Millennium Thrives after Takeda Takeover

Often when a larger company takes over a smaller one, the organizational structure of the acquisition is absorbed into purchaser’s hierarchy. In the process, the smaller company is stripped of its rank-and-file employees and executives, its corporate culture, its strategic autonomy, and much of its identity.

Millennium Pharmaceuticals, an American biotech firm that a year ago agreed to be taken over by Takeda Pharmaceuticals, has managed to escape this typical fate. Takeda Pharmaceuticals is a global powerhouse based in Tokyo, Japan. It acquired Millennium Pharmaceuticals in a deal valued at $8.8 billion.

When ranked by revenue, the merged company is now the world’s 11th largest manufacturer of oncology drugs. Its 2008 oncology revenues reached approximately $1.5 billion.

Millennium Morphs Into Oncology Subsidiary

Instead of being folded into Takeda’s existing infrastructure, Millennium was allowed to remain intact. It has essentially been set up as a stand-alone subsidiary, retaining its CEO and key decision makers; its Cambridge, Massachusetts, headquarters, as well as its other facilities; and all 1000 of its employees. Millennium has also been allowed to maintain significant control over its research and development process, its pipeline, and its product portfolio.

This may be one of the few recent mergers in the pharmaceutical industry where instead of dishing out pink slips, the company is issuing help wanted ads. Responsibility for Takeda’s entire line of cancer drugs—including compounds in development and on the market—has been shifted to Millennium in an effort to position the company as the seat of Takeda’s oncology business. This is reflected in the rechristening of the company as Millennium, a Takeda Oncology Company. To carry out its new cancer-centric mission, Millennium needs to hire 150 to 200 additional employees, who, along with the existing staff, will now focus exclusively on the oncology sector.

As Japan’s largest drug maker, Takeda pursued Millennium partly because of the smaller company’s expertise in cancer drug development, as evidenced by its robust oncology pipeline. In an effort to retain Millennium’s stellar researchers, Takeda granted the management pre-merger levels of autonomy. Deborah Dunsire, MD, CEO, Millennium, has retained much of her decision-making authority, though she ultimately answers to Takeda president Yasuchika Hasegawa, who answers to the board of directors.

Like most marriages, the Millennium-Takeda union has not been devoid of challenges. In recent interviews with various finance and industry publications, Dr. Dunsire has been frank in discussing some of the hurdles the merged company has worked to overcome in the past 12 months. These include language barriers between Millennium employees and their Japanese counterparts, cultural barriers, a 13-hour time gap, and differences in corporate philosophy.

Millennium is a fast-moving biotech that has always operated in a nimble, flexible, decisive manner, with an egalitarian philosophy; whereas, big pharma Takeda tends to be more conservative, careful, and deliberative, with decisions trickling down from the top.

Millennium’s Pipeline Sizzles

Judging by Millennium’s post-merger successes, some of the early challenges appear to have been largely resolved. Millennium executives reinforced this with a confident, exuberant presentation at Takeda’s Tokyo headquarters. They described near- and long-term objectives and shared highlights from the company’s oncology pipeline. According to Dr. Dunsire, one of Millennium’s most crucial objectives is to climb the ladder in global oncology revenue rankings.

Velcade (bortezomib), a treatment for multiple myeloma and lymphoma, remains the centerpiece of Millennium’s oncology offerings. According to Millennium executives, Velcade sales increased more than 40% in 2008, topping $1.1 billion worldwide.

Millennium said it has 13 oncology drugs at various stages in the development continuum. Dr. Dunsire wants Millennium to introduce 3 or 4 new drugs into clinical trials each year. “We aspire to cure cancer,” she told Takeda’s executives at the meeting. “We believe this will inspire us to bring forward extraordinary medicines.”

Dr. Dunsire said Millennium hopes to develop drugs that target cells in new ways or via new pathways or create experimental compounds effective against targets with demonstrated therapeutic promise.

Dr. Dunsire and her team offered Takeda a partial review of Millennium’s oncology pipeline.
Electing to highlight those candidates they believe are the most promising. These include MLN-9708, MLN-8237, and MLN-4924.

MLN-9708 is an oral proteasome inhibitor in animal stages of testing for a range of solid tumors and hematological malignancies, such as multiple myeloma. Dr. Dunsire compared MLN-9708 to Velcade, characterizing it as a sort of next-generation formulation of the blockbuster drug. Millennium’s researchers are hoping the agent will prove safer than Velcade and have superior absorption characteristics.

MLN-8237 is an Aurora kinase blocker designed to disrupt the cycle of cancer cells. It is being tested in several types of cancer as monotherapy and in combination with different chemotherapy regimens. Millennium expects MLN-8237 to progress to mid-stage trials later in 2009. If MLN-8237 survives the clinical trial process, it may become the first approved therapy in the Aurora kinase blocker class. Millennium is in a race, however, with research and development divisions at other pharmaceutical companies that are testing their own Aurora kinase blockers.

The third experimental drug, MLN-4924, is designed to inhibit the NEDD8 activating enzyme, a new therapeutic target identified by Millennium scientists. MLN-4924 works by blocking signaling pathways cancer cells need to access for growth and survival. MLN-4924 is currently in early stage clinical trials for solid tumors and blood cancers, and Millennium researchers expect it to move to phase II trials in 2009.

New Deal with Seattle Genetics

Millennium recently announced it has entered into a collaborative agreement with Seattle Genetics, Inc to develop antibody-drug conjugates (ADCs). ADCs are synthetic monoclonal antibodies that deliver potent, cell-killing agents to tumors.

Millennium is paying $4 million to license an exclusive ADC from Seattle Genetics that binds to an antigen initially expressed in solid tumors. Millennium has also secured the rights to exercise options for exclusive licenses to other ADCs. In a press release announcing the agreement, Dr. Dunsire said, “The collaboration with Seattle Genetics enhances our pipeline.”

A team of genomics prodigies from the Massachusetts Institute of Technology founded Millennium in 1993, when genomic research was surging. Its stock initially skyrocketed before diving sharply as Millennium failed to achieve its expected success. Now with Takeda’s vast resources backing the company, Millennium may finally bring some of its agents in its bulging pipeline to fruition.

Provenge A Shot in the Arm for Dendreon Stock

Investors and executives who held onto shares of Dendreon Corporation stock even after the price plummeted to an all-time low of $2.55 last March can count their blessings—and their dollars. Shares rocketed to more than $27 the day after researchers at the annual meeting of the American Urological Association in Chicago, Illinois, announced that Provenge (sipuleucel-T), a novel vaccine for advanced prostate cancer, prolonged survival an average of 4.1 months compared with placebo.

This ignited a major sell-off, as some of the company’s top executives unloaded thousands of shares that had been relatively worthless for the past 2 years. Dendreon CEO Mitchell Gold, a major shareholder of the Seattle-based company, divested 600,000 shares for $11.4 million. Board member Douglas Watson, who purchased 26,000 shares at $1.82 each, turned them around for a $568,125 profit. For many shareholders, it was the first time their shares had attained a value greater than the purchase price.

David Penson, MD, University of Southern California Keck School of Medicine, was one of the study’s authors. At a press conference, Dr. Penson said Provenge extended survival in men with advanced hormone-refractory prostate cancer by 38%; nearly 31% of patients treated with Provenge survived 3 years compared with 23% who received placebo.

The phase II trial included 512 men whose prostate cancer no longer responded to androgen blockers. Half the men received a series of 3 injections of the Provenge vaccine over 1 month. The others were given placebo. Average survival for the men in the Provenge arm was 26 months versus 22 months for those in the placebo group. Patients had few treatment-related adverse effects, aside from flu-like symptoms that tended to resolve in a few days, according to Dr. Penson.

Unlike chemotherapy regimens that use toxic chemicals to induce apoptosis in tumor cells, Provenge uses dendritic cells taken from the patient and treated with a protein from the patient’s tumor. Reintroduction of the modified cells stimulates the patient’s immune system to attack the cancer.

The trial did not compare Provenge to docetaxel (Taxotere), currently the only approved treatment with a proven survival benefit in hormone-refractory metastatic prostate cancer. Patients sometimes discontinue therapy with docetaxel because of toxicities, and these men have no other treatment option. Dendreon said it plans to renew its bid for FDA approval of Provenge by the end of the year. Previous applications were denied pending additional information after earlier trials had failed to demonstrate that Provenge slowed disease progression in men with prostate cancer.

Some experts like Otis Brawley, MD, chief medical officer of the American Cancer Society, expressed caution about the results, noting that the trial did not show Provenge cured prostate cancer. Critics also said the size of the trial was too small and the results needed further examination. They agreed that Provenge appeared to be effective against the disease, however, and expressed optimism about its future.

If the FDA shares this optimism and approves Provenge, Dendreon’s stock may get another boost. Mr. Gold, who the Wall Street Journal says retains 500,000 shares of the Dendreon stock, may very well be banking on it.

Avastin’s New Indication Brightens Roche/Genentech Honeymoon

Last month, Oncology & Biotech News reported that an FDA panel had unanimously recommended approval of Avastin (bevacizumab) as a second-line treatment for glioblastoma multiforme (GBM). The FDA heeded the panel’s advice, and in the first week of May, GBM became the 4th indication for Avastin. The FDA gave accelerated approval for using Avastin in patients whose GBM progresses during or after first-line therapy. Some analysts say the approval could net $500 million in revenue for Roche.

The approval will likely ease the sting from a phase III trial on early stage colon cancer in which Avastin demonstrated activity but failed to meet the study’s primary endpoint of reducing recurrence. Following Genentech’s announcement of the trial’s results, Roche shares dipped sharply, but it is likely this latest approval will bring some of those investors back. Roche is not giving up on another colon cancer indication for the drug, which could double Avastin’s annual sales.

Avastin is being tested in more than 400 clinical trials in a variety of solid tumors, including colon, lung, breast, gastric, ovarian, and prostate cancers. It is also being investigated as a treatment for lymphoma. Hal Barron, MD, chief medical officer at Genentech, said a phase III trial to evaluate Avastin in patients with newly diagnosed GBM is also in the works. Meanwhile, investors have reasons to keep an eye on this company. Results from ovarian and prostate cancer trials are expected this year. Roche also has an application pending at the FDA for Avastin as a first-line treatment in metastatic renal cell carcinoma and plans to apply for an indication for Avastin as a first-line treatment in HER2-negative metastatic breast cancer.
Three New Oncology Tests for Treatment & Diagnosis

The frenetic drive to personalize oncology care has spurred an eruption of diagnostic tests. We summarize 3 that recently hit the market.

### Cervical Cancer Screening Tests by Hologic Inc

Hologic describes its mission as “serving the healthcare needs of women.” It recently announced that the FDA has granted premarket approval for the Cervista HPV HR (High Risk) and the Cervista HPV 16/18 tests. Approval was based on results of a late-stage clinical trial in which Cervista HPV HR demonstrated 100% sensitivity in detecting cervical intraepithelial neoplasia (CIN) 3, the precursor to cervical cancer. HPV HR detects 14 high-risk types of HPV and has been approved for screening patients with atypical squamous cells of undetermined significance.

HPV 16/18 is the first test approved for genotyping the 2 types of HPV associated with nearly 70% of cervical cancer cases. The test is an adjunctive screening tool for women aged ≥30 years, to be used with conventional cytology and, in some cases, Cervista HPV HR.

In a press release, Jack Cumming, chairman and CEO of Hologic, said, “Our state-of-the-art Cervista HPV tests, individually and in combination, are designed to provide significant advantages over the existing technology and should help solidify our leadership in cervical cancer screening.”

### Clarient Develops Test to Stratify Breast Cancer Risk

In May, Clarient Inc announced the launch of the Clarient Insight Dx Breast Cancer Profile, a screening tool to help oncologists assess the likelihood of cancer recurrence and the need for adjuvant chemotherapy. Clarient said the prognostic test has been “clinically validated for women with early stage, HR-positive breast cancer.” The test applies an algorithm to the combination of tumor size, tumor grade, and lymph node status plus 7 molecular markers (ER, PR, HER2, EGFR, BCL2, p53, and MYC) to generate a risk score that can be used to categorize patients as high- or low-risk for recurrence.

An independent Australian study compared the test’s predictions with clinical progression in patients with breast cancer. The researchers found that women classified by Clarient’s test as low-risk had a 3% recurrence rate over 10 years, for a negative predictive value of ~97%; the study placed the test’s positive predictive value at 39%.

Clarient said other studies, including one in the February 2009 issue of International Journal of Cancer, support the benefits of the Insight profiling system.

### Myriad Genetics Secures Rights to OnDose from Salada Biomedical

The biopharmaceutical firm Myriad Genetics will be launching OnDose, a tool that helps oncologists optimize dosing of 5-fluorouracil (5-FU) by measuring the agent’s area under the curve. 5-FU is routinely used in chemotherapy for colon cancer, and the company estimates 175,000 patients will be candidates for OnDose, and each will require approximately 8 tests (at $300 each) during a full treatment course.

The agreement gives Myriad exclusive rights to market OnDose in North America and any other Salada discoveries related to 5-FU. Salvate Salamone, CEO, Salada, expressed his satisfaction with the deal in a news release, saying, “This is a win-win situation for all involved—Myriad, Salada, doctors, payers, and most importantly, cancer patients.” In a May blog post, Grant Zeng, CFA, an analyst with Zacks Investment Research, rated Myriad stock a “buy.”

——Christin Melton

More Mergers to Come in Biotech?

If any business turns a profit this year, it might be the companies hired to print stationery and business cards for biotech firms. The pace of mergers and acquisitions is hard to track, but Ernst & Young Global Ltd gives it a shot with Beyond Borders: Global Biotechnology Report 2009, the company’s 23rd annual report on the industry. Here are a few notable deals that transpired in 2009:

- Takeda purchased Millennium for $8.8 billion
- Teva Pharmaceuticals bought Barr Pharmaceuticals for $7.19 billion
- Life Technologies Corp (formerly Invitrogen) bought Applied Biosystems Group for $6.7 billion
- Eli Lilly purchased ImClone Systems for $6.5 billion
- Novartis acquired Speedel, a Swiss biotech, for $932 million

The acquisition/merger trend continued in 2009, with a few blockbuster deals:

- Pfizer acquired Wyeth for $68 billion
- Roche purchased Genentech for $46.8 billion
- Merck merged with Schering-Plough for $41 billion

Ernst & Young and other Wall Street analysts are predicting more consolidation in the biotech industry as the global economic crisis squeezes smaller firms and patent losses cut into revenues at larger firms. According to the report, 44% of the 162 publicly traded biotech firms were sitting on less than 1 year’s worth of cash in December 2008.

The report notes that although many biotechs are restructuring or negotiating creative deals in an attempt to survive the economic crisis, consolidation appears inevitable. A drought in financing means many smaller biotech companies will be forced to close unless they can attract a buyer.

Glen Giovannetti, global biotech leader at Ernst & Young, told Reuters a cheap purchase price is not enough to draw big pharma’s interest these days. In this tumultuous economic climate, investors are leery of risk, and companies will be looking for what appear to be safe bets as they select from among the many small struggling biotech firms. Mr. Giovannetti said companies would not throw money away on a company that does not have demonstrated market potential or a solid research and development model. Instead, big pharma companies are looking to expand their pipelines and biotech resources, particularly in the oncology sector.

The report cautioned that the old way of doing business in the biotech world is no longer a viable option. It outlined 4 “paradigm-shifting trends” companies must be proactive in incorporating in their business model if they are to survive. These include expansion of the generic market, which should add room in healthcare budgets to purchase innovative drugs; US healthcare reform, likely to reward innovation; the drive toward personalized medicine, adding a premium to the value of research and early development; and globalization, with emerging markets opening up new revenue-generating opportunities. Ernst & Young recommend western biotechs struggling to stay afloat look to Asian business models for solutions.

The report noted that the biotech sector did well in 2008 despite the economic downturn, with revenue increasing 12% in 2008 and US profits totaling $400 million. Globally, the industry reported a $1.4 billion loss, but this was less than the $3 billion loss in 2007.

The continued success of the biotech industry will depend on its ability to get new products to market. With American and European companies struggling to raise capital, some biotech concerns may find it hard to fund the long, expensive drug development process.

Wall Street is predicting 3 or more mega deals to come this year. Bristol Myers Squibb and Bayer have been proposed as likely targets for acquisition.

——Christin Melton