The Emerging Market for Diagnostics-Supported Drugs

The Personalized Medicine Revolution

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Due to the rising costs of R&D and the high rates of clinical failure, the pharmaceutical industry has been forced to reconsider the traditional blockbuster drug model. Fortunately, recent advances in genomics and proteomics offer an alternative approach – personalized medicine.

In this article, we analyze specific examples of how pairing drugs with targeted diagnostics can create profitable growth opportunities. Our analysis suggests that pharmaceutical companies must integrate personalized medicine into their business strategies now in order to more effectively compete in the future.

The traditional blockbuster drug model was built around a symptoms-based approach to medicine. In this environment, pharmaceutical companies invested primarily in developing drugs that targeted the largest patient populations or the most common unmet needs. Drugs developed in this manner, however, were sometimes only effective in a fraction of the target population and sometimes caused serious adverse effects in certain patient subsets.

Several industry trends suggest that the blockbuster drug model is losing its ability to drive sustainable growth. The need for larger and longer late-stage clinical trials, driven by increased concern over drug safety and higher cost/benefit hurdles on efficacy improvements, is driving up R&D costs (estimated to be ~$900 million per approved drug in 2003) and effectively reducing marketing exclusivity periods. The competitive landscape for mass market indications is becoming crowded with “me-too” drugs, and generic manufacturers are now aggressively challenging patents well in advance of patent expiry.

To address these challenges, some in the industry are turning to personalized medicine approaches to allow for greater segmentation in healthcare. Diagnostics that screen for genetic or molecular markers can identify those patients most likely to respond well to certain drugs. Drugs developed under this model would generally be safer and/or more effective, but target a more limited addressable market.

The personalized medicine model addresses many of the challenges facing the pharmaceutical industry today. For instance, by targeting pre-screened likely responders, diagnostic-supported drugs will require far smaller Phase III trials to demonstrate statistically significant therapeutic benefits, thus reducing costs and accelerating clinical development. Furthermore, companies can build stronger patent estates that protect the drug, the diagnostic, and the method of use, which will help deter competitors from pursuing “me-too” drugs and generic manufacturers from issuing patent challenges.

The technologies of personalized medicine have advanced significantly in recent years, but generally the pharmaceutical industry has been slow to embrace the concept. There are, however, a few early examples of product strategies driven by personalized medicine approaches, and in particular the use of diagnostic testing to drive product sales.
Genentech’s Herceptin, a leading targeted therapy for breast cancer with $1.3 billion in sales in 2007, would likely not be on the market today had it not been coupled with key diagnostic tests. Herceptin works by blocking activity of the HER2 protein, which causes breast cancer cells to grow and spread more aggressively. As such, Herceptin is most effective in the 20-30% of breast cancer patients who over-express HER2.

Without diagnostic tests to screen for patients who over-express HER2, the Phase III clinical trial for Herceptin would have required five times as many patients and taken six times longer to achieve the same statistical result as achieved in the targeted clinical trial among pre-screened subjects. This is because Herceptin has a 50% response rate among HER2-overexpressing patients, versus a 10% response rate among all breast cancer patients (see Exhibit 1). Further, the low efficacy rate may have blocked approval based on a cost/benefit analysis, or relegated Herceptin to second- or third-line status, preventing some patients access to the product.

By coupling Herceptin with diagnostic tests to pre-screen for likely responders, Genetech accelerated time-to-market and improved the cost/benefit profile.

Since the introduction of Herceptin, it has become standard practice to perform a HER2 assessment on every primary breast cancer patient to determine whether Herceptin would be an appropriate treatment. Furthermore, these tests have become reimbursable under almost all insurance plans because providing HER2 diagnostics to all breast cancer patients is more cost effective than treating all patients with Herceptin. By coupling Herceptin with diagnostic tests to pre-screen for likely responders, Genentech was able to significantly accelerate time-to-market and improve the cost/benefit profile of this highly successful drug therapy drug.

Exhibit 1: Impact of HER2 Diagnostic on Clinical Costs and Results

<table>
<thead>
<tr>
<th>Challenge</th>
<th>With Test (Actual)</th>
<th>Without Test (Estimated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Number</td>
<td>470</td>
<td>2,200</td>
</tr>
<tr>
<td>Response Rate</td>
<td>50%</td>
<td>10%</td>
</tr>
<tr>
<td>Years Follow-up</td>
<td>1.6</td>
<td>10</td>
</tr>
<tr>
<td>p-value</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>Result</td>
<td>Expedited Approval</td>
<td>Not Approvable</td>
</tr>
</tbody>
</table>
**The Personalized Medicine Revolution**

Eli Lilly’s Xigris, launched in 2001, is the only drug approved by the FDA for adults with severe sepsis. Despite having demonstrated a 29% reduction in death, Xigris has been administered to fewer than four percent of patients with severe sepsis, driven largely by under-diagnosis of the condition. Due to a lack of clear clinical definitions of the disease, accurate and timely diagnosis and management of sepsis remains a clinical challenge, compounded by the fact that symptoms of sepsis are often attributed to other conditions.

In 2006, Eli Lilly announced a collaboration with Biosite to develop a rapid, point-of-care diagnostic capable of measuring protein C levels, a key biomarker of sepsis. If approved, the physician will be able to use a diagnostic to determine whether the patient has severe sepsis, and whether Xigris is the appropriate treatment. Additionally, the diagnostic can then be used to monitor the patient over the course of the treatment and adjust dosage of Xigris to keep protein C levels within the optimal range.

If approved, the physician will be able to use a diagnostic to determine whether the patient has severe sepsis, and whether Xigris is the appropriate treatment. If all cases of severe sepsis were identified using this diagnostic, then the market opportunity for Xigris would approach $5 billion, 28 times its 2007 sales level of $183 million (see Exhibit 2). Expanded usage of Xigris could potentially prevent nearly 65 thousand of the 215 thousand deaths in the U.S. each year caused by severe sepsis.

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**Exhibit 2:** Potential Impact of Protein C Diagnostic on Xigris Sales

<table>
<thead>
<tr>
<th>Annual Occurrence of Severe Sepsis</th>
<th>Diagnosis Rate</th>
<th>Cost of Treatment Course</th>
<th>Annual Sales</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2006 Figures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>800,000</td>
<td>100%</td>
<td>$8,000</td>
<td>$5 billion</td>
</tr>
<tr>
<td>750,000</td>
<td>3.5%</td>
<td>$6,800</td>
<td>$3 billion</td>
</tr>
<tr>
<td>600,000</td>
<td>0%</td>
<td>$4,000</td>
<td>$2 billion</td>
</tr>
<tr>
<td>500,000</td>
<td>0%</td>
<td>$2,000</td>
<td>$1 billion</td>
</tr>
<tr>
<td>400,000</td>
<td>0%</td>
<td>$0</td>
<td>$0</td>
</tr>
<tr>
<td><strong>If All Cases Were Diagnosed</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>800,000</td>
<td>100%</td>
<td>$8,000</td>
<td>$6</td>
</tr>
<tr>
<td>750,000</td>
<td>100%</td>
<td>$6,800</td>
<td>$5.10</td>
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<td>600,000</td>
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<td>$4,000</td>
<td>$3</td>
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<tr>
<td>500,000</td>
<td>0%</td>
<td>$2,000</td>
<td>$2</td>
</tr>
<tr>
<td>400,000</td>
<td>0%</td>
<td>$0</td>
<td>$1</td>
</tr>
</tbody>
</table>
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**Drive Adoption by Improving Safety Profile**

Clozapine was approved by the FDA in 1989 as an anti-psychotic against treatment-resistant schizophrenia, as well as several mood disorders. Although it is relatively effective and low cost (generics are available), physicians have been reluctant to prescribe it because in approximately one percent of patients, it causes agranulocytosis, a dangerous drop in white blood cell count. Therefore, few patients are prescribed this drug today, and those who are must undergo frequent blood tests to ensure safe white blood cell levels, which is uncomfortable, inconvenient, and costly.

PGxHealth, the genetic testing division of Clinical Data, Inc., is developing a diagnostic that will determine whether a patient has a low or high risk of developing agranulocytosis if treated with clozapine. The test looks for two specific genetic mutations, which occur in approximately one-quarter of patients, that can increase the risk of agranulocytosis five-fold. This diagnostic should allow physicians to prescribe clozapine to more patients and reduce the frequency of testing for those “low risk” patients using the drug. Since clozapine is a generic drug, PGxHealth’s agranulocytosis diagnostic will likely be marketed to neurologists who would like to prescribe clozapine to more of their treatment-resistant schizophrenia patients.

**Adapt Business Strategy to Leverage Personalized Medicine**

The potential for lower development costs, higher clinical success rates, and greater adoption within targeted markets makes personalized medicine an attractive alternative to the traditional blockbuster model. As such, interest and investment in diagnostic technologies that support drugs will only grow in the coming years, and each company will have to decide where and how to make their investments.

Personalized medicine approaches can leverage products at any stage of the development lifecycle. During discovery and early development, genetic marker(s) predictive of therapeutic success can be identified and then used to screen for patients well-suited for the therapy. This approach, as used by Genentech with Herceptin, could help improve the clinical profile while narrowing the addressable market. In late-stage development, with products which miss clinical end points, or marketed products that fail to meet commercial targets, pharmaceutical companies may still be able to reanalyze their initial clinical data results to either identify predictive biomarkers (e.g., protein C levels for Xigris) or to identify patient sub-segments that show a superior clinical response (e.g., clozapine). This approach could provide a means of “rescuing” struggling drugs that fail to show clinically significant efficacy among the entire target group, but appear to be effective for some patients.

To achieve these technical and commercial objectives, however, a number of key issues will need to be addressed:

- **Identifying biomarkers**—most diseases are caused by a complicated combination of environmental and genetic factors
- **Developing diagnostic tests**—must be unambiguous and prescriptive
- **Promulgating clinical trial practices**—collecting sufficient data on which to do testing
- **Addressing ethical issues**—patient privacy, interpretation of genetic testing results, communication of those results

The decisions each company makes regarding how and where to invest in personalized medicine will depend on their individual product portfolio, needs, and resources. However, given the challenging environment facing the blockbuster model, it is our view that many players in the pharmaceutical industry would benefit from developing a strategy for integrating personalized medicine into their business model today.

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