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Balancing the opportunities and challenges of developing companion diagnostics: part one of two

The pharmaceutical industry continues to come under increasing growth and development pressures. Not only is the rate of blockbuster drug launches continuing to decline but the hurdles for gaining approval are increasing on a number of fronts. To the extent that payers are generally willing to pay for innovation, it has to result in meaningful benefits. Providers want more effective ways to manage and treat their patients. Patients are moving closer to the center of the sphere of influence, exerting more control over wellness and health care. In light of these rising pressures, the pharmaceutical industry is once again turning its attention to opportunities in personalized medicine where one focus is on developing diagnostics in tandem with specialized therapies tailored for specific patient sub-groups.

Companion diagnostics, also known as theranostics, aim to identify patient sub-groups and guide therapeutic choices targeted to a patient's specific type of condition. A standard example has been the use of the FISH (fluorescence in situ hybridization) test to identify cases of HER2-positive breast cancer that are likely to be particularly susceptible to treatment, first with Herceptin and now also with Tykerb or Perjeta. Less than one percent of currently marketed therapies are associated with a companion diagnostic, but revenues generated by these diagnostics were estimated to be $1.3 billion in 2010;[1] some suggest growth to be as much as $40 billion by 2020.[2] Technological advances, such as genomic sequencing, have made the development of biomarkers, for the purpose of screening appropriate patients, a realistic consideration for an increasing number of therapies, and more pharmaceutical companies are investing in diagnostics to accompany early-stage pipeline therapeutics.

Opportunities

To manufacturers, the benefits of companion diagnostics can be substantial and may include:

- Shorter development times;
- Smaller and more cost-effective clinical trials;
- Better clinical trial outcomes;

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[1] Visiongain. *Companion Diagnostics: World Market Outlook 2011–2021*, August 22, 2011.

[2] Michael Harris, "Recent Companion Dx Nods a Win for Personalized Medicine," BioWorld, February 15, 2012.

- Superior market penetration; and
- Premium pricing through increased effectiveness in narrower populations.

However, to realize these gains (and to comply with the FDA's July 2011 draft guidance regarding contemporaneous development of therapeutic products and companion diagnostics[3]), manufacturers need to pursue companion diagnostic technologies and investigate biomarkers early in the development cycle. Furthermore, there can be substantial marketplace and organizational challenges that will need to be overcome; these challenges will be discussed in detail in a subsequent article (in Part Two of "Balancing the Opportunities and Challenges of Developing Companion Diagnostics").

Despite the challenges and the shifting market and regulatory environment surrounding companion diagnostics, a number of manufacturers have enjoyed success through effective pairing of therapeutic innovations with companion diagnostics. The following examples demonstrate three different circumstances where companion diagnostics became a critical tool for capturing the value of an innovative therapeutic: 1) to turn around a compound that failed initial clinical testing; 2) to help physicians target a therapy to appropriate patients with lower side effect risks; and 3) to shorten drug development time.

Case studies

1. Clinical development turnaround

Situation: In December 2010, Syndax Pharmaceuticals reported data showing that its compound entinostat, in combination with Tarceva (erlotinib), failed a Phase II trial in patients with advanced non-small cell lung cancer (NSCLC). Specifically, the combination failed to show any statistically meaningful improvement in median progression-free survival and overall survival versus placebo plus erlotinib. Historically, this result typically would have meant the compound would be shelved. However, Syndax was able to prospectively define a subset of the treated patients (those with elevated expressions of E-cadherin, a molecular marker of epithelial tumors) where the combination therapy actually significantly improved median overall survival versus placebo plus erlotinib. E-cadherin positive tumors represent a significant portion of advanced NSCLC patients, perhaps 40% of the 200,000 newly diagnosed patients each year. [4] Syndax expects to start a pivotal trial in the identified subgroup in the second half of 2012 after partnering with Ventana Medical Systems (a Roche company) to develop a companion diagnostic that would identify patients with E-cadherin expression.

Lesson: It is becoming more common for organizations to include speculative biomarker analysis as part of early clinical development programs. The fact that the biomarker analysis had been included in the study and the subsequent post-hoc statistical analysis allowed Syndax to identify a sub-segment of individuals that appear to have a clinically meaningful response. Their product can now potentially be validated in an appropriately designed Phase III trial.

2. Alleviating physician concerns

Situation: Biogen Idec and Elan's Tysabri (natalizumab) is indicated for patients with relapsing multiple sclerosis (MS). Tysabri has generally not been used as a first-line treatment for MS due to the

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[3] "Draft Guidance for Industry and Food and Drug Administration Staff: In Vitro Companion Diagnostic Devices," FDA, accessed October 24, 2012, http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf.

[4] Aaron Bouchie. "Marking a Subgroup." BioCentury Publications, January 10, 2011.

potential to cause a fatal brain infection, progressive multifocal leukoencephalopathy (PML). In 2011, Tysabri's FDA-approved label showed the risk of developing PML was 1.5 cases per 1,000 patients for two to three years of treatment. In January 2012, however, FDA updated Tysabri's label to show that the risk for developing PML significantly increased if a patient has antibodies against the JC virus (JCV-positive), compared to JCV-negative patients. The label states that JCV-positive patients not receiving prior immunosuppressants have a 4 in 1,000 chance of developing PML after two years of treatment, but, if the patient is JCV-negative, the risk drops to 0.10 in 1,000. It is estimated that 53.5% of MS patients are JCV-positive. [5] To help physicians apply these findings and stratify the risk in prescribing Tysabri to MS patients, FDA recently approved the Stratify JCV Antibody ELISA test manufactured by Quest Diagnostics.

Lesson: Tysabri uptake has been hampered by concerns regarding PML. The launch of the JCV test may help alleviate some of those concerns regarding the use of Tysabri in JCV-negative patients, appropriately increasing access to the therapeutic.

3. Decreasing clinical development time

Situation: Xalkori, developed by Pfizer to treat the 3% to 5% of NSCLC patients with an anaplastic lymphoma kinase (ALK) mutation, reached the market in just four years after its biomarker was discovered. When Pfizer began Phase I testing in 2006 for Xalkori, it screened patients for one of two mutations, including ALK. Soon after the company started Phase I testing, researchers published a study showing that ALK might be a driver of NSCLC. Because patients were pre-screened, Pfizer was able to adapt to these findings. The company expanded its Phase I trial in ALK-positive patients and began a Phase II trial in an ALK-positive population. Both trials, which showed treatment response rates significantly better than standards of care, were used to support FDA accelerated approval in 2011.

Lesson: Inclusion of scientifically validated biomarkers early in the clinical development process can accelerate the time to market. A better understanding of the molecular makeup of tumors and the correlating impact on clinical response should increase the number of compounds coming to market that are tailored to specific patient groups.

The effective incorporation of companion diagnostics into drug development and commercialization can benefit multiple stakeholders: patients, payers, physicians, and ultimately pharmaceutical companies. For payers, companion diagnostics may expedite the process of finding the most effective therapy and lower unnecessary health care spending. Physicians view companion diagnostics as a mechanism for delivering a more targeted and personalized therapy to achieve higher rates of treatment success while limiting the risk of adverse events.

Patients may feel reassured when they receive personalized therapy that addresses their specific genetic makeup, allowing them to avoid side effects associated with medicines that are unlikely to work.[6] As outlined earlier, for pharmaceutical companies, companion diagnostics can be applied in various settings to help a drug succeed clinically and commercially.

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[5] "New TYSABRI Data Presented at 64th Annual AAN Meeting Highlight Biogen Idec & Elan Commitment to Improving Outcomes in Multiple Sclerosis," Biogen Idec, accessed October 24, 2012, http://www.biogenidec.com/press_release_details.aspx?ID=5981&ReqId=1688002.

[6] UnitedHealth: Center for Health Reform & Modernization, "Personalized Medicine: Trends and Prospects for the New Science of Genetic Testing and Molecular Diagnostics," March 2012.

Of course, like the opportunities, the challenges associated with personalized medicine generally, and companion diagnostics in particular, are substantial. In a subsequent article, we will describe some of the challenges that manufacturers are likely to face as they co-develop companion diagnostics and therapeutics—regulatory issues, stakeholder acceptance, and organizational complexities—and discuss some of the implications for developing an integrated theranostics strategy that can unlock the growth potential promised by companion diagnostics.

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