Molecular Diagnostic Renovates Drug Development: Overcoming Challenges of Co-Development of Theranostics

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Molecular diagnostics uses molecular signatures for disease identification, monitoring treatment effectiveness and even predicting a patient's response to a new treatment. It may offer the opportunities of understanding the underlined biology of disease, the development of highly targeted individualized diagnostics, and the selection of most effective therapy for patient. As a vast majority of pharmaceutical companies focus on the development of targeted therapy, biomarkers and pharmacogenomics are crucial in drug development and regulatory decision making. Discoveries in the fields of biomarker identification and pharmacogenomics are leading healthcare workers and pharmaceutical companies to a new middle ground in drug and diagnostics development. This is the area of a new form of healthcare development called theranostics. Theranostics can be defined as using diagnostic testing to identify the disease, select a treatment regimen, and monitor the response of the patient to therapy. It is a therapy with a companion diagnostic linked by underlying cause and effect. Essentially, the same tests that researchers developed to understand disease pathology and the effect of a new drug are being used to monitor how the drug works in patients to bring them back to health. Recent advance in testing technology and genome informatics has accelerated the speed of developing molecular diagnostic test, which could not only expedite the development of drugs but could also decrease the attrition rate. Stratification of the population based on predictive biomarkers could increase efficacy and safety of drugs developed for targeted populations. A well-known case of such co-development is Herceptin (trastuzumab) by Genentech (www.gene.com) and the HER-2 test by Dako (www.dakousa.com). Overexpression of the HER-2 receptor is linked to decreased patient survival. Herceptin was approved in 1998 to treat metastatic breast cancer in patients who overexpressed HER-2 protein. Its FDA approval was dependent on the concomitant approval of a diagnostic immunohistochemistry (IHC) assay of HER-2 protein level. Another example of theranostic development is LpPLA2 (lipoprotein-associated phospholipase A2) immunoassay developed by diaDexus (www.diadexus.com) and approved for predicting the risk of heart disease and isechemic stroke. GlaxoSmithKline (www.gsk.com) is developing a small molecule designed to inhibit this enzyme, thus reducing the risk of adverse cardiovascular events.

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Big pharmaceutical firms and biotechnology companies with drug and diagnostic kit development arms, such Roche (www.roche.com) who has both Pharmaceutical and diagnostic divisions, are the early adopters of theranos-

tics development. As with any new business model, for the most part, the industry seemed to lag behind. It is because although the test offers the opportunity to distinguish the drug from its competitor by increasing its efficacy, it can also reduce the market share of the drug. In addition, due to the complexity of disease biology, the test is often not 100% specific and sensitive to the drug. However, the FDA views the theranostic drug and test co-development as the Holy Grail as personalized medicine. In 2005, FDA released a draft preliminary discussion document entitled "Drug-Diagnostics Co-Development Concept Paper" that offers the organization's initial thoughts on this subject. The document is designed to elicit comment from the public, which the FDA will use to eventually draft guidelines on development and testing. Throughout the document, the authors make it clear that the diagnostics development process should occur as early as possible in the drug development process. Recently, there is a significantly increased amount of activities in co-development of drug and test. At a conference on personalized medicine at Harvard Medical School in October 2007, Felix Frueh, head of the FDA's Interdisciplinary Pharmacogenomics Research Group, noted that co-development of drug and test was happening as we speak. He mentioned the outlook of companion diagnostic in Ventana (www.ventanamed.com) which included 164 targeted oncology programs, 105 companion diagnostic candidate programs. In the same month, the Critical Path Institute (www.c-path.org), a publicly funded non-profit and FDA sponsored initiative, announced its collaboration with Ventana for submission of a lung cancer test on Benchmark XT, an automated tissue testing platform that assesses protein expression by immunohistochemstry and gene amplification by *in situ* hybridization. The test is used for the C-Path EGFR project. The real driver of theranostic development is the progress made in recent years in medical science of understanding disease and its therapeutics. It become unavoidable for pharmaceutical companies to incorporate a strategy of coordinate the development of a drug with the development of a test when a biomarker appears to be useful tool to determine efficacy and/or safety in a sub-population.

The challenges of co-development of theranostics, however, are daunting. There are many assumptions. First, at the level of science, there are an estimated 30,000 human genes, only a small fraction of them are studied and understood at a functional level. It is assumed that reliable biomarkers will be identified in each of the scenarios for each disease, and that a reliable association can be established between the molecular target and the biomarker. However, in most cases, identifying disease-associated biomarkers could potentially take many years. In his recent review article in the journal of Expert Review of Molecular Diagnostics, Dr. Malcolm Warld summarized biomarker research in association with Alzheimer's disease (AD), a horribly debilitating disease that will increase in prevalence as the populations of the USA and Europe continue to age. It is expected that the USA alone will see some 16 million cases by 2050. Despite of many year's worldwild research, there is still no cure for the disease and early diagnosis is all but impossible. There is a need for biomarkers associated with AD to aid the diagnosis of this disease and to detect progression. Especially needed are biomarkers to monitor the effect of new drugs and therapeutic strategies as they are developed. Second, at the level of development process of theranostics, standardized methods for validation processes will have to be developed for both the biomarker and diagnostic over time, particularly as different candidate biomarkers for the same disease are identified. Then, it is assumed that a targeted therapeutic that is both safe and effective in an economically sustained sub-population of the disease can be developed or identified, approved, manufactured and distributed. Eventually, the long-term efficacy of the targeted therapeutic will have to be established. Lastly, at the level of clinical utility, standardized methods will need to be adapted and, in some cases newly developed, to compare the incremental value of the targeted diagnostic and companion therapeutics to those alternatives which already exist before clinicians prescribe or health plans pay.

Implementing theranostics is extremely challenging. *First*, it poses considerable economic challenges for industry stakeholders. For example, current health care reimbursement model encourages drug developers to concentrate on developing blockbuster drugs, rather than multiple small-batch therapeutics. It is also believed that inadequate reimbursement is arguably a key reason that companies are not developing diagnostic products. Additionally, funding from government sources is shrinking, directly impacting academic medicine, which fields most of studies for biotech and pharmaceutical companies. The commercial future of theranostic may depend, in part, on whether manufactures decide that there is enough financial benefit from therapies that help only small segments of people. *Second*, from regulatory perspective, the process and the timelines for drug development and test development are very different, which present another challenge for developing theranostics. The average timelines involved in developing a drug (10-15 years) and an assay (3-5 years) are our of sync, there is a clear discrepancy between the development times, naturally, this also poses a challenge on the strategy of co-development. The key to success is to integrate these two very different complex processes of drug and device development. There is still no proven development pathway for FDA approval of the necessary companion diagnostic tests and their associated targeted therapies. One needs to develop strategies to coordinate the development of a drug with the development of a test when a biomarker appears to be a useful tool to determine

efficacy and /or in a subpopulation. Recently, NCI and FDA held a workshop on development of markers for clinical decision-making with the goal of formulating a set of recommendations that will assist investigators in optimizing the process for predictive biomarker development and/or co-development of drugs and devices. *Third*, the clinicians are expected to be resistant to the routine use of pharmacogenomics in medical care. Clinical phase of drug development program will provide evidence of clinical utility of the diagnostic test, claim for test would be for use with drug, drug cross-labeled for use with diagnostic will be required. Adoption of theranostic will represent a major change for the provider community, thus, it will take time.

These challenges of implementing theranostics are far too big for any one individual or corporation to address. Solving them will require collaboration across traditional health care industry stakeholders including diagnostic companies, pharmaceutical companies, healthcare providers and payers with the government including regulatory agencies. Recently, the Critical-Path Institute (www.c-path.org) received a $2.1 M award from Arizona State to work with FDA and NCI to develop standards for evaluating companion diagnostics and drug submissions. The industry must collectively address two major issues that will impact the development and adoption of theranostic: the need for education and the need for better alignment between the economics and the science. Currently, the average clinician or average patient does not completely understand theranostics at the level of sophistication they will need to fully participate in a genomic future. Educational program should address to wide audience, including clinician scientists, legislators, public health officials, regulators, the FDA regulators, health care professionals, providers, payers and patients. The clinician scientists should design the appropriate clinical trials to validate novel diagnostics and therapies that can be adapted to a subgroup of patients. The legislators and public health officials need to understand how to cortically interpret studies and to be prepared to shape legislation to balances the needs of individuals and society. The FDA regulators need to understand the new technology in order to enforce the regulation for public protection. Physicians need to administer the test and understand the results, then prescribe the therapeutics. Payers need to decide how to reimburse. Patients need to understand the associated risk and benefit of theranostics. Educational efforts among professionals and the public will be required to drive adoption, implementation and use of the theranostics. The other more difficult issue to resolve is the alignment of economics and science. Progress in targeted therapies comes at a cost and that cost requires investment by life sciences and health care community. Finding ways to define the value and return of targeted therapies should be a primary focus for healthcare industry. In order for the science and economics to come to together, there need to be proper incentives in place and aligned across the life sciences and health care value chain, for examples, payers must be convinced that the incremental improvement to the quality of care over time by theranostics justifies the investment; spending on diagnostics is worthwhile for pharmaceutical company; and patients see the value in assuming a greater cost of routine care.

We are at the beginning of theranostics. Matching therapy with diagnostics is science driven and a paradigm change. It requires collaboration across all stakeholders in the industry to reach the ultimate goal of improved healthcare of each individual.