the generic manufacturer did not have immediate or less costly access to the market because they had to undertake the same costly and time-consuming process as required for an NDA.

II. Life with Hatch Waxman

The Hatch-Waxman Act was "designed to balance incentives for continued innovation among research-based pharmaceutical companies with opportunities for market entry by generic drug manufacturers." Title I of the Act established an expedited approval process for generic copies of brand-name drugs by allowing the generic manufacturers to submit an Abbreviated New Drug Application (ANDA) utilising the safety and efficacy data previously submitted in the NDA and, further, providing the first generic manufacturer filing an ANDA with 180 days of exclusivity during which the FDA could not approve any other ANDA for the same brand-name drug. Generic makers were also provided "safe harbor" protection from claims of patent infringement for its activities in connection with the ANDA.

Addressing the concerns of brand-name manufacturers, Title II of the Act extended the patent term for patents relating to the drug undergoing FDA approval by restoring to the patent term the time lost during the approval process. The extension only applied to those patents listed in the FDA's "Orange Book." Furthermore, if any ANDA claimed patent invalidity or non-

infringement with respect to a patent listed in the Orange Book, the brand-name drug company could file a patent infringement lawsuit that would trigger an automatic thirty months stay on the a ANDA's approval.

Brand-name and generic drug companies, however, found several ways to use the rules (not as intended), to profit by preventing entry of generic drugs in the market. Complex agreements between brand-name and generic companies were formed to utilise the 180 day marketing exclusivity and the thirty months stay to prevent the sale of new generic drugs, which increased the brand name's market exclusivity. These types of agreements often occurred (i) in the context of patent litigation between the parties, (ii) with substantial payments from the brand name company to the potential generic entrant, and (iii) with the underlying litigation settling by the generic being taken off the market.

III. 2003 Amendments to Hatch Waxman

In response to such conduct, the "The Medicare Prescription Drug, Improvement and Modernization Act" was enacted in December 2003 and Article XI therein includes several key amendments to Hatch Waxman, namely that:

1. Brand-name companies are limited to one thirty-month stay per drug product, rather than per patent that relates to the drug, and only patents listed in the Orange Book prior to submission of the ANDA are eligible to trigger the thirty month stay;
2. the 180 day exclusivity for generic drugs is subject to certain "forfeiture events," namely for a failure to market within 75 days after approval of the ANDA, and that 180 day exclusivity period is determined on a drug-by-drug basis; and
3. any agreement between generic and brand name makers must be filed with the Federal Trade Commission and the Department of Justice the earlier of ten business days after execution or prior to marketing the subject drug.

The implementation of these amendments are intended to put Hatch Waxman back on track to accomplish its initial goal of balancing the competing policy interests of brand-name companies and generics. By extending the exclusivity period for the brand name manufacturers, while reducing the cost of entry to the market for generic competitors, the amendments provide sufficient economic incentive to promote innovation and competition, both of which are necessary to benefit the public interest. ■

Sedesh Doobay is senior of-counsel at Ferskos LLC.

Better *Nouveau* Than Never

BY RAYMOND S. FERSKO

I. Managers must be nimble

When it comes to surviving in this biotech market the experienced executive needs to be an innovator. Cast experience to the wind if experience is based on solving the problems of the past. The problems confronting biotech companies today require original thought unencumbered by the rigidity of old solutions.

The ability to cast out the old and think out of the box is the catalyst for enabling innovation to flourish. Good technology is a must, but it will never see the light of day if it stays in the hands of a management that lacks the ability to innovate.

Assets are financed for their anticipated value. Ultimately, the investor must believe that a company can generate statistically significant data to bring a product to market. That predictability in and of itself may be a product. The company that can enhance by 20 percent the predictability of reaching an end point acceptable to the regulators may have a product that is more valuable than that which is in development.

Whether it is 800 million dollars to bring a product to market or 100 million, speeding up the process and saving 20 percent of the cost is valuable to companies managing a burn rate while developing a product.

II. Expect change

Biotech companies must be ready to change their underlying platforms if that is the only way to obtain the necessary capital. The future is a constantly moving target. Future value may be in the resurgence of previous disparaged technology such as monoclonal antibodies and antisense enabled by discovery tools like functional genomics, proteomics and bioinformatics.

III. Utilise every asset

Biotechs with their first product in late stage phase 2 trials, but without any products, are often forced to tool up manufacturing capability to meet regulatory requirements. There are companies that are starting to train a sales force in anticipation of the product license and launch. While awaiting the NDA filing, these companies need to license in products that have completed phase 3 controlled studies to enable them to utilise supporting and peripheral resources that have been assembled.

Discovery companies need to consider licensing in potential

products in late stage clinical trials if the platform technology is not generating sufficient revenues. These companies rely upon big Pharma to, at minimum, pay a fee for service and then upfront fees, milestones and the "holy grail" – reach through royalties on net sales of the ultimate product. It is fine to sell the picks and shovels and collect a royalty on the gold, but have a plan until striking gold or if it is never found.

IV. License in

Other companies that cannot obtain financing to continue with their present technology need to consider taking advantage of government money available for programs such as bioterrorism. Licensing in new technologies that are further along in development and thus able to attract more investment is another option.

It is not easy to find investors with patience for companies that have products that do not show increasingly better performance on a quarterly basis. Biotechs without products must be nimble enough to employ any one or more of the foregoing strategies, or, better yet, new ones.

V. License out

Not to be overlooked, is the ability to license-out when possible a product in development and/or partner-up with other companies or government entities like the NIH or the MRC. Foundations and patient advocacy groups may provide what is necessary to keep a young company alive. Partnering with big Pharma despite a bureaucracy and the unsettling effects of successive acquisitions, mergers and personnel changes, provides the best chance to realise the potential in commercialising successful collaborations; and by the investment community perceives the collaboration to be a vote of confidence.

Similarly, taking a lead from the specialty pharma companies by licensing in products that big pharma is losing interest in faster than the patents are expiring can be a basis to establish a presence in a market that may be a strategic fit.

To rely upon that which has already been done may be a drawback when new thinking unencumbered by solutions to old and different problems is called for. Hence, I follow the wisdom of an early innovator – Groucho Marx – “Better Nouveau than Never.” ■

Raymond S. Fersko is the founder and managing member of Ferskos LLC.