Organisation de Coopération et de Développement Économiques
Organisation for Economic Co-operation and Development

10-Nov-2008

English - Or. English

DIRECTORATE FOR SCIENCE, TECHNOLOGY AND INDUSTRY
COMMITTEE FOR SCIENTIFIC AND TECHNOLOGICAL POLICY

DSTI/STP/BIO(2008)36
Unclassified

Working Party on Biotechnology

ANALYTICAL PAPER: INDUSTRY STRATEGIES AND BIOMARKERS BUSINESS MODELS

By Dr. Arsia Amir ASLANI, Araxes Associates, France

This analytical paper was submitted for discussion at the Workshop on Policy Issues in the Development and Use of Biomarkers in Health held on 6-7 October 2008 in Hinxton, United Kingdom. It is submitted for information to the WPB.

For further information, please contact: Ms. Marie-Ange Baucher, Tel: +33 1 45 24 94 22; email: marie-ange.baucher@oecd.org; or Ms. Benedicte Callan, Tel: +33 1 45 24 15 93; Fax: +33 1 44 30 63 36; email: benedicte.callan@oecd.org.

JT03254956

English - Or. English

NOTE BY THE SECRETARIAT

This analytical paper was submitted as background material for discussion at the expert workshop organised by the Biotechnology Division on "Policy Issues in the Development and Use of Biomarkers in Health" held in Hinxton, United Kingdom on 6-7 October 2008. This workshop contributes to the fulfillment of Output Result 5 of the 2007-2008 PWB entitled "Analytical and policy reports on the impact of molecular markers and targeted therapies on Biomedicine".

This analytical paper was provided by Dr. Arsia Amir Aslani, of Araxes and Associates. It describes how industry is reacting to the development of biomarkers and identifies main trends in biomarker discovery and product development as well as promising strategies and business models.

This analytical paper, along with others developed for the Biomarker Workshop, will be used as input for the Policy Report entitled "Policy issues in the Development and Use of Biomarkers in Health" that will be submitted to WPB in early 2009.

Delegates to the Working Party on Biotechnology are invited to:

- **Note** the analytical paper.

Table of Contents

ABSTRACT

Biomarkers will constitute a critical component of the health care delivery system in order to detect, diagnose and monitor diseases and other medical conditions as well as to evaluate treatment options and effectiveness. Interest in such techniques is growing rapidly among regulators and contract research organizations. However, scientific and commercial hurdles remain.

1. Introduction

As the genetic roots of disease, disease progression and treatment effectiveness are uncovered; the demand for sophisticated prognostic, diagnostic and monitoring tests will increase. Moreover, the role of laboratory testing will expand beyond diagnosis into virtually every facet of health care delivery, including detection of genetically based health risk factors, evaluation of treatment options and effectiveness, and monitoring of patient health status.

The use of biomarkers will accelerate over the next decade due to the continued development of new technologies and therapies; increasing linkage of diagnosis and therapy; changes in care protocols which emphasize new diagnostic tests, increased testing for infectious and genetic diseases and oncology; and the aging of the population. In particular, developments in genomics are having, and will continue to have, a radical impact on the clinical laboratory industry. The utilization of "omics" technologies, such as transcriptomics, proteomics, toxicogenomics and metabolomics will further help in the identification and validation of biomarkers.

The process of identifying the genetic basis for drug receptivity is typically referred to as pharmacogenomics. Pharmacogenomic advances are already having a significant impact in oncology, infectious disease, and genetics.

While diagnostic breakthroughs typically precede therapeutic advances, the presence of new therapies can stimulate the demand for testing. Therapeutic advances that create new and improved treatments for diseases such as cancer, AIDS, and hepatitis C will drive demand for testing. Clinical laboratory testing has been, and will continue to be, dramatically influenced by the introduction of sophisticated new technologies that enable more precise and timely diagnosis and prognosis.

The dual combination of diagnostics and therapeutics suggests that it offers attractive business opportunities in the near and long term because of increasing demand for laboratory services. Such business opportunities will play an increasingly important role in the strategies of biomarker focused companies in expanding their capability and expertise within the drug discovery value chain. The concept of biomarkers directly challenges the business models of both drug discovery and diagnostics companies. The main question that remains to be answered is how will the biomarker paradigm alter these companies' innovation and commercialization strategies. Whereas developing drug targets may offer greater long-term value, initial commercial opportunities often arise in diagnostics. While companies are developing business models that will emphasize greater technological prowess in their products, others will promote more of a

service orientation to customers. Some will have great off-the-shelf technology, while others will emphasize the ability to make customized solutions for various diagnostic problems.

2. Drug discovery Industry: Using biomarkers in drug discovery and development

Historically competitive forces in the pharmaceutical industry have obliged companies to focus on blockbuster drugs (drugs with sales exceeding USD 1 billion) and to maximize profits through heavy marketing. This strategy has allowed companies to secure adequate resources to offset the cost of expensive research and development (R&D) programs. However, studies have shown that many drugs may be efficacious in only a slim majority of the prescribed population. In effect, the blockbuster model does not provide the necessary level of predictability in developing innovative, safe and effective treatments for patients with specific disease subtypes.

Biomarkers can play a crucial role in understanding patient differences and help the drug discovery industry evolve toward a business model that focuses on targeted treatments. However, for molecular biomarker testing to outweigh its inherent costs, the testing procedures should be integrated into the total disease assessment value chain in order for it to realize its true financial impact. In effect, a biomarker based approach uses information based medicine which combines both clinical and biomedical data (including genomic, transcriptonomic, proteomic and imaging), to ultimately help the drug discovery industry address its innovation deficit, cost structure and R&D productivity problem.

2.1 Reducing cost of drug development

Drug discovery is an increasingly costly and time-consuming process. In 2003 it costs for major drug discovery companies from USD 500 to 800 million to develop a new pharmaceutical product and of that 75% represents risk in the form of products that fail [1,2]. Bains (2004) has reported that these costs are shared fairly evenly between the discovery and pre-clinical studies (39.7%) and clinical development (43.9%) and the remaining 6.4% being devoted to the registration/approval phase of drug development [3]. However, the main cause of inefficiency is due to the fact that almost half of drug candidates fail during the development phase. Failure of compounds in late preclinical development, in the clinic and even worse while being marketed, represents a very important economic burden for the pharmaceutical industry. By incorporating biomarkers in preclinical and clinical trials, drug discovery companies can create knowledge feedback loops into their development strategy. These steps spawn operational efficiency and give a company a competitive advantage.

2.2 Speeding drug development

Other than the costs and uncertainty of drug development, the length of time that it takes for a drug candidate to successfully reach the market is also of major concern to the drug discovery industry. The total development time for a successful drug candidate is around 12,5 years [3]. More specifically, major pharmaceutical companies spend on average between 40 to 60 million dollars annually per compound being investigated or between USD 109,000 to 175,000 on a daily basis for their R&D efforts for each drug candidate until it reaches the market. It is fairly obvious that any technology capable of shortening the drug development time frame will have considerable impact on a company's R&D cost structure. Furthermore, any shortening of this time frame will also help maximise profits by extending a product's life cycle through an increase of the commercialisation period. An innovative therapeutic product is protected by patents for a period of roughly 20 years of which 12.5 years is economically "wasted" while the product is progressing through development. This leaves the pharmaceutical company basically 7.5 years to fully enjoy commercialisation. Considering that it will take 3 years to reach peak sales of over

a billion dollars for a blockbuster drug, this will leave the company with a period of basically 4.5 years to commercialize aggressively its therapeutic product. Consequently, for a drug generating a billion dollars annually any extra day of commercialization will help the company secure USD 2.7 million of sales. Thus, by reducing the time that it takes to bring an effective drug to market, a company can benefit greatly from an unchallenged market position and extend the period of patent protected sales.

2.3 Avoiding Adverse Drug Reactions (ADR)

On Sep. 29 2004 in the largest drug recall in history Merck & Co withdrew its popular arthritis drug Vioxx from the market, acknowledging it caused increased risk of stroke, heart attack and death. After its approval in 1999, Vioxx was used by two million people and had earned for Merck USD 2.5 billion dollars in 2003 alone. The Vioxx case is the most visible and largest recall, yet several other drugs have been withdrawn from the market over drug safety issues since 1993.

As highlighted by the Vioxx case, addressing Adverse Drug Reactions (ADR) is a major problem from a public health perspective as well as for the development of new medicines. Lazarou et al., have demonstrated that ADR is between the fourth and sixth cause of death in the United States, accounting for more than 100,000 deaths in 1994 [4]. Furthermore, Lasser et al. (2002) concluded that one in five new drugs has unrecognized ADRs that do not show up until after the drug has been approved [5]. The study analyzed 548 drugs approved from 1975 through 1999 and discovered that 56 of them were later given a serious side-effect warning or even taken off the market completely. The study specifically focused on "black box" warnings, which highlight the most serious side effects that were added to the drug's label after its release. If one of the more life-threatening side effects is not detected prior to release, it can cause major problems and create a serious hazard for the general public once the drug is on the market. The approval and marketing of drugs which are ultimately found to pose far greater risks than any benefit they may have had.

Thus, employing biomarker technologies that improve the early identification of drugs that are likely to suffer failure in clinical trials is an essential strategy in order to address high failure rates in the development stages. The result is a radical change in the lead compound selection process with better use being made of information for revealing pharmacological and genetic toxicity [6-9].

2.4 Better understanding the complexity of disease pathways

Over the past two decades, genetic engineering has unravelled many detailed disease mechanisms but the translation of this knowledge into profitable drug development has been painfully slow and burdened with many failures. This problem is now starting to be recognized by policy makers. The 2004 FDA white paper "Innovation or Stagnation' explicitly stated that: "Today's revolution in biomedical science has raised new hope for the prevention, treatment and cure of serious illnesses. However, there is a growing concern that many of the new basic discoveries may not quickly yield more effective and more affordable and safe medical products for patients"[10]. In response, the FDA is advocating much greater emphasis on translational and critical path research focused on the clinical assessment of novel products. The sequencing of the human genome has not only considerably simplified the search for genes that predispose people to develop certain diseases but has also provided the drug discovery industry with a wide spectrum of new opportunities for the discovery of innovative drugs and improved treatments [11-13]. As a consequence, biomarker discovery tools being applied today will provide the opportunity to find the underlying genetic factors in complex polygenetic diseases.

The FDA recognizes biomarkers as a critical element in evidence-based medicine. Without new markers, advances in targeted therapy will be limited and treatment will remain largely empirical. Thus, it is imperative that biomarker development is accelerated along with the development of new therapies.

2.5 Better dosing regimen

The recent success of several targeted drugs has changed the rationale for drug discovery and development. Drugs such as Gleevec, Iressa, Herceptin, and Velcade--some of which have genetic markers for identifying the most suitable patients--aim for maximum biological efficacy which differs from traditional treatment that was based on maximum tolerated doses.

2.6 Streamlining clinical trials

Undertaking extensive safety tests in large and heterogeneous populations prior to market approval would significantly increase the time and cost of clinical evaluation and creates a significant barrier to drug development. Patient stratification based on biomarker tests can allow scientists to develop a trial design comprised of a genetically differentiated patient pool, using genomic biomarkers to predict response of a group of individuals to a therapeutic. In undifferentiated patient pools, the number of non-responders could jeopardize a trial's endpoint, thereby possibly preventing advancement of a therapeutic to a genetically responsive subpopulation. In effect, researchers have highlighted that Iressa (Gefitnib) has a profound effect on a small population of patients (10 to 20% of the patients). This small number of respondive patients in the clinical trial was most probably diluted out by the lack of response from the other patients [14].

For example, overexpression of epidermal growth factor receptor (EGFR) occurs in many types of cancer and has become a target for cancer therapy. The EGFR tyrosine kinase inhibitor (TKI) Iressa targets the tumor protein to treat non-small cell lung cancer (NSCLC). Specific mutations on EGFR gene correlate with clinical response and screening for these mutations has become increasingly integrated into clinical practice to identify those individuals who will most benefit from treatment.

Similarly, using biomarker testing to predict HER-2 overexpression as a means to stratify breast cancer patients eventually paved the way to a successful New Drug Application (NDA) for Herceptin. Also, in a Phase III clinical trial designed to evaluate CML patient response to Gleevec, biomarker testing was able to identify a 31-gene biomarker within the patient population that predicted clinical response with 94% accuracy [15]. Moreover, in a Phase II clinical trial designed to evaluate Myeloma patient response to Velcade, biomarker testing identified a 30-gene biomarker that predicted responders with 71% accuracy and non-responders with 84% accuracy [16].

Toxicogenomics and pharmacogenomics have led to several valid genetic tests that provide clinical dosing recommendations by the FDA. Moreover, a list of DNA based biomarkers of enzyme or transporter activity currently considered as "exploratory" biomarkers can be found in Huang, S.-M., and Lesko, L. J. 2005 [17]. For such markers the correlation between certain genotypes and enzyme or transporter activities was observed *in vitro* only.

2.7 Project prioritization

Pharmaceutical profiling has resulted in a strong need for appropriate biomarkers at the clinical end of drug development process for patient population profiling. Profiling data assists the diagnosis of compound performance at various barriers, assists prioritization and optimization, and highlights factors that affect development attrition. The application of this approach to compounds at different stages of pre-clinical testing would allow the elimination of unfavourable compounds early in development, and increase the quality level of lead selection. As highlighted earlier, any reduction in risk during the early phases of the process will have a multiplier effect on added value.

First, it can impact the quality of drug development pipelines by providing more specific information as to the mechanisms of drug pathologies and providing it earlier in the discovery-development process.

Second, it can improve the efficiency of the process because biomarker information complements genomic target identification and characterization methods used in discovery and leads to reduced attrition during drug development for unfavorable compounds.

3. Diagnostics industry: Development strategies to embrace biomarkers

The diagnostics industry is being revolutionized by current advances in the public and private human genome projects and by the development of new technologies for DNA testing. Microarray technologies and bioinformatics have the potential to allow the rapid diagnosis of multigenic diseases; antibody engineering is creating ever-more sophisticated diagnostics reagents, and diagnosis is becoming less reliant on invasive procedures that are painful and inconvenient to patients. However, few diagnostics companies are successful by the criterion of stock price performance (Table 1 – Publicly listed companies with commercial interest in biomarkers). Despite this economic activity, diagnostics and diagnostic technology companies are not attractive investments to the public stock market. Why, with this level of corporate activity and a clear need for new diagnostics, is there such an apparent lack of enthusiasm from investors for diagnostics companies? The answer resides in three interlinked reasons: commercial, scientific and technological.

Table 1 – Publicly listed companies with commercial interest in biomarkers

(As of May 30, 2008)

Company	Market Capitalization	Activity	Location	2007 Revenues
Avalon	USD 28.8 M	Technology platform	USA	USD 0.81 M
Bio-refernce labs	USD 337 M	Clinical and genetic testing	USA	USD 250 M
Clinical data	USD 393 M	Pharmacogenomics	USA	USD 63.7 M
Combimatrix	USD 58 M	Technology platform	USA	USD 6.03 M
Curidium	UK£ 47 M	Companion diagnostics	UK	No revenue
Diagnocure	CAN$ 98	Diagnostics and lab services	Canada	CAN$ 3.5 M
DNA Print genomics	USD < 1M	Genetic testing, SNP analysis	USA	NA
Epigenomics	€ 54 M	DNA Methylation biomarkers	Germany	€ 2.6 M
Exact Sciences	USD 49 M	DNA testing	USA	USD 1.8 M
Gene News Ltd	CAN$ 55 M	Molecular diagnostics	Canada	CAN$ 2.17 M
Genomic Health	USD 487 M	Molecular diagnostics	USA	USD 64 M
Genetic Technologies	USD 38 M	Genetic testing and services	Australia	USD 11.7 M
Genoptix	USD 460 M	Laboratory service provider	USA	USD 59.3 M

Table 1 (cont'd) – Publicly listed companies with commercial interest in biomarkers (As of May 30, 2008)

Helicos Biosciences	USD 99 M	Genetic testing	USA	USD 0.58 M
IVAX Diagnostics	USD 20.8 M	Diagnostics	USA	USD 20 M
Imaging diagnostics systems	USD 13 M	Molecular imaging	USA	USD 0.07 M
Interleukin Genetics	USD 48 M	Genetic tests	USA	USD 9.7 M
Medtox	USD 129 M	Lab services and diagnostics	USA	USD 80 M
Monogram Biosciences	USD 155.6	Lab services and diagnostics	USA	USD 43.2M
Nanogen	USD 24 M	Technology platform	USA	USD 38.2 M
Nanosphere	USD 211 M	Technology platform	USA	USD 1.2 M
Orchid Lexmark	USD 90.8 M	DNA testing	USA	USD 60 M
Ore Pharmaceuticals	USD 11 M	Drug repositioning	USA	USD 1.6 M
Oncomethylome	€ 112 M	Cancer detection tests	Belgium	€ 2.6 M
Pacific biometrics	USD 7.6 M	Lab service for clinical research	USA	USD 8.5 M
Radnet	USD 223 M	Diagnostics imaging	USD	USD 425 M
Rosetta Genomics	USD 52M	MicroRNA diagnostics	Israel	No revenue
Transgenomic	USD 39 M	Genetic testing	USA	USD 23 M
Vermillion	USD 14 M	Diagnostics	USA	USD 0.04 M

The low margins of the diagnostics business has made it extremely difficult for these companies to generate enthusiasm within the healthcare arena! In effect, the trials needed to evaluate a test used with a drug can be more expensive than traditional drug trials. It is useful for companies seeking finance for new products or commercial developments to understand this viewpoint, so that they can position their product appropriately to "sell" it to the investment community. The primary concern from the investment community's perspective for such consideration has been scientific. Does the new technology actually work, does it help the practice of medicine, and is there a way of realizing it both in terms of a product and potential users.

Early genomics companies with capabilities in pharmacogenomics such as Genset, Genaissance and Variagenics do not provide a satisficatory benchmark in gauging biomarker business models since they were acquired by Serono, Clinical data and Hyseq respectively. The challenge for a biomarker specialized company is to implement a business model capable of bridging the gap of its intellectual property value and the reality of the business environment. In effect, value is determined not only by the perception of competitive advantage, but also by the prospect for it to be sustainable.

3.1 Barriers for new companies

There are substantial "barriers to entry" for a new diagnostics-based company: organizational or economic barriers which limit the ability of a new company to sell products effectively. These make the realization of a new technology idea very difficult, and hence achieving their commercial potential is less likely. Just as the use of genomics and proteomics is rapidly changing the practice of drug discovery, those technologies are changing the experimental needs of life science researchers. As a result, the business plans of suppliers of reagents and instruments are evolving to keep up with their increasingly sophisticated customers.

For example in June 2007 Qiagen NV, the world's premier supplier of solutions for preanalytical sample preparation, announced the acquisition of publicly listed molecular diagnostics firm Digene for approximately $1.6 billion. Digene holds a leading position in HPV (human papillomavirus) targeted molecular diagnostic testing. This transaction allowed Qiagen to gain instantaneous market and technology leadership in molecular diagnostics and strategically position the company for future growth. Similarly, in October 2006, Qiagen NV acquired Genaco Biomedical Products, Inc. (Genaco), an early-stage company applying a proprietary PCR-based multiplexing technology, Tem-PCR, to develop Templex TM molecular diagnostic tests. Multiplex assays are typically applied in situations in which one or more of several pathogens or disease markers could be present in one sample. Depending on the number of markers present in a sample, the Templex TM products provide a qualitative and a semi-quantitative answer. Multiplexing is typically used in cases where patients present symptoms which could be caused by one or more of a significant number of different pathogens or other causes.

Also, Affymetrix, Inc. a major player in the field of gene chip technology spun-off in October 2000 a new genomics subsidiary called Perlegen Sciences, Inc. in order to utilize Affymetrix' latest DNA scanning technology to identify the millions of genetic variations between individuals and find patterns in those variations. Perlegen's business objective is to secure alliances with major pharmaceutical partners in order to associate the patterns with health factors and drug responses.

The dual combination of diagnostics and therapeutics suggests that it offers attractive mergers and acquisitions opportunities in the near- and long term because of the increasing demand for laboratory services. Technology oriented mergers will play an increasingly important role in the strategies of clinical research organizations, clinical laboratory companies (e.g. Laboratory Corporation of America or Quest Diagnostics), tools and equipment companies and biotechnology companies in expanding their capability and expertise within the drug discovery and development value chain.

3.2 Market access dominated by few players

Diagnostics products are overwhelmingly purchased from large established companies. This is in part because most diagnostics are still performed in central laboratories, and these require large systems that are well supported and that run a battery of tests. Neither the test battery nor the international support and service structure is practical for a small company to create, and so such a company's ability to gain access to its market is limited. The company must sell its technology to one of the dominant companies in the field. This applies to new technologies, but especially to new tests applied on old technologies, which must run on "existing platforms" if they are to sell at all.

As a consequence the market value of a new test can only be established when it is brought to market, not (as in therapeutics development) in stages during its development. One of the highest risk aspects of development is in the launch and successful marketing of the product. To suggest that a new company should develop the science and its medical application, and also develop the diagnostic product for that application is probably over-optimistic, given the concerns about development costs and time-scales.

3.3 Requirement for therapeutic utility

Biomarkers could revolutionize both the development and use of therapeutics. The ideal biomarker would be highly predictive of clinical response. If the efficacy studies take several years and a large number of patients, a biomarker that could predict clinical response early, or even be a surrogate for the clinical endpoint, would be extremely valuable.

Torcetrapib's recent failure in clinical trials highlights that correlation between a certain biomarker and the health outcome does not necessarily mean causation. Torcetrapib acts by inhibiting cholesteryl ester transfer protein, driving higher HDL and lower LDL cholesterol levels. Historical data demonstrates an unambiguous correlation between high HDL/low LDL and a slower progression of atherosclerosis. However, the drug failed to demonstrate any benefit on carotid artery thickness, a measurement that reflects accumulation of atherosclerotic plaque. HDL/LDL is not the only example of biomarkers that correlate with health outcome but demonstrate no causative effects.

Linked to fitting in with diagnostic practice is the requirement that a diagnostic be directly linked to a decision on therapy? Linking a diagnostic to a therapeutic decision is often extremely challenging. Biomarker based molecular diagnostics have encountered some difficulty in getting accepted by the medical community. For example, it has taken about three years for Genomic Health Inc.'s breast cancer assay Onco*type* Dx, which was offered as a service in 2004, to be included in the American Society of Clinical Oncology's (ASCO) clinical practice guidelines, where it is recommended for use in the selection of breast cancer therapies. As of September 2007, the assay had been approved by Medicare and an increasing number of insurance companies.

As a consequence, it is critical to understand what type of biomarker is being measured. Upstream biomarkers may be indicative of the effect on the target, whereas downstream biomarkers capture the convergence of various mechanisms and processes that result in the disease. It is highly unlikely that a biomarker will be found that fully predicts the clinical outcome of novel classes of medications. To understand the significance of each biomarker and its hierarchy in disease development requires enormous amounts of biological information.

4. Biomarker Industry strategies in the short-term

Over the next decade, genotyping will be routinely integrated into drug development and clinical decision making for a broad range of disease states. This expansion will be driven by the identification of a large number of single nucleotide polymorphisms. SNPs are essentially variations in the fundamental

genetic components of individuals. These differences can be related to disease susceptibility, severity, and progression, and to responsiveness to therapy. Since SNPs will make it possible to identify potential disease states earlier and with greater sensitivity than is currently possible. Over time, the identification of SNPs may enable researchers to identify versions of genes that increase the risk of disease and to develop therapies base on those genetic differences.

4.1 Pharmacogenomics

Pharmacogenomics is an example of such a "fundamentally different" approach. It leads to the concept of personalized, patient-centered healthcare, where individual variation defines the therapies given, and even then reward and penalties for "genetically inadvisable" behavior. Genetic "diagnosis" is now being used quite widely in clinical trial stratification, and is being discussed widely in the healthcare industry.

Pharmacogenomics will no doubt result in an explosion of patient testing. What remains less clear is the format tests will take and how they will be marketed. Pharmacogenomics tests will encompass a broad array of markers, such as DNA, RNA or protein.

In the short-term, the opportunities for diagnostics companies will be the development of tests that are linked to currently marketed therapies. Currently marketed drugs that could benefit from a test to identify optimal responders are near-term target markets for diagnostics companies.

4.2 Oncology services Market

Unfortunately cancer continues to be a large and growing disease that is responsible for one in four deaths in the US. The market is moving away from general chemotherapy toward targeted therapy or "predictive oncology". A greater percentage of treatment decisions are now being made based on data that is unique to a particular patient as opposed to based on population averages. As previously noted, targeted therapies are becoming more prevalent. As cancer treatment and therapies have become more sophisticated, specialized diagnostic and prognostic tests will assume increased importance.

4.3 Infectious disease testing

The demand for complex infectious disease testing is expected to grow at a rapid pace mainly driven by the development of new tests as well as the availability of new therapies to treat AIDS and hepatitis C. AIDS and hepatitis C are viral infections diseases that can be incurable and lethal. Patients with these diseases undergo prolonged courses of treatment, which necessitate ongoing lab testing. The current treatments for these diseases are inadequate due to limited efficacy, poor compliance, or the emergence of viral resistance. These problems also drive the demand for testing.

One of the fastest growing new technologies is phenotyping. While genotyping identifies genetic mutations, phenotyping determines how such mutations respond to specific environmental factors. Most importantly, phenotyping is used to determine whether a virus is resistant to a specific therapy as a consequence of a genetic mutation. Although the market for phenotyping is currently quite small it is expect that it could grow dramatically over the next decade. The growth will be driven by the introduction of additional therapies and by the fact that phenotyping provides a more precise method for predicting therapeutic response.

The demand for resistance testing is being driven by an increase in the number of patients being treated and by treatment limitations. These limitations include: high rates of viral breakthrough (HIV can rapidly mutate and develop resistance to specific therapies), increasing frequency of primary transmission of resistant viral strains, and the complexity of current treatment protocols. Since particular strains of HIV

are resistant to particular drugs and since patients may develop new, drug resistant strains of the virus during the course of treatment, patients must be tested to determine whether specific "drug cocktails" will be effective. Today, genotyping is the most common technology employed for resistance testing for HIV. Genotyping is a technology for detecting genetic mutations that may trigger resistance to certain therapies. Over time, we expect that another technology, phenotyping, will become a standard application for HIV resistance testing. Phenotyping is used to more precisely determine whether a virus is resistant to a specific therapy as a consequence of a genetic mutation.

5. Concluding remarks

The gradual evolution of emphasis from therapeutics to diagnostics has created new dynamics of interaction comprising major pharmaceutical companies, clinical laboratory companies and biotechnology companies. Furthermore, the stock market valuation of a great majority of biomarker based companies demonstrates the enormous difficulty that these companies experience in implementing adequate business models in order to capture the value of their knowledge assets and convey the realism of their business strategy to industrial partners, existing shareholders and potential institutional investors. Therefore, the need for a new way of looking and assessing the value created at each level, determining what capabilities are available in order to build an organization capable of coordinating across boundaries will become increasingly important.

While new molecular diagnostic assays are already proving their worth in screening patients for their susceptibility to commonly prescribed drugs such as Warfarin dosing and Rituxan response others are helping select the appropriate patients for clinical trials of experimental therapies. This approach has been especially important to the development of the new AIDS drugs Selzentry and Isentress, both of which aim at new targets.

Because of the low test quality and validation problems only a few biomarkers have been validated and required by the FDA in guiding prescribing (drug/indications: Erbitux/Colon cancer, Selzentry/ HIV and Herceptin/Breast cancer). Even if such a linkage between diagnostic and therapeutic can be achieved in principle, the time taken from discovery of the marker to achieving sales of a diagnostic product can be substantial. The time needed to develop, launch and gain market acceptance for a new diagnostic product should not be underestimated. However, such issues and the scarcity of early successes in biomarkers have made it very difficult to convince major drug discovery companies that the biomarker strategy is feasible.

Those biotechnology companies with an expertise in biomarkers that can demonstrate their ability to increase drug discovery productivity will be the partners of choice of pharmaceutical and larger clinical laboratory companies. However, the main challenge facing biomarker focused companies is that drug discovery, clinical laboratory and tools and equipment companies have the possibility of choosing among a vast array of technologies and approaches. In each case, a major partner's ability to implement a biomarker strategy wisely will have a large impact on the performance of its R&D organization in terms of time to market, productivity and product quality.

The impact of biomarkers on the health care delivery will continue to grow as major players involved in drug discovery and clinical testing fully integrate this technology into the core of their discovery efforts and commercial offerings. However, in a dynamic environment, formulating a successful business strategy depends to a significant degree on learning new directions and on recognizing opportunities that materialize during that process. It is crucial to understand the nature of change in the industry and to exploit this knowledge by identifying areas where resources should be committed.

REFERENCES

1. J.A. DiMasi, R.W. Hansen, H.G. Grabowski**.** The price of innovation: new estimates of drug development costs. J. Health Econ. 22 (2003) 151-185.

2. Dickson, M., Gagnon J.P. Key factors in the rising cost of Drug Discovery and Development. Nat. Rev. Drug Discov. 3 (2004) 417-429.

3. W. Bains, Failure rates in drug discovery and development: will we ever get any better? Drug Discovery World Fall (2004) 9-18.

4. J. Lazarou, B.H. Pomernaz, P.N. Corey, Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA 279 (1998) 1200-1205.

5. K.E. Lasser, P.D. Allen, S.J. Woolhandler, D.U. Himmelstein, S.M. Wolfe, D.H. Bor, Timing of new black box warnings and withdrawals for prescription medications. JAMA 287 (2002) 2215-220.

6. C.A. Shillingford, C.W. Vose, Effective decision-making: progressing compounds through clinical development. Drug Discov. Today 6 (2001) 941-946.

7. AP Li, Screening for human ADME/Tox drug properties in drug discovery. Drug Discov. Today 6 (2001) 357-366.

8. A-E. F. Nassar, A.M. Kamel, C. Clairmont, Improving the decision-making process in structural modification of drug candidates: reducing toxicity. Drug Discov. Today 9 (2004) 1055-1064.

9. Oberemm, L. Onyon, U. Gundert-Remy, How can toxicogenomics inform risk assessment. Toxicol. App. Pharm. 207 (2005) S592-S598.

10. FDA, Innovation &Stagnation Challenge & Opportunity on the critical path to new medical products. March 2004. http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html

11. H. Kubinyi, Drug research: myths, hype and reality. Nat. Rev. Drug Discov. 2 (2003) 665-668.

12. D. Noble, Will genomics revolutionize pharmaceutical R&D? Trends Biotechnol. 21 (2003) 333-337.

13. Y. Baba, Development of novel biomedicine based on genome science. Eur. J. of Pharm. Sci. 13 (2001) 3-4.

14. M. Fogarty, The reality of targeted therapies. The scientist 16 (2002) 35.

15. L. A. McLean, I. Gathmann, R. Capdeville, M.H. Polymeropoulos, M. Dressman, Pharmacogenomic Analysis of Cytogenetic Response in Chronic Myeloid Leukemia Patients Treated with Imatinib. Clinical Cancer Research 10 (2004) 155-165.

16. J.O. Claudio, A.K. Stewart, Advances in Myeloma Genetics and Prospects for Pharmacogenomic Testing in Multiple Myeloma. American Journal of PharmacoGenomics 5 (2005) 35-43.

17. S.-M. Huang, L.J. Lesko, Correlation between genes, diseases and biopharmaceuticals, in "Modern Biopharmaceuticals- Design, Development and Optimization Application of Pharmacogenomics in Clinical Pharmacology—in Volume I: Molecular Medicine., J. Knablein and R.H. Muller, eds, Wiley, VCH, 2005.