

GEN Biobusiness

GEN's Annual Wall Street Analyst Roundup

Even with the possibility (some would say it's already a reality) of a recession in the U.S. this year, the biotech stock analysts we interviewed for our Annual Wall Street Roundup feature express caution yet also optimism about the prospects for the bioindustry in 2008.

Company cash reserves, burn rates, and FDA regulatory oversight raise caution flags with our financial pros. Positive product stories and selective investment opportunities, however, are cause for optimism among potential biotech investors in the year ahead, according to these experts.

Our respondents were **Viren Mehta (VM)**, managing member of Mehta Partners, **Jason Napodano (JN)**, senior biotechnology analyst at Zacks Investment Research, **William Tanner, Ph.D. (WT)**, managing director, biotechnology at Leerink Swann, **Rod Raynovich (RR)**, principal at Raygent Associates, **Nola E. Masterson (NM)**, managing director of Science Futures, and **Benjamin J. Conway (BC)**, managing director of Johnston Blakely & Company.

Describe the current state of the industry and what trends you see for 2008.

VM: The themes from recent years promise to continue to shape the opportunities for 2008. Globally diversified positioning of your biopharmaceutical investments is especially timely for the current year. Consider Japanese and other selected generic companies, along with Indian and Chinese firms. On the new-science side, exercise special care and focus on the proof-of-concept stage opportunities and underweight large pharma and mature biotech companies. New science investments have yet to create the critical mass for predictable productivity and, in fact, accentuate the safety flags with their refined tools. It is likely that this transition period will extend through at least another five years.



Viren Mehta

JN: Things have been difficult in biotech investing over the past year. Both large-cap and small-cap names struggled throughout 2007. Small-cap biotech performance is determined by three factors: the general positive feeling of the industry, which is driven by performance of the large-cap names, the potential for M&A activity, and a favorable FDA. All three legs of the stool broke in the second half of 2007.



Jason Napodano

WT: We suspect that the bark of changes wrought by the election may be worse than the actual bite. Implementation of healthcare reform measures on which some candidates campaign may be more difficult than is the general perception. While healthcare stocks, especially those of drug developers, could struggle in the first part of the year, their value will perhaps begin to lift as the election draws nearer amid the realization that whatever the election outcome, the impact on healthcare will not be significant over the near-to-intermediate term.



William Tanner, Ph.D.

We believe the trend suggests that biotech investors have continually become more risk averse, especially since the bursting of the bubble in 2000. It seems logical to us that a general avoidance of healthcare stocks in 2008 because of the election may adversely position some small-cap equities that are more difficult to value and for which a lack of catalysts and liquidity could further dampen interest.

RR: The biotechnology sector lived up to its reputation in 2007 by being volatile and contrary. Many of the companies that perennially outperform lagged, like **Amgen (AMGN)**, **Celgene (CELG)**, and **Genentech (DNA)**, and new leaders surfaced.



Rod Raynovich



Despite the stock volatility and regulatory issues, I expect that biotech and more broadly healthcare will again beat the S&P 500 in 2008. Stocks will continue to be driven by new products, M&A activity, technological breakthroughs, and overall demand for new treatments. Any economic slowdown or political clouds should not have a significant macro effect on healthcare spending.

Biotech stocks in general can be erratic, so be mindful of seasonality and news hype. January frequently shows a top for small and mid caps, but there are good buying opportunities in August for a Q4 rally. Look at chart patterns especially whether stocks hold up after news.

NM: It is accepted wisdom in biotech investing that prices climb as development-stage hurdles are cleared and so does a firm's value. Over the last few years, however, this wisdom was tested by a large number of companies that have not been rewarded by the market until late in the process.



Nola E. Masterson

FDA approval to market a new drug is now needed to lure backers. In fact, even the agency's requirement of post-market data can influence the price of the stock.

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News Inside Industry

Invitrogen to Acquire CellzDirect for \$57M

Invitrogen (www.invitrogen.com) plans to purchase CellzDirect for approximately \$57 million in cash. CellzDirect provides hepatocyte-based cell products and related services used in the testing of new drugs.

The transaction is expected to close in the first quarter of this year. The acquisition should be EPS neutral in fiscal 2008 and become accretive in fiscal year 2009.

CellzDirect's revenue for calendar year 2007 is expected to be approximately \$18 million, according to Invitrogen.

Sysmex and bioMérieux Form Joint Venture Targeted at Japanese IVD Market

Sysmex (www.sysmex.com) will take a 34% equity stake in bioMérieux Japan (www.biomerieux.com) to form Sysmex

bioMérieux. The new entity will promote and commercialize bioMérieux' entire product range in Japan starting April 1.

bioMérieux has been operating in the Japanese clinical diagnostics and industrial testing market through bioMérieux Japan. As per the current arrangement, the joint venture will manage the regulatory filing and marketing activities for bioMérieux in Japan. The sales and customer service activities will be contracted out from the joint venture to Sysmex.

RxElite Buys FineTech for About \$18.3M

RxElite (www.rxelite.com) purchased FineTech Laboratories in a deal valued at approximately \$18.3 million. The firm will pay \$6.2 million in cash and 18,632,383 shares. RxElite expects this acquisition to bolster its ability to develop and manufacture complex generic drugs.

FineTech conducts R&D as well as manufactures complex APIs at its manufacturing facility in Israel. RxElite acquired the physical facilities, intellectual property, and patents of FineTech and has retained all FineTech employees. The firm will operate as a separate division, through a wholly owned subsidiary.

Ark Therapeutics to Take Over Lymphatix for €2.25M

Ark Therapeutics (www.arktherapeutics.com) agreed to acquire Lymphatix in an all-share transaction equivalent to €2.25 million. The acquisition will give Ark royalty-free rights to the vascular endothelial growth factor genes, VEGF-D and VEGF-C, for the development of gene-based drugs in the fields of angiogenesis and lymphangiogenesis. Ark says that it will incorporate the VEGF portfolio with other genes including its own VEGF mutants.

Wall Street Roundup

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Benjamin J. Conway

BC: M&A activity will likely continue to be the overarching market theme for 2008, influenced by an array of considerations. Perhaps the biggest impact on M&A activity in 2007 was the visibility of foreign buyers, an influence unlikely to change in 2008. Taking advantage of the eroding dollar, foreign firms made their presence felt in many of the largest life science deals of 2007: Eisai's (TSE:4523) \$3.9 billion bid for MGI Pharma, Royal Philips Electronics' (PHG) \$5.1 billion offer for Respironics, Siemens' (SI) \$7 billion takeover of Dade Behring, and AstraZeneca's (AZN) \$15.6 billion acquisition of MedImmune.

The presidential election is also certain to influence the industry in 2008. With the Democrats apparently poised to do well, and healthcare reform likely to be central to their platform, companies may reconfigure business models in anticipation of change.

What are your top and bottom picks for the year?

VM: Merck & Co. (MRK) is one of the few exceptions among the global pharma companies, as relative performance of most of the other global pharma will be uninspiring, if not downright painful. This may also be the case with some of the larger Japanese pharma companies.

WT: After an utterly disastrous 2007, we believe Amgen shares could be poised for a rebound in 2008, driven largely by anticipation of positive data from denosumab for treating bone disorders such as postmenopausal osteoporosis or osteoporosis that is secondary to cancer treatment. The lack of investors desiring to show Amgen as a holding as of YE:07 could give way to renewed interest in 2008. Concern over the safety of erythropoiesis-stimulating agents, though, should continue to be an overhang for the stock.

Back to business as usual for Biogen Idec (BIIB) hopefully entails more active marketing of Tysabri even if it were to mean cannibalization of Avonex. Over the next few quarters, for Biogen Idec stock to perform well, aside from speculation about being acquired, we believe investors will want to see increasing uptake of Tysabri especially as it begins to frame the reasonableness of 100,000 patients being treated with the drug in 2010. We believe Biogen Idec's MS market presence with the top-selling injectable and infused therapies as well as a strong pipeline positions the company well to reshape the future MS market.

Elan (ELN) continues to be one of our top biotech picks. We believe 2008 could be a breakout year for the company. The single most important event would be the release of Phase II data for bapineuzumab (AAB-001) to treat Alzheimer's disease

(AD). Elan's stock will also be impacted by continued commercial success for Tysabri to treat MS as well as the emerging Crohn's disease opportunity.

Genzyme (GENZ) could dodge the last obvious bullet after full release of Phase II data of Amicus Therapeutics' (FOLD) competing drug, Plicera, for treating Gaucher disease in mid March. Data from the Phase II trial of Amigal, Amicus' small molecule chaperone for treating Fabry disease, showed that clinical efficacy appears to be modest at best. If those data are proxy for the effectiveness of the chaperone technology, it could be predicted that the Plicera data will not be overly encouraging. Genzyme's Cerezyme for Gaucher and Fabrazyme for Fabry will account for approximately 40% of revenues in 2007. Thus, any competitive threats to those franchises could have a significant impact. We believe investors will continue to be attracted to Genzyme stock by virtue of the valuation and the company's financial discipline.

We continue to believe that Gilead Sciences (GILD) is the best managed large-cap biotech company and that 2008 will be another solid year. The HIV franchise continues to expand, and European approval of Atripla should create new commercial opportunities.

Additionally, we suspect that investors will look to evidence of the commercial expansion of other businesses, particularly in the cardiopulmonary area with the continued uptake of PAH drug, Letairis, and approval of streptomycin lysine for treating pulmonary infection in patients with cystic fibrosis. The only negative, a minor one we believe, would be the extent to which sales of Tamiflu decline on a year-over-year basis as the result of less pandemic flu stockpiling.

RR: Life science stocks will do as well as if not better than 2007, so a 10% return is achievable with the right mix of stocks. The wild card for 2008 will be trading in stem cell stocks with scientific developments such as the use of skin cells to bypass embryonic stem cells. My investing model is a balanced portfolio with a core position in exchange-traded funds (ETFs) and large caps.

25% in the S&P ETF XBI: I don't know how S&P does it, but they consistently outperform mutual funds and other ETFs.

50% in large-cap biotech and pharmaceuticals: I am going with a Dogs of the Dow type of strategy, with these beaten-up large-cap picks, all of which are 2007 losers—Amgen, Celgene, Genentech, and Pfizer (PFE). Growth stocks that are core long-term holds are Abbott Laboratories (ABT), Becton Dickinson (BDX), Biogen Idec, Cephalon (CEPH), Elan, Genzyme, and Gilead.

25% in small- and mid-cap life science and diagnostics firms: Alnylam Pharmaceuticals (ALNY), Sangamo BioSciences (SGMO), Cubist Pharmaceuticals (CBST), Celera (CRA), Epix Pharmaceuticals (EPIX), Isis Pharmaceuticals (ISIS), Martek Biosciences (MATK), Seattle Genetics (SGEN), Myriad Genetics (MYGN), and Viropharma (VPHM).

Speculative micro caps: Gene Logic, which is now Ore Pharmaceuticals (ORXE), Micromet (MITI), and Genelabs Technologies (GNLB).

NM: Amgen lost 31% during 2007, as the FDA slapped its toughest warning label on its anemia drug, Aranesp. Also, Vectibix failed to show increased survival in colon cancer, and 1,500 people were laid off. Hence, it may be a good time to accumulate, since the company has a great pipeline of products in clinical stages through its recent acquisitions, and sustained earnings will be maintained by cost-cutting measures.

Biogen Idec's gross margin is more than 91% of other companies in the biotechnology and pharmaceutical industry, which means it has more cash to spend on business operations as compared to its peers. As indicated by the operating margins, Biogen Idec controls its costs and expenses better than 94% of its peers. Tysabri, its expensive treatment for MS, will continue to gain momentum in 2008. With the failure of Biogen Idec to find a buyer for itself, the stock has been depressed, yet it earns

over \$3 a share. This stock may be a bargain if it continues to slide while looking for a buyer.

Genex Biotechnology (GNBT) is an undercover gem. It is engaged in the development of technologies and formulations of large molecule drugs delivered to the oral cavity, using a hand-held aerosol applicator.

Genomic Health's (GHDX) first test, Oncotype DX, is already covered by government insurance plans and many private insurers. It is used in early-stage breast cancer patients to predict the likelihood of recurrence, patient survival within 10 years of diagnosis, and chemotherapy benefit.

Gilead had a great run up in 2007 and it could see more upside as the products continue to expand market share.

The past five years has seen Illumina's (ILMN) stock grow 250%, making this another good stock pick.

La Jolla Pharmaceutical's (LJPC) lead product in development, Riquent, is designed to treat lupus renal disease by preventing or delaying renal flares. The company represents a valuable investment.

BioMarket Trends

Phalanx of Treatments

Recombinant Growth Factor Therapies Are Predicted to Be Up-and-Coming Players

Bruce Carlson

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To order "Wound Care Markets, Vol. II, Burn Treatments" or find out more about the report go to:

www.kaloramainformation.com.

Burn injuries, which have reached epidemic proportions in recent years, are considered a healthcare problem more serious than the polio epidemic was at its peak. According to the CDC, on average in the U.S. in 2005, someone died in a fire about every two hours (143 minutes), and someone was injured every 25 minutes.

Burn victims, more so than many other accident victims, face a multitude of roadblocks on the road to recovery. Beyond the shock and trauma of the initial incident, they must endure agonizing pain, the ever-present risk of infections, and the excruciating treatment of their wounds, which often entails scraping the burn site to promote new skin growth.

Burn pain is an extremely unpleasant form of suffering, and can be difficult to treat. An estimated 2.1 million Americans seek medical care each year for burns. Approximately 100,000 are hospitalized, and 72,000 require intensive care services. An estimated 11,000 of these people die annually as a direct result of their burns. Children and elderly adults account for more than two-thirds of all burn fatalities.

Fortunately, a new array of treatment methods have arrived in the clinical setting in time to meet the growing need. Developments in treatments of burns have

made tremendous strides in the last decade. Recently, however, these advances are taking place on a daily basis with the most significant changes seen in the past 30 years.

In addition to the always-improving synthetic dressing materials, newer technologies in wound treatment include the xenogeneic tissue scaffold, bilayered human dermal substitutes, recombinant growth factors, endoscopic subfascial ligation of venous perforators, endovascular arterial repair techniques, and hyperbaric oxygen therapy.

The growing incidence of burn wounds and these new methods to approach the problem point to a robust market for those companies that make products to treat burns. Kalorama Information estimates in "Wound Care Markets, Vol. II, Burn Treatments" that the worldwide burn-treatment market reached revenues of nearly \$1.9 billion in 2006.

The burn treatment market will continue to grow in revenues reaching \$2.6 billion revenues in 2011, with a compound annual growth rate of 6.9% during that timeframe. The bulk of revenue in the burn-treatment market originates from conventional thera-

Pharmasset (VRUS) has three product candidates to treat viral infections. It is developing two of these alone and one with **Roche** (ROG.VX). The firm has a small market cap of \$300 million, so good news and good data should help propel the stock. The company is sitting on approximately \$65 million in cash and a big pharma partner to take on the clinical costs. This was one of the best IPOs of 2007.

Sirtis Pharmaceuticals' (SIRT) stock was recently hit with venture selling and is in the low end of its range.

Repros Therapeutics (RPRX) is developing Proellex for the treatment of uterine fibroids and endometriosis and Androxal for secondary hypogonadism with the potential for use in metabolic syndromes and diabetes. Based on these two compounds with multiple indications, Repros appears undervalued and looks to be an attractive investment.

Wyeth Pharmaceuticals' (WYE) value has been falling on concerns that its blockbuster heartburn drug, Protonix, could face generic competition sooner than expected. On December 24, Wyeth said that it plans to sue

Teva Pharmaceutical Industries (TEVA) for patent infringement. Teva launched a generic version of Protonix, even though Wyeth's patents are not due to expire until July 2010. This could make for unrest in the stock.

BC: We continue to believe diagnostics will factor prominently in the future of healthcare and so would favor stocks such as **Quidel** (QDEL), **Inverness Medical Innovations**, and **Meridian Bioscience** (VIVO). We also like many of the pharma services companies including **Covance** (CVD), **Pharmaceutical Product Development** (PPDI), **Charles River Laboratories** (CRL), and **ICON Clinical** (ICLR), which we believe will benefit from current industry trends.

We would tend to stay clear of big pharma names as well as certain big biotech firms such as **Eli Lilly**, **Wyeth**, **Bristol Myers Squibb** (BMS), **Schering Plough** (SGP), **Abbott Laboratories**, and **Amgen**. While we believe these companies' efforts to retool discovery may ultimately be rewarded, their exposure to the crosshairs of presidential politics likely leaves them vulnerable through this year.

Define the role of M&A activity, collaborations, venture capitalists hedge funds, and IPOs?

JN: M&A activity is looking weak. In December 2007, **Biogen Idec** announced that the company had completed its strategic review and chose to remain independent. The stock dropped nearly 30% on the news. The truth is **Biogen Idec** didn't receive any solid offers. The fact that no pharmaceutical company wanted to pay the hefty premium **Biogen** was looking for does not bode well for future M&A activity in the industry.

ImClone (IMCL), **Sepracor** (SEPR), and **PDL BioPharma** (PDLI) all hired bankers to "explore strategic alternatives," i.e., put themselves up for sale. As yet, there are no takers. Big deals in biotech such as **Eli Lilly's** (LLY) acquisition of **Icos** or **AstraZeneca's** buyout of **MedImmune** are the minority. M&A is extremely important to small-cap biotech stock performance, and right now pharmaceutical stocks seem to be shying away.

M&A activity has not completely dried

up, though; we just think that the large-cap names will continue to be picky about the deals they do.

VM: At a pace that is difficult to predict, and for targets that may not be readily identifiable, we believe pharma will continue to seek growth through acquisition of biotech companies. Recently announced deals that include **Eisai's** intent to acquire **MGI Pharma** (MOGN) and **Celgene's** offer to buy **Pharmion** (PHRM) highlight product-focused acquisitions. Additionally, **Merck & Co.'s** purchase of **Sirna Therapeutics** suggests that large pharma may have an appetite for promising technologies.

It will be of interest to monitor the impact of emerging biotech shareholder activism as a new force that could accelerate the pace of acquisitions by driving companies into the arms of others.

RR: We can expect the healthcare area to capture an increasing share of investor funds. Hedge funds will continue to be a driving force for stock performance. They

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Propels Burn Market

pies such as anti-infectives, burn management, and pressure-relief devices. Here the market has for the most part reached maturity. But the lion's share of the growth is coming from the novel therapies that result in decreasing healing times and subsequent cost savings.

High-Growth Burn Treatment Areas

An example of one such area is in biologic dressings. Obtained from humans (homografts), from other animals (xenografts or heterografts), or amnion from human placentas, these treatments are being used on large burns. These coverings provide a temporary wound closure until autografting is complete and are also used to debride dirty wounds after eschar separation. They decrease evaporative fluid and protein loss, protect new nerve endings, and provide a bacterial barrier enhancing reepithelialization.

When the biologic dressing appears to be taking, or adheres to the granulating wound surface with a minimum of underlying exudates, the patient is ready for permanent placement of an autograft. Because of the cost of biologic dressings, synthetic substitutes have also become available, such as **Biobrane** and artificial skin.

While still in the beginning stages of devel-

opment, they demonstrate a large opportunity for continued growth. These dressings earned \$85.8 million in 2006 and are expected to grow at a 23.6% compound annual rate to an estimated \$109 million by 2011. **Johnson and Johnson**, with its **Promogran** and **NUGEL** brands, dominates this area with 26% of the market share.

Silver wound dressings, containing stabilized antimicrobial silver, have also proven their effectiveness. Products such as **AcryMed's** **SilverSorb** single-use sheet, **Argentum's** **Silverlon** multilayer fabric pad, and **Johnson and Johnson's** **Actisorb Silver 220** will lead this category of burn care to 12 times its current market size by 2011, or nearly \$175 million.

Vacuum-assisted or sub-atmospheric pressure have established a key role in speeding up the wound-healing process. Numerous clinical studies show that vacuum-assisted therapy can promote wound healing significantly better than conventional methods. Vacuum-assisted products make up \$108 million of the burn-care market and show promise in the future.

Miscellaneous treatments will be an important part of a comprehensive strategy to treat burn wounds. Electrostimulation

transfers energy in the form of electric current through an applied surface electrode pad that is in wet contact with the external skin surface and/or wound bed. Hyperbaric oxygen, 100% oxygen delivered at two to three times ambient pressure, is also a powerful treatment to speed up wound healing. These miscellaneous treatments make up \$117 million of the market and in tandem with vacuum-assisted therapies will grow to \$335 million by 2011.

Development has certainly not stopped with these therapies, and there are many others in development.

Recombinant Growth Factors

Another wound treatment that is not visible yet in terms of revenues but is expected to provide real results in coming years is recombinant growth factors. Recombinant growth factors are laboratory-cloned replicas of peptides that have small biochemical differences. Recombinant growth factor manufacturers strive to make the laboratory-generated growth factors similar to the original human growth factor, with equal or greater bioactivity. This has been the major problem for manufacturers of growth factors to overcome.

Medical studies have shown that growth factors stimulate normal growth, as well as help regenerate and accelerate the repair of aged or injured muscle, skin collagen, bone, cartilage, and nerve tissues.

In addition, growth factors can be used as an effective topical application for burns, injuries, and skin rejuvenation. For some time researchers have known that endogenous growth factors released at the location of

wounds are conducive to wound healing. The identification of these growth factors and the roles they serve in wound healing has changed the outlook of wound care in general.

Growth factors are a large and diverse group of peptides that coordinate all aspects of interactions between cells. They are signal proteins released from local tissues or blood products that activate target cells to replicate or migrate. They can be produced outside the body by two methods.

The first entails centrifuging blood to isolate platelets and then adding thrombin (e.g., platelet-derived wound-healing formula). This produces a crude preparation with uncertain concentrations of different growth factors. The second method uses recombinant techniques to isolate the gene that produces a specific growth factor protein. The gene is used to create a purified quantity of a single type of growth factor, for example, basic fibroblast growth factor, epidermal growth factor, and platelet-derived growth factor.

Another example of a growth factor used in wound healing is placental angiogenic growth factors. Growth factor preparation is applied as a topical salve, and reportedly stimulates the regrowth of soft tissue, capillaries, and skin.

There is only one growth factor product on the market, **RegranX**, which is not indicated for burns at this time. But the theoretical case can be made and the use of this biological solution for burn treatment is anticipated. It is these unutilized approaches as well as the many creative products in use and in development that will be of most importance in understanding the long-term future of the burn market.

Global and U.S. Yearly Incidence of Burns by Type

Burns	U.S.	Global
Hospitalized for burn wounds	100,000	1,000,000
Outpatient visits for burn wounds	1,100,000	7,000,000
Second-degree burns	40,000	N/A
Burns covering more than 25% of body surface	20,000	N/A
Deaths attributed to burn wounds	9,500	1,200,000
All burns	2,500,000	27,000,000

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do their homework and control their destiny with small and mid caps. Most biotech stocks have a small float, and that means the big players can move their favorite stocks. Sponsorship is the key element to stock appreciation.

NM: The need for financings remains high for biotech companies. Approximately 20% of the firms burning cash in the *BioWorld* Stock Report universe have less than a year's worth of operating cash on the balance sheet, and 60% have less than two years cash. Also, approximately 36% of these companies are burning around \$2 million per month.

Big pharma, on the other hand, is flush with cash. The 15 companies in the Amex Pharmaceutical Index collectively hold \$87 billion. Six other major companies based in Europe and Japan have an additional \$58 billion in cash.

Many companies have completed stock offerings this past year, and more will be available in 2008. Introducing new institutional investors, however, did not propel the stock price. Most U.S.-based institutional and individual investors no longer back public development-stage biotech companies. The remaining European institutional investors are now redeeming from biotech/healthcare funds at an unprecedented rate. This makes it unlikely the current depressed prices in development-stage biotech firms will change significantly in 2008.

Secondary activity will continue to exceed IPO issuance in the coming year. Rule 415 interpretations are likely to slow private investment in public equity activity. Public biotech companies will need to access the capital markets over the next 12 months without regard to market conditions, possibly leading to market terms that deteriorate from current levels.

Modest public valuations relative to the supply of quality M&A targets having late-stage compounds validated in large clinical trials will magnify strategic activity in 2008. In general, M&A-induced demand for equity products will continue. By October 2007, there was over \$25 billion in equity removed from U.S. markets through cash acquisitions.

BC: This year's M&A activity will top out an already frenzied deal-making pace. M&As for 2007 was up 20% over 2006, which itself witnessed a nearly 30% increase in number of completed deals. More significantly, despite the shakeout impacting the broader market, transaction activity for 2007 in the life science sector hit its high for the year in the Q4.

Perhaps equally notable was big pharma's acquisition focus. Despite headlines lamenting a lack of pipeline depth, completed agreements suggest broad-base core discovery technologies have the priority. And the numbers bear this out. Of the 20 or so acquisitions by big pharma over the past two years, the majority have involved not late-stage products but rather differentiated technology platforms: witness Glaxo SmithKline's acquisition of Domantis, Merck & Co.'s buyout

of GlycoFi, and Bristol Myers Squibb's takeover of Adnexus. This deal focus may also be indicative of big pharma's diminished impression of the intrinsic value of the vast majority of late-stage candidates.

The sector's performance in the equity market is likely to follow the broader market, remaining tepid in the wake of the real estate downturn and credit crunch. While Q4:07 IPO activity did seem to show some resilience, other indicators suggest a more cautious investment environment. Private financings were down sharply in the 2H:07, and dollars committed to life science deals down 50% from 1H:07.

What business models and/or disease focuses will be the most profitable?

VM: Companies focused on orphan diseases or with clearly differentiated drugs offer safer upside. Genzyme and **Biomarin** (BMRN), which both concentrate on niche populations and have little competition, showed a strong rise in 2007, which should

M&A activity in 2007 was significantly greater than 2006. In particular, foreign firms found themselves taking advantage of the falling dollar and doled out some of the biggest bucks. This trend is likely to spill into 2008.

Don Farrall/
Getty Images



continue. In the pulmonary arterial hypertension market, **United Therapeutics** (UTHR) nearly doubled in 2007. Sales from Remodulin and a launch for Viveta position the company well for 2008.

We await a new wave of more effective and convenient therapies for diabetes, hepatitis C, multiple sclerosis, and rheumatoid arthritis in late-stage development, and recommend taking selected positions. In addition, biologics for new therapeutic areas, for example **Renovo's** (RNVO) Juvista for skin scarring, has no competition and strong early data, and thus a long-term growth opportunity.

While the first disease-modifying drugs for AD are poised to enter late-stage clinical studies, this first-generation crop seems risky and likely to join many earlier attempts that have failed. AAB-001, the antibody-based therapy in development by Elan/Wyeth, targets a risky mechanism of action and deserves a cautious watch. **Myriad Genetics'** (MYGN) Flurizan has a more promising mechanism but is still not a sure thing in light of its mixed Phase II data.

Perhaps not so surprisingly, yet paradox-

ically, what little R&D productivity exists is within the same limited number of targets, creating quite an over-crowding. This will make it challenging to launch new products and expect to recoup R&D investments. For example, **Somaxon** (SOMX) has had difficulty finding a partner for its insomnia treatment, Silenor, and likely will have to struggle to gain market share.

Similarly, generics as well as a large number of branded alternatives will make it tough for **King Pharmaceuticals** (KP) to advance its Altace tablet or **H. Lundbeck** (LUN.CO) to grow in the antidepressant market, assuming its recent **Takeda Pharmaceutical** (TSE) partnership is eventually successful.

JN: Buy small-cap biotech stocks that are developing one product with multiple potential indications. These are so-called platform drugs like Rituxan, Remicade, Humira, and Enbrel, which are approved for up to five indications. All of these drugs are mega-blockbusters.

The beauty of this strategy is that these

Phase I trials for type 2 diabetes also represents a platform drug. The firm anticipates that this compound has potential in other indications including RA, systematic juvenile idiopathic arthritis, and gout. If the data looks good, expect significant buying interest around this opportunity.

Compounds under development for pain probably offer the next best pipeline-in-a-product opportunity. The pain therapeutic market has been an area several large pharmaceutical companies are looking to expand. Both Pfizer and Eli Lilly recently entered into transactions specifically focusing on TRPV1.

There are two firms developing capsaicin-based products for pain indications that target the TRPV1 site. **Anesiva** (ANSV) is developing a high-dose injectable capsaicin product, Adlea, for postoperative surgical pain. Other potential indications include interdigital neuroma, tendonitis, and osteoarthritis. **NeurogesX** (NGSX) is developing NGX-4010, a capsaicin patch for potential neuropathic pain indications such as postherpetic neuralgia and painful diabetic neuropathy. NeurogesX is also developing NGX-4010 for HIV-associated distal sensory polyneuropathy.

The final area that offers the best opportunity to develop multiple indication products is in neuropsychiatry. **Acadia Pharmaceuticals** (ACAD) has amassed early-stage insomnia and Parkinson's disease psychosis data to help convince a large pharmaceutical partner that pimavanserin would be an excellent in-licensing option as a pipeline product.

The biggest potential is in using pimavanserin as an adjunctive therapy with atypical antipsychotic agents for the treatment of schizophrenia. In a Phase II trial Acadia proved that pimavanserin, when added to a low-dose of **Johnson and Johnson's** (JNJ) Risperdal, is as effective as high-dose Risperdal with significantly lower side effects and improved tolerability. This is a big opportunity in our view given the high discontinuation and switching rate among patients on atypical antipsychotics.

We would avoid biotech firms that are developing me-too products. The FDA has been steadily increasing the hurdle rate for approval of products that seem to add little value over the existing market; just ask **Neurocrine Biosciences** (NBIX). We would also avoid companies that are repurposing failed drug candidates. This is an approach we just don't have confidence in, no matter how much cash they have.

RR: Many biotech companies are evolving the orphan drug model, which Genzyme pioneered, to minimize competition and potential regulatory issues. Development of blockbusters such as Lipitor, Nexium, and EpoGen has become harder than ever, because competition in these large markets means greater FDA scrutiny of potential side effects.

Biomarin is the latest winner in the boutique category, with FDA approval in December of Kuvan, its enzyme replacement therapy for phenylketonuria. Pricing

for these niche compounds can be aggressive, with revenues of around \$50,000 per year, per patient. Expect to see more niche drugs for smaller diseases through licensing and M&A activity.

AD also has huge potential. The market for diagnosis and treatment is huge and growing. Treatment breakthroughs, however, have not been forthcoming. Most drugs currently on the market only alleviate symptoms without treating underlying disease. There are several companies that could show progress for treating AD. Elan will have Phase III data this year on AAB-001, which is being developed with Wyeth. Another candidate ELND005 is also in Phase II with Transition (TTHI) as a partner. Epix' Phase II trial with PRX-03140 reportedly showed compelling results. The company is working with GlaxoSmithKline (GSK). Also, Myriad Genetics' Flurizan is in two Phase III trials for mild AD.

How do you anticipate companies with pharmacogenomic-based technology and molecular diagnostics/prognostics will fare?

RR: Beginning with the July 2007 "American Association of Clinical Chemistry Meeting" in San Diego, there was a huge rally in diagnostic stocks. Among the winners were: Abaxis (ABAX), Cepheid (CPHD), GenProbe (GPRO), Idexx (IDXX), Inverness Medical Innovations (IMA), and Myriad Genetics.

The diagnostics sector should do well again in 2008, although many of these stocks have run up considerably in 2H:07. They represent holds or should be bought on weakness.

Drivers continue to be revenue growth and buyouts. Over this past year, Inverness has been an aggressive buyer, and Roche has an offer out to take over Ventana Medical Systems (VMSI). Cepheid was the rocket of the group with a 3X appreciation and is a good example of institutional dominance. Celera should do well in 2008 after its breakup from Applied Biosystems (ABI).

What effects will FDA oversight, patent reform, and the anticipation of biosimilars and generics have on the biotech industry?

VM: With about 40% of product sales losing patent protection in the next five years amid slow R&D productivity and stricter safety regulatory standards, the industry woes are further aggravated by the recent patent rulings such as KSR. The managed-care organizations in the U.S. and payors around the world are smarter in adopting evidence-based reimbursement policies that demand more rational life-cycle management strategies for the older drugs. In short, fewer new product introductions are on the horizon, just when life-cycle opportunities such as me-too drugs become more limited.

JN: Perhaps the most important factor to drive small-cap biotech stocks

higher is a favorable FDA. Nothing could be further from reality at this point. The FDA is not taking any chances in this post-Vioxx, post-Bextra, post-Tysabri, post-Avandia world. This scenario is certainly not inspiring much confidence.

The FDA, however, will start approving

drugs again; the agency will just require more proof of safety.

RR: The outlook for 2008 must be hedged by the regulatory risk. Political activism by patients and industry may actually provoke an attitude adjustment at FDA. Many industry executives feel the agency

has become too conservative to the point of discouraging breakthrough therapies particularly in cancer and other life-threatening diseases. In general, additional data requests and protocol requirements from the FDA will mean more clinical trials and limited growth in new product flow; only 16 NMEs were approved in 2007. **GEN**



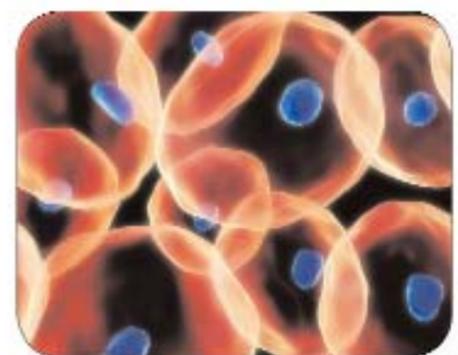
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