Biotech Watchlist 2013 Update: Exciting Ideas Have Explosive Potential

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COMPANIES MENTIONED

- Amarin Corp.
- Astellas Pharma Inc.
- Bayer
- Cardinal Health Inc.
- Celsion Corp.
- **Galena Biopharma Inc.**
- Hyperion Therapeutics Inc.
- Medivation Inc.
- Navidea Biopharmaceuticals Inc.
- Novartis AG
- Onyx Pharmaceuticals Inc.
- Peregrine Pharmaceuticals Inc.
- Pfizer Inc.
- Pharmacyclics Inc.
- Prana Biotechnology Ltd.
- Sangamo BioSciences Inc.
- Sarepta Therapeutics
- Trius Therapeutics Inc.
- Vertex Pharmaceuticals Inc.

In January 2013, *The Life Sciences Report* debuted its biotech Watchlist, which outlined ideas for investors keyed to catalysts in the drug development process that typically move biotechnology stocks. All stocks are affected by catalysts, but nowhere do they provide more leverage (or deleverage) than in biotech. We predicted the new year would present legitimate prospects for portfolio growth. So far, that has been the case. Although the party has given way to some fatigue, the punch bowl is still on the table and the biotech upswing continues.

Source: George S. Mack of *The Life Sciences Report*

Back in January, our friends and collaborators at San Diego-based Sagient Research, publishers of the BioMedTracker, offered important information about market-moving data and events that can make or break smaller companies. In addition, a group of key biotech analysts weighed in on their best ideas—17 stocks in all. It was the perfect storm of individual ideas combined with a biotech wind from 2012 still billowing the sails. As of April 22, the NASDAQ Biotechnology (NBI) index is up 26.6%. Have the biotech companies that made inaugural Biotech Watchlist—and their stocks—met the targets identified in the first quarter of 2013? Are there new catalysts? Check out the progress in the updated April 2013 Biotech Watchlist.

Getting a Lift from the Drug Development Process

Sagient's Scientific Analyst Robert Jeng is looking at new regulatory developments that may provide lift to biotechnology stocks going forward. The regulatory process is always looming, and drug developers, analysts and investors are thinking about it between waking up and going to bed. First enacted in 1992, the Prescription Drug User Fee Act (PDUFA) is probably the most significant piece of legislation affecting the development path of drugs. PDUFA was designed to speed up the process of drug development by getting product sponsors to pay the freight for hiring new U.S. Food and Drug Administration (FDA) employees to shepherd new compounds forward. The idea was to make the regulatory and review process move ahead without the staggering bureaucratic delays often associated with large government agencies. Although there have been jarring potholes in the road, 39 new molecular entities (NMEs) were approved in 2012, a 15-year high. Nine NMEs have been approved in 2013.

Now, with the most recent renewal of the act in July 2012, PDUFA V brings the total fees collected up to $712.8 million ($712.8M) for fiscal 2013. Moreover, "PDUFA V will usher in new timelines for regulatory review," says Jeng. The target for review of new drug application (NDA) submissions is now 12 months for standard submissions and eight months for priority reviews.

"There is also an increased emphasis on presubmission meetings with the FDA,"

Streetwise Reports LLC
101 Second St., Suite 110
Petaluma, CA 94952
Tel.: (707) 981-8107
Fax: (707) 981-8998
bfung@streetwisereports.com

he says. Participants, in the FDA's words, are "strongly encouraged to discuss the planned content of the application with the appropriate FDA review division at a pre-NDA/BLA (biologics license application) meeting." Although these changes appear modest at first glance, the idea is to make sure NDAs and BLAs are filed with minimal errors and with agreed-upon disease indications, and that sufficient time is allotted for sponsors to act on FDA feedback. The FDA is also emphasizing discussion of risk evaluation and mitigation strategies at the presubmission meetings. It is the product sponsor's responsibility to make certain that the benefits of a new drug or biologic outweigh the risks, and the FDA would love to have this aired out in advance.

Updated Biotech Watchlist (April 2013)

The FDA now allows drug developers to request that a product be designated a "breakthrough therapy." This request can be submitted with the investigational new drug application (IND), which must be filed prior to clinical trials, or it can be an amendment to a pending submission. The first breakthrough therapy designations came through in Q1/13. They include Vertex Pharmaceuticals Inc. (VRTX:NASDAQ) cystic fibrosis (CF) drug Kalydeco (ivacaftor; now approved), designed specifically for patients who have the *G551D* gene mutation, and also Vertex's VX-809 (lumacaftor), which is in phase 3 and being studied in combination with Kalydeco for CF patients with the *F508del* mutation.

Another breakthrough therapy was awarded to ibrutinib, now in late phase 2 studies, which is being developed by Pharmacyclics Inc. (PCYC:NASDAQ) in a lead indication for chronic lymphocytic leukemia (CLL). Ibrutinib's breakthrough therapy designation, however, is for Waldenstrom's macroglobulinemia and mantle cell lymphoma. Another breakthrough therapy is Novartis AG's (NVS:NYSE) non-small cell lung cancer (NSCLC) phase 2 drug, LDK378, which is a specific inhibitor of anaplastic lymphoma kinase (ALK), prevalent in a range of cancer types.

The FDA promises to act on a breakthrough therapy request no more than 60 days after submission. But what does it actually mean? "Although the significance is still unclear," says Jeng, "it may signal an early favorable opinion from the FDA, as well as a potentially shorter regulatory path to approval."

Data in the Driver's Seat

Data, of course, also propels stocks. Jeng makes an observation that never seems to get old. "Oncology data can be very exciting," he says, "especially when there are well-defined survival endpoints."

But sometimes the letdowns at these endpoints feel like that first drop on the big coaster at the local theme park. In Q1/13, Celsion Corp.'s (CLSN:NASDAQ) ThermoDox (liposome-encapsulated doxorubicin) had a letdown after release of phase 3 HEAT trial data for hepatocellular carcinoma (primary liver cancer), which resulted in a single-day stock drop of 84%. This is a textbook case of a binary event affecting a one-product pipeline and causing shares to tumble dramatically. The stock is down another 49% since that day.

In contrast, Jeng points to an unusual event in the biotech industry regarding a secondary analysis performed on data from a phase 2b study of Peregrine Pharmaceuticals Inc.'s (PPHM:NASDAQ) monoclonal antibody bavituximab as a second-line therapy in NSCLC. After the company announced the results of the analysis on Jan. 7, shares popped up 73% on the unexpected good news.

Here is the history: On Sept. 24, 2012, the company reported that it had discovered

a coding error with the drug-containing vials (some of the vials were barcode-mislabeled) in its 121-patient phase 2b randomized, double-blind, placebo-controlled study of bavituximab in NSCLC. At the time, the company was preparing for an end-of-phase 2 meeting with the FDA to plan a pivotal phase 3 study. This was a complete surprise to the company and not what investors were looking to hear, not to mention patients in the study. The discovery prompted an internal review to determine how the coding error happened.

Now the twist. "The coding discrepancy may have invalidated the entire study, but Peregrine was able to salvage results," says senior biotechnology analyst George Zavoico of MLV & Co. "The stakes were very high. It's a case where luck played a role."

The company deserves credit for its solution. The trial had three arms: placebo, low-dose and high-dose. Peregrine's investigation, which involved testing the residual contents of not-yet-discarded vials of both the actual product and placebo used in the trial, as well as stored patient blood samples and just about anything else that might shed light on the coding error, revealed that only the low-dose (1 mg/kg) and placebo arms of the bavituximab trial were mislabeled. "Luckily, the company found no evidence that the most important, high-dose (3 mg/kg) arm of bavituximab was administered in error," says Zavoico. Peregrine was fortunate that enough spent materials were still available for testing, but especially lucky that the high-dose arm was not mistakenly coded.

How Are They Doing? Update on the Progress of Expert Picks

But to salvage the trial, the high-dose arm had to be compared to something. "Peregrine then decided to combine the results of the placebo and low-dose arms into a new control arm, and compare the median overall survival (mOS) to the high-dose arm," says Zavoico. This might have extended mOS in the control arm, if the low-dose arm had an effect on overall survival, thereby putting the high-dose experimental arm at some statistical disadvantage. Instead, "What the company found was a meaningful, but not statistically significant, 4.4-month increase in mOS, from 7.3 months in the new, combined control arm, to 11.7 months in the high-dose arm. This is a 60% improvement," says Zavoico. It was also all the company needed to proceed to phase 3, since the small trial was not powered to show a statistically significant improvement in mOS.

Now Peregrine can map out its end-of-phase 2 meeting with the FDA, which should occur by midyear, and emerge from the meeting with a pivotal phase 3 trial designed in consultation that will, hopefully, begin by year-end. Meanwhile, in Q2/13, Zavoico expects the company to announce mOS results from its phase 2b study of bavituximab as a first-line therapy in NSCLC (in combination with carboplatin + paclitaxel), as well as phase 1 results from a pair of investigator-sponsored trials of bavituximab in HER2-negative breast cancer (with paclitaxel) and liver cancer (with sorafenib).

Back in late December 2012, Zavoico said Prana Biotechnology Ltd. (PBT:ASX) represented one of the biggest risk/reward opportunities of this year with its investigational drug PBT2, which has restored cognition in mouse models of Alzheimer's disease (AD). PBT2 is currently in a phase 2b trial for AD and in phase 2a for Huntington's disease. The stock is up about 1% as of April 22 but has been volatile, due in part to its micro-cap status, with a $66M market valuation.

But does Zavoico's original thesis hold? "Perhaps even more now than before," he

says. Zavoico is excited about the FDA's new draft guidance to the industry for developing drugs to treat early-stage Alzheimer's. "That was recognized as being a potential game-changer—when two FDA physicians, Nicholas Kozauer and Russell Katz, wrote a "Perspective" piece on how the FDA is considering changes to its criteria for approving drugs for early AD," he says. The piece was published online in the *New England Journal of Medicine* in March.

"They wrote that innovative approaches to trial design and endpoint selection are 'urgently needed.' The take-away message is that they would like to see the FDA approve drugs shown to have a beneficial effect on cognitive function alone, since there may not be any overt symptoms of functional deficits in early stages of the disease, especially before dementia. They are also supportive of biomarkers of disease, such as brain-amyloid load and cerebrospinal fluid levels of beta-amyloid and tau proteins," says Zavoico.

"It remains to be seen whether the FDA adopts the proposals in its draft guidance as written. The public comment period is over now, so we expect the next iteration of the guidance to appear soon. What is relevant to Prana is that the design and endpoints of its ongoing phase 2b trial in Alzheimer's may already be what the FDA will consider approvable," Zavoico explains. The implication is that Prana might be able to expand its phase 2b into a pivotal phase 3 study just by adding patients, and without major modifications to trial design, thereby steering clear of a larger and lengthier phase 3 study measuring both cognitive and functional endpoints. This would diminish the burden immensely. "It means," Zavoico says, "that if this and a pivotal trial deliver positive results, then regulatory approval of PBT2 for the treatment of early AD could come as much as two or three years sooner than projected."

Success Does Not Always Translate

Navidea Biopharmaceuticals Inc. (NAVB:NYSE) received approval of its radiopharmaceutical diagnostic medium Lymphoseek (technetium Tc99m tilmanocept) on March 13. Lymphoseek is not a dye, but rather an isotope sensed intraoperatively with a gamma detector by the surgical oncologist. After a rocky ride, with the FDA postponing the PDUFA date and issuing a complete response letter, Lymphoseek was approved to map the location of lymph nodes draining and disseminating metastatic disease from primary breast cancers and melanomas. Primary tumors can be seen by oncologists, but the cells giving rise to micrometastatic lesions are the hidden killers in oncology. If sentinel lymph nodes are shown to have disease, they are excised. If not, tissues, lymph vessels and the drainage they provide can be preserved, as opposed to wholesale unnecessary removal.

Aiming for new disease indications, the company was conducting a phase 3 study of Lymphoseek in head-and-neck cancers, which become severely disfiguring and can prevent patients from taking nourishment by mouth in the advanced stages. Therefore, early detection of advancing disease is critical. On April 4, the company told investors that the independent data safety monitoring committee was recommending a halt to the trial because sufficient data had been collected to determine that results were conclusively favorable. While this story is holding together as investors might have hoped, the stock is down nearly 30% since the product received approval, and down more than 17% as of April 22. This is now a story about further approvals for new disease indications, uptake by surgeons and hospitals and actual product revenues. Lymphoseek will be marketed through Cardinal Health Inc. (CAH:NYSE), the largest sales channel for diagnostic isotopes in the U.S.

Tales of Science and Profit

Two drugs produced by Onyx Pharmaceuticals Inc. (ONXX:NASDAQ) made it to the market in 2012. The stock's share price doubled last year, and so far this year it is up a promising 30%. Onyx has launched both its unpartnered proteasome inhibitor Kyprolis (carfilzomib) for multiple myeloma, and its multikinase inhibitor Stivarga (regorafenib) for metastatic colorectal cancer (mCRC) and gastrointestinal stromal tumor, which is being developed by Bayer (BAYN:XETRA). Stivarga was approved on March 25 for mCRC in Japan. Onyx will derive a 20% royalty from sales of Stivarga.

Now with about a $7 billion ($7B) market cap, the company plans to begin phase 3 studies of Stivarga in liver and colorectal cancers. Big preparations are in progress for evaluations of Kyprolis in myeloma indications in various combination therapies, as well as plans to test it as a monotherapy in solid tumors. Another Onyx product, Nexavar (sorafenib), is also partnered with Bayer and is approved in unresectable liver cancer, as well as advanced kidney cancer. Nexavar is now in phase 3 for thyroid and breast cancers. The sky could be the limit for Onyx as it develops its extraordinary oncology franchise over the next five years.

Sarepta Therapeutics (SRPT:NASDAQ) is up 26% as of April 22, but shares tumbled more than 15% on April 15 when the company announced that the FDA would be considering an accelerated approval for eteplirsen.

Last year, Sarepta was up 481% as investors began to anticipate a true disease-modifying therapy for Duchenne muscular dystrophy (DMD). Sarepta is an antisense drug development company working on what could be a revolutionary therapy for DMD, which occurs in approximately 1 of every 3,500–6,000 male births, according to the Centers for Disease Control and Prevention. Normally, a patient with DMD becomes incapable of walking between age seven and 13, and may not live beyond the second or third decade of life. At the beginning of April, the company put out top-line data on its exon-skipping drug eteplirsen (AVI-4658); its phase 2b study showed a "sustained benefit" in patients through 74 weeks in a walking test given to boys with DMD.

See the Approval Process in Action

Eteplirsen is a short, modified, synthetic, nucleic acid-type structure that is highly specific to the messenger RNA (mRNA) gene it will engage. Eteplirsen modifies protein synthesis to skip exon 51 of the *dystrophin* gene, making the resulting dystrophin protein shorter but still serviceable. It's a structural and functional repair that can slow, or perhaps prevent, muscle breakdown in DMD patients.

DMD is surely one of the toughest disease indications ever confronted by biotech. One of the issues looming over eteplirsen is that it is intended for lifetime use, thereby making safety issues a real concern. If this novel product should gain acceptance and ultimate approval, investors could see another giant leap in Sarepta's share price, but some investors have already reaped a five-fold profit. In mid-December the company raised $125M in a public offering, an achievement that required the assistance of sophisticated investors, people who are professional skeptics.

Hyperion Therapeutics Inc. (HPTX:NASDAQ) received approval for Ravicti (glycerol phenylbutyrate; formerly HPN-100) on Feb. 1 for urea cycle disorders. Shares are up 115% as of April 22, and product rollout is in progress.

As scheduled, Amarin Corp. (AMRN:NASDAQ) filed its supplemental NDA (sNDA)

for Vascepa (icosapent ethyl), for mixed dyslipidemia, on Feb. 26. The company expects to hear by mid-May whether the sNDA is accepted. Although the company has lost half its market value since Vascepa was approved for hypertriglyceridemia on July 26, 2012, this new indication could be a significant value driver.

On April 1, Medivation Inc. (MDVN:NASDAQ) and partner Astellas Pharma Inc. (ALPMF:OTCPK) told investors they had updated the interim analysis plan for their randomized, double-blind, placebo-controlled phase 3 PREVAIL trial of Xtandi (enzalutamide) in chemotherapy-naïve patients with castration-resistant prostate cancer. Still expected in 2013, these data could herald Xtandi as a best-in-class agent compared to Johnson & Johnson's (JNJ:NYSE) Zytiga (abiraterone acetate).

Original Biotech Watchlist (January 2013)

Trius Therapeutics Inc. (TSRX:NASDAQ) delivered news on March 25, releasing data from its phase 3 ESTABLISH 2 trial with tedizolid phosphate (TR-701) for acute bacterial skin and skin structure infections (ABSSSI), including the difficult indication of methicillin-resistant Staphylococcus aureus. The study met ABSSSI primary endpoints determined by both the FDA and the European Medicines Agency. Tedizolid likewise met all secondary efficacy endpoints. ESTABLISH 2 confirmed the positive results of the ESTABLISH 1 study, and together they support an NDA to be filed in H2/13, as well as a marketing authorization application in the EU. Tedizolid is a member of the oxazolidinone family of antibiotics, and it would compete with Pfizer Inc.'s (PFE:NYSE) Zyvox (linezolid), also in the same family and now doing approximately $1.4B in annual sales.

Sangamo BioSciences Inc. (SGMO:NASDAQ) is developing DNA-binding proteins to regulate genes. Year to date, the stock is up nearly 71% on news surrounding its phase 2 study of SB-728-T, which the company believes may be a "functional cure" for HIV/AIDS. SB-728-T modifies the *CCR5* gene, which produces the CCR5 protein, the main co-receptor employed by HIV to infect and kill CD4+ T cells, which play a principal role in immunity.

In early March, the company presented new data from a phase 1 study showing that a single treatment with SB-728-T produces a "durable reconstitution of the immune system" by expanding memory CD4+ T cells, which have the capacity to recall and then rapidly respond against HIV and other foreign antigens. The increase in CD4+ T cells appears to be both an immediate and long-term phenomenon. In an age where personalized medicine and associated biomarkers have gained credibility with regulators, data from this study also demonstrate that specific cell surface markers, as well as gene expression characteristics, might predict which patients would be most responsive to SB-728-T. Regulators love specific biomarkers attached to proposed therapies in clinical studies. There are more than 33M people globally who have HIV, with an estimated 1.2M in the U.S. This program is unpartnered.

Galena Biopharma Inc. (GALE:NASDAQ) is testing its immunotherapeutic product NeuVax (nelipepimut-S or E75) in a phase 3 trial called PRESENT. NeuVax is a peptide developed from the extracellular domain of the HER2 antigen, and is combined with granulocyte macrophage-colony stimulating factor (GM-CSF), an immune stimulant. NeuVax stimulates cytotoxic (CD8+) T cells that target tumor cells expressing any level of HER2. Over the course of three years patients receive a total of 11 immunizations, and the goal of the trial is to prevent or delay return of disease following standard-of-care therapies. The primary endpoint will be disease-free survival. A phase 2b trial with 300 patients is also in progress, using NeuVax in combination with Herceptin (trastuzumab). In addition, Galena has begun a phase

1/2 study with its second targeted cancer immunization agent, folate-binding protein (FBP) in ovarian and endometrial cancers, and results from the phase 1 study with FBP will be announced in June at the American Society of Clinical Oncology (ASCO) annual meeting.

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