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COMPANION BIOMARKERS IN DRUG DEVELOPMENT

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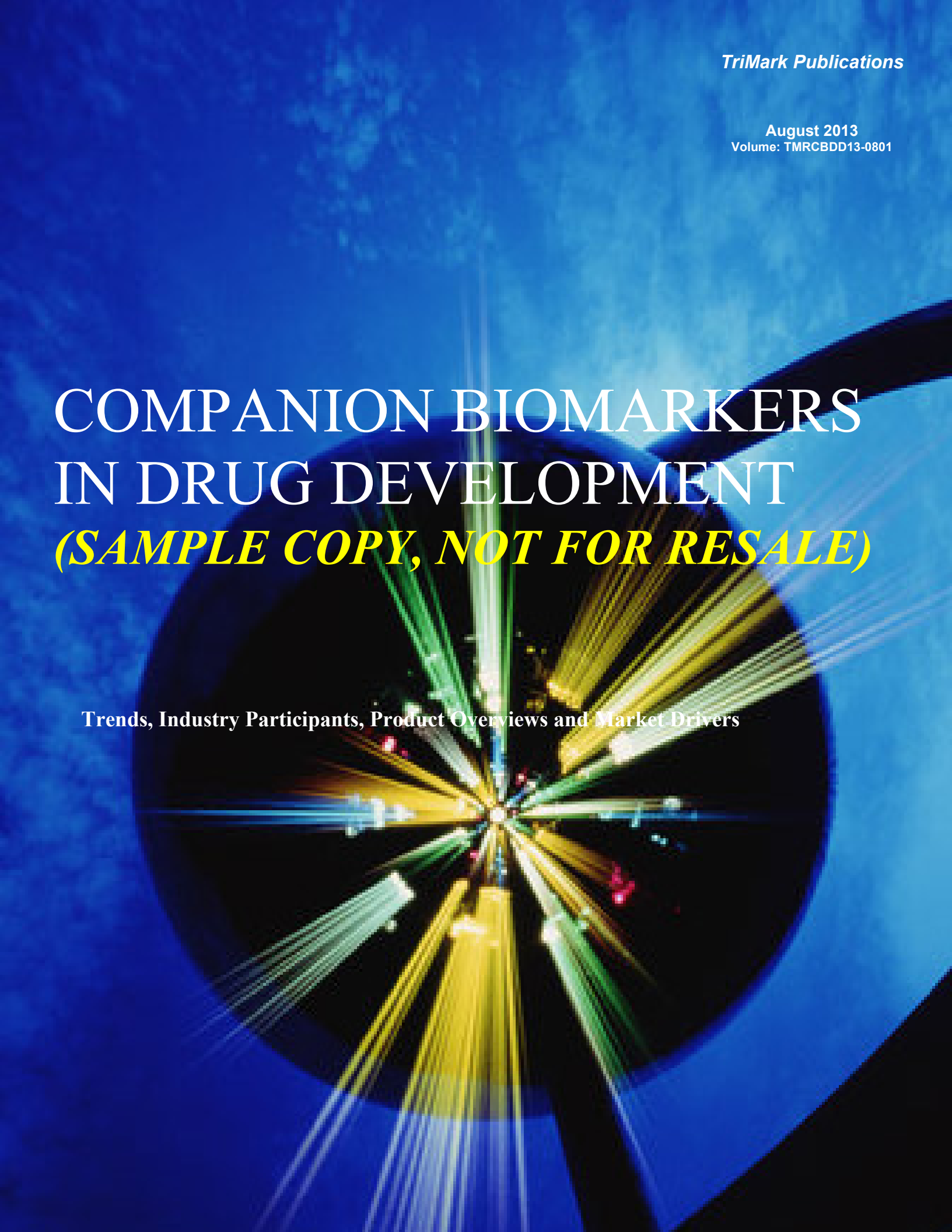
Trends, Industry Participants, Product Overviews and Market Drivers



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1. Overview

1.1 Statement of Report

The term "companion biomarker" means that a particular diagnostic test is specifically linked to a therapeutic drug either during its development or in the clinic. This linkage can be an important component of the drug development process; or alternatively, the companion biomarker can be useful in ameliorating the regulatory process for the drug, or acting as an aid to therapeutic use in the clinic. This TriMark Publications report focuses on the role of companion diagnostic tests in drug development. This report will provide an in-depth discussion and analysis of the application of companion biomarkers to drug development and targeted therapeutics, as well as their use in clinical trials and the regulatory forum. This examination emphasizes new and developing technology platforms meant to aid in development of drugs for therapeutic use, and sometimes to be available as companion tests for these drugs in the clinic.

1.2 About This Report

This report describes new biomarker technology platforms developed for the analyses of drug targets that are connected to the effectiveness of therapeutic agents in a clinical setting. The emphasis is on those companies that are actively developing and marketing new companion diagnostic tests for performing biomarker tests during drug development, as opposed to the more routine and clinically accepted companion markers that are manufactured and marketed by large diagnostic companies for routine clinical use.

This review focuses on biotech and pharmaceutical companies who have new products and procedures for drug development. Traditional diagnostic companies in the process of developing new ideas for clinical diagnostic purposes are not reviewed in any detail here. However, many pharmaceutical companies take great pains to point out that they are not diagnostic development companies, and as new drugs reach the clinic, some of the companion diagnostic tests that are used internally by pharmaceutical companies in their clinical trials and FDA applications can be turned over to diagnostic companies for further development in the clinic.

1.3 Scope of the Report

This analysis differs from TriMark's *Personalized Medicine* and *Companion Diagnostics for Personalized Medicine and Cancer Therapy* reports in that it emphasizes diagnostic tests that are linked in their usage to development stage work on therapeutic agents. This study emphasizes pharmaceutical and biotech companies that are actively developing new technology platforms for performing companion biomarker diagnostics tests in the clinical trial and early drug development setting.

1.4 Objectives

The main objectives of this review are:

- Identifying viable technology drivers through a comprehensive look at platform technologies for *in vitro* diagnostic tests used as biomarkers, which are used to monitor the efficacy of therapeutic drugs.
- Obtaining a complete understanding of the new companion biomarker diagnostic tests—*i.e.*, predictive, screening, prognostic, monitoring, pharmacogenomic and theranostic—from their basic principles to their applications.
- Discovering growing market opportunities in drug development by identifying high-growth applications in different biomarker areas, with a major focus on the biggest and expanding markets in oncology (*e.g.*, biomarkers for cancer therapeutics).
- Focusing on global pharmaceutical industry development through an in-depth analysis of the major world markets for companion diagnostics, including growth forecasts.

The report discusses the various market trends and opportunities using biomarkers in drug development. The reader should consult other TriMark Publications reports at http://www.trimarkpublications.com for detailed discussions of important individual market segments related to the companion diagnostics market. TriMark provides a separate market report called *DNA Sequencing and PCR Markets*, which emphasizes the analytical methods and PCR technology platforms used in companion diagnostics. A sister report, *Pharmacogenomics for Clinical Use and in Drug Development*, on the use of companion diagnostic tests in treatment selection for patients in the diagnostic sector is recommended as a companion report to this one. The biotech sector developing new companion biomarkers for drug development is the focus of this examination.

Specialty companion diagnostics testing such as pathology screening methods and special tissue stains to examine companion cells *in situ* are mentioned, since they are often part of the overall analytical focus of companies that market companion technology platforms. However, no effort is made to quantify this older and broader market. These subjects are discussed in other TriMark Publications reports. Leading companies are discussed in-depth, with sections on the companies' histories, product lines, business and marketing analyses, and subjective commentary on the companies' market positions.

The report examines:

- Opportunities and hurdles in the development of companion biomarkers in drug discovery using proteomics and genomics.
- Secreted proteins as biomarkers.
- Adaptive design using biomarkers.
- Pharmacodynamic biomarkers identified with broad-based phenotyping as companion diagnostics.
- Tools for improving measurement, safety and validation of biomarkers in drug development.
- Filling the gap between discovery and clinically validated biomarkers.
- Enabling technologies for oncology biomarker discovery.

This analysis answers the questions:

- How can pharmaceutical companies identify which agents need to be developed with a companion diagnostic and which do not?
- Is the stratification of disease markets a reason to avoid targeted therapies and companion diagnostics?
- Which diagnostics' companies are developing biomarkers that might be potential targets for licensing or acquisition?
- What are the latest developments in the biomarker field with regard to drug development?
- What are the advantages of going the CLIA certified lab route?
- Are all companion diagnostics likely to need FDA approval in the near term?
- Which companies are utilizing cutting-edge technologies to develop, validate, and implement companion biomarkers for clinical use in the drug development and clinical trial setting?
- What impediments still exist to incorporating promising biomarkers into clinical trials?
- Which companion biomarkers show the most promise for use in drug approval?
- How can regulatory oversight drive approval and adoption of new technologies?
- Which alliances show the greatest synergy in bringing valid biomarkers to drug development?
- Which shared technologies are driving the most encouraging development?
- What is the current FDA stance on biomarkers and their potential to increase efficiency in drug development?
- How will insurance companies react to the use of biomarkers for pre-disposition and personalized medicine?
- What is the FDA's Critical Path Initiative?
- Do biomarkers really speed up the approval process?
- What stages does a biomarker need to go through for the FDA to consider it validated?
- What is the FDA viewpoint on pre-competitive cooperation on biomarker studies?
- What are the key opportunities in biomarker discovery, development and commercialization?
- What are the current obstacles in biomarker implementation?

- How do business strategies, such as those relating to acquisition, drive biomarker strategies?
- What is the right balance between using external partnerships and developing internal infrastructure?
- How might novel biomarker development lead to acquisition strategies and their implications for deal making?
- Which types of biomarkers should be developed at various stages in the drug pipeline?
- What strategies help translate biomarkers from preclinical to clinical development?
- In what class of drugs is the value of using biomarkers in decision making the highest?
- How are clinical trial costs increased by including biomarkers?
- How can Big Pharma co-develop biomarkers in a cost-sharing model for regulatory acceptance?

Key features of this report:

- Analysis of leading pharmaceutical and biotechnology companies and academic groups at the forefront of biomarker discovery, validation and utilization.
- Examination of the key trends which are currently affecting the discovery and application of biomarkers such as the development of molecular diagnostics and the application of valid, probable valid and exploratory biomarkers in drug discovery.
- Assessment of the pivotal role that biomarkers play in the development of new diagnostic devices both in conjunction with drugs as targeted therapies and in areas of unmet medical need.

1.5 Methodology

The author of this report holds a Ph.D. in biochemistry from the University of Minnesota and has had post-doctoral experience at the University of Connecticut School of Medicine. He has taught at Quinnipiac University and the Tufts School of Medicine, and has been a senior scientist at Pfizer Pharmaceutical Laboratories in drug development. He also has many decades of experience in science writing and as a medical industry analyst. He has over 30 years of experience in laboratory testing and instrument and reagent development technology as a licensed clinical laboratory director, as well as extensive experience in senior level management positions in biotech and medical service companies. The editor of this report is a Ph.D. in biochemistry from the University of Liverpool and an MBA from Oxford Brookes University with many decades of experience in science writing and as a medical industry analyst.

Company-specific information is obtained mainly from industry trade publications, academic journals, news and research articles, press releases and corporate websites, as well as annual reports for publicly-held firms. Additional sources of information include non-governmental organizations (NGOs) such as the World Health Organization (WHO) and governmental entities such as the U.S. Department of Health and Human Services (HHS), the National Institutes of Health (NIH), the Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC). Where possible and practicable, the most recent data available have been used.

Some of the statistical information was taken from Biotechnology Associates' databases and from TriMark's private data stores. The information in this study was obtained from sources that we believe to be reliable, but we do not guarantee the accuracy, adequacy or completeness of any information or omission or for the results obtained by the use of such information. Key information from the business literature was used as a basis to conduct dialogue with and obtain expert opinion from market professionals regarding commercial potential and market sizes. Senior managers from major company players were interviewed for part of the information in this report.

Primary Sources

TriMark collects information from hundreds of Database Tables and many comprehensive multi-client research projects, as well as Sector Snapshots that it publishes annually. TriMark extracts relevant data and analytics from its research as part of this data collection.

Secondary Sources

TriMark uses research publications, journals, magazines, newspapers, newsletters, industry reports, investment research reports, trade and industry association reports, government-affiliated trade releases and other published information as part of its secondary research materials. The information is then analyzed and translated by the Industry Research Group into a TriMark study. The Editorial Group reviews the complete package with product and market forecasts, critical industry trends, threats and opportunities, competitive strategies and market share determinations.

TriMark Publications Report Research and Data Acquisition Structure

The general sequence of research and analysis activity prior to the publication of every report includes the following items:

- Completing an extensive secondary research effort on an important market sector, including gathering all relevant information from corporate reporting, publicly available databases, proprietary databases, direct meetings and personal interviews with key personnel.

- Formulating a study outline with the assigned writer, including important items:

    - Market and product segment grouping and evaluating their relative significance.
    - Key competitors' evaluations including their relative positions in the business and other relevant facts to prioritize diligence levels and assist in designing a primary research strategy.
    - End-user research to evaluate analytical significance in market estimation.
    - Supply chain research and analysis to identify any factors affecting the market.
    - New technology platforms and cutting edge applications.

- Identifying the key technology and market trends that drive or affect these markets. Assessing the regional significance for each product and market segment for proper emphasis of further regional/national primary and secondary research.

- Launching a combination of primary research activities including two levels of questionnaires, executive-direct focused, company-specific, and region-specific communications to qualified and experienced senior executives worldwide.

- Completing a confirmatory primary research assessment of the report's findings with the assistance of Expert Panel Partners from the industry being analyzed.

1.6 Executive Summary

The companion diagnostics market represented by pharmaceutical, medical device, and diagnostic companies is estimated at $[redacted] and is expected to grow by [redacted]% annually reaching $[redacted] by [redacted]. Rapid changes in drug company pipelines and research and development (R&D) investment requires that current status of drug development programs be reviewed and updated. Drug development is being significantly influenced by biomarkers and companion diagnostics. Industry experts estimate that [redacted]% to [redacted]% of Phase II clinical trials have incorporated companion biomarkers; and this number is thought to be even higher in oncology.

- [redacted]% of existing drug programs have a CDx test associated.
- [redacted]% to [redacted]% of drugs in Phase III have a CDx association.

Pharma and diagnostic companies are being forced to change their business models both internally and in partnerships. The regulatory agencies may need to create new structures/categories to deal with the combination of therapeutics and diagnostics.

The number of IVD licensing deals with pharmaceutical companies for companion diagnostics increased significantly during [redacted], with [redacted] deals in [redacted], [redacted] deals in [redacted], [redacted] deals reported in [redacted], with [redacted] deals in [redacted] and [redacted] in [redacted].

- *Drivers*: The strong appetite for companion deals was driven by increasing signals from regulators and payers, stressing the importance of biomarkers and diagnostics to improve drug performance and allow for more cost-effective allocation of tight healthcare budgets.

- *Barriers*: Companion diagnostics have had notable disappointments in which a CDx has not been adequately developed, is not needed for drug approval after all, or faces commercial hurdles. These hurdles include FDA approval of a test that is not reimbursed and the substitution of the FDA-approved CDx with another test.

In this emerging paradigm, diagnostic platform companies do not have clear guidelines to determine whether to develop a CDx. Pharma is adapting by making more systematic use of companion diagnostic programs to increase drug response rates and reduce side effects.

Diagnostic companies with strong molecular and tissue diagnostic capabilities have been active at developing tools to respond to pharma's specific needs. The pharma industry is concerned about the companion diagnostics use adversely affected by current pricing and reimbursement practices, as well as patient demographic use.

Many diagnostics partners feel they are not getting a fair share of Rx-Dx partnership values.

- *Pharma Partners*: While Big Pharma dominated, niche therapeutics specialists also showed an interest in diagnostics partnerships. Big Pharma remained dominant among the pharma partners in [redacted].

- *Diagnostic Partners*: In [redacted], larger diagnostics companies became more active partners for the pharmaceuticals industry.

- *6 Outlook*: The appetite for companion deals will remain strong because the same drivers will continue and intensify in [redacted] and beyond.

By [redacted], if drug-diagnostic co-development becomes routine, most leading pharma companies are expected to change their business model to incorporate significant in-house diagnostics capabilities. The volume of external alliances is expected to remain high, but the trend may lose momentum.

Key Findings:

- The global biomarker market is estimated to be $[redacted] by [redacted], growing at a compounded annual growth rate (CAGR) of [redacted] % from [redacted] to [redacted], driven by the high demand for the biomarkers in the field of drug discovery. The markets for biomarker tools and services are expected to grow at a CAGR of [redacted]% and [redacted]%, respectively. The increasing use of biomarkers in clinical services is boosting the overall biomarker service market.

- It has been estimated that the global market for companion biomarkers was valued at $[redacted] in [redacted]. This had increased to an estimated $[redacted] in the year [redacted]. By the end of the forecast period, it is predicted that the market will have increased in value to $[redacted] (CAGR [redacted]%).

- The sales of marketed companion drugs was enhanced by companion diagnostics, with six drugs achieving blockbuster status. The application of pharmacogenomics to targeted studies, in which patient populations are enriched with potential responders, can lead to cost savings of around $[redacted] through the streamlining of clinical trials.

- The market for molecular diagnostics is gaining momentum, with Roche's AmpliChip P450 which was the first to receive regulatory approval to a recent FDA approval of Gen-Probe's PROGENSA® PCA3 assay to

determine need for repeat-prostate biopsies and FDA approval of BD Max™ MRSA test developed by BD Diagnostics. Tests for areas of high unmet need, such as certain types of cancers, cardio-vascular diseases Alzheimer's disease, and rapid-detection tests for respiratory infections are set to drive further growth in the market to [redacted].

- The role of biomarkers spans all aspects of drug discovery and development from target discovery and validation, lead prioritization and optimization, study of drug and disease mechanisms, toxicity profiling and proof-of-concept in preclinical studies, to use in clinical trials as secondary and surrogate endpoints.

- In [redacted], over [redacted]% of the new molecular entities (NMEs) were approved with a pharmacogenomic biomarker by the FDA, with nine premarket authorizations (PMAs) for five indications in [redacted].

- In terms of value, over [redacted]% of the sales in the companion drugs market was contributed by drugs indicated for cancer.

Oncology Companion Diagnostics

- As noted above, much of the activity in Companion Diagnostics has been focused in the area of oncology. A number of Companion Diagnostic markers have been developed for targeted therapeutics such as Herceptin (Genetech), Tarceva (OSI Pharmaceuticals/Genetech), Iressa (Astra Zeneca) and Erbitux (Imclone/Bristol Myers Squibb). Recently the wild type K-ras gene has been identified as a predictor of treatment response to Erbitux as well as Vectibex (Amgen).

- In addition, there has been considerable activity in the use of Companion Diagnostic markers to predict toxicity, efficacy and drug dosage in order to ensure hitting critical endpoints.

- The overall companion drugs market is dominated by three leading companies—Roche Laboratories, Novartis and Pfizer. Together these companies accounted for over [redacted]% of the companion drugs market in [redacted].

- There are several personalized medicine diagnostics in the market, with companion diagnostics constituting its subset. Companion diagnostics represented approximately [redacted]% of the personalized medicine diagnostics market in [redacted].

- The pipeline for companion diagnostics is robust, with most products being developed by a collaborative effort of pharmaceutical and diagnostics companies. Many start-ups diagnostic companies are also engaged in partnerships with large pharmaceutical companies for developing companion diagnostic tests.

- The U.S. was the largest market for companion diagnostics in [redacted], accounting for over [redacted]% of the total market.

The introduction of biomarkers to drug development will help bring new medicines by:

- Identifying the right patients faster.
- Reducing the time of developing new drugs.
- Improving the ability to predict success in drug development.
- Decreasing the attrition rate among developmental candidates.
- Lowering development costs.
- Aiding in monitoring dugs during the regulatory process.
- Bringing greater efficiency to clinical trials.

More recently, biomarkers have begun to assume a greater role in drug discovery and development. The challenge for biomarkers in drug development is to improve the introduction of earlier, more robust drug safety and efficacy measurements into the drug development pipeline. TriMark sees its role in drug development as continuing to grow for the foreseeable future. The world pharmaceutical industry, driven by scientific and technological advances, new

drug discoveries, advances in therapeutic knowledge and changes in government and regulatory controls, generally is very successful. The combined global pharmaceutical markets were valued at $[redacted] in [redacted], up [redacted]% from [redacted]. Global pharmaceutical sales grew at a CAGR of [redacted]% to [redacted]% from [redacted] to [redacted], and for the last two years the CAGR has been ~[redacted]%. The pharmaceutical drug sector is projected to reach $[redacted] worldwide by [redacted], with a CAGR of [redacted]%.

Though the pharmaceutical industry remains one of the most profitable and stable industries, several variables are threats to continued growth and are causing fundamental changes in the industry structure. The accelerating cost of medical care and, in particular, the escalating cost of drugs (particularly to the elderly) has the drug industry under attack. We believe that this presents a golden opportunity for new technologies in drug development, *i.e.*, biomarkers. The use of companion diagnostic tests (*e.g.*, biomarkers) in drug development will:

- Yield safer and more efficacious drug products.
- Reduce clinical trial and development costs.
- Improve post-marketing safety profiles.
- Salvage therapies that otherwise would not be granted approval.

Biomarkers must have the following operational characteristics to be applicable to drug development programs:

- Readily available source material.
- Minimally invasive.
- Multiple sampling possible.
- Surrogacy: changes in the biomarker are linked to clinical outcomes.

Biomarkers have been used in drug development to establish:

- A minimally biologically effective dose (MBED).
- Optimal biologically effective dose (OBED).
- Selection of optimal dose and schedule for Phase II and Phase III trials.
- Make effective "go"/"no-go" decisions.

Selectivity is an important aspect of biomarker development as companions in drug development:

- Careful selection of targets for clinical trials.
- Careful and deeper analysis of toxicity screening.
- Proper patient selection for late stage trials.
- More data for the FDA.
- Possible companion diagnostic tests for patient selection and efficacy in the clinic.
- Partnering of early stage discovery companies with contract research organizations (CROs) and traditional pharma companies.

In addition, the larger pharmaceutical companies are utilizing biomarkers to look for efficacy or toxicity of their lead compounds in patient subpopulations. The classic example here is screening for HER-2/neu over expression before using the biologic therapeutic Herceptin in breast cancer therapy. Potential benefits of biomarkers as companion diagnostics:

- Streamline drug discovery programs.
- Provide a target for therapy.
- Identify potential responders to a drug.
- Identify individuals at risk for adverse events.
- Tool for monitoring response to drug therapy.

The global market for biomarkers in the form of companion diagnostics is much more of a developing market, and user segments in the clinical and drug development space are still diffuse. As such, TriMark feels that the

companion diagnostic market is still in its infancy, making it difficult to accurately predict the growth trajectory of this space. Key points noted include the following:

- An initial lag exists as awareness is generated in the clinical marketplace, followed by recruitment of early adopters who generate new applications. This drives early revenue generation in the marketplace and more interest in developing companion diagnostics for clinical trials. For companion diagnostics, this occurred in the interval of [redacted] to [redacted].

- Rapid growth as the broader market is recruited by the initial papers and due to the excitement generated by early adopters. The growth rate of the clinical user market is high as new applications are developed and vendors commercialize products aggressively. The market is beginning to fragment as drug developers begin to routinely add companion tests to their programs; this is the near term outlook for companion diagnostics.

- Despite a slowdown of the growth rate, revenues in the market keep increasing as new products are introduced in the clinic, new applications developed and new clinical trials are recruited. TriMark expects this to continue through [redacted] and [redacted] for the companion diagnostics marketplace.

Companion Biomarker Trends

- The relative contribution of therapeutic development and clinical trials using personalized medicine is small; they account for only [redacted]% of the total end-user applications.

- The current personalized medicine marketplace is not heavily-weighted towards therapeutic development and clinical trials.

- A large proportion of this marketplace—[redacted]% in total—is composed of participants that are involved with developing technologies or products for personalized medicine. The emphasis is more "upstream" in this marketplace, as opposed to more "downstream" applications—such as therapeutics development, conducting clinical trials, etc.

- The industry still does not contain enough molecular signatures which are predictive of biological outcome to create a large supply of companion biomarkers, and this remains a significant market opportunity for the market participants.

Results/Takeaways from the Market Model

This market opportunity is focused in three spaces:

- Drug development targets.
- Drug development efficacy.
- Clinical end points.

Cost per experiment is only for direct cost of the reagents/consumables and does not include salaries, other personnel costs, equipment/instrumentation, or license fees. This market model is highly conservative, and TriMark feels that it appropriately reflects the industry revenues harvested from direct sales of products into the biomarker space. Pharma companies are intensely interested in examining the role of biomarkers in:

- Early-stage drug discovery.
- Preclinical studies.
- Late-stage clinical trials of drug development.

Changes in pharma business models are reported on a regular basis. R&D expenditures, mass layoffs, and the much feared end of the "blockbuster" era are driving both the pharma and diagnostic industries to change their paradigms. New stakeholders such as PBM's, and CLIA lab diagnostic models, which have evolved over the past few years, are

adding to the rapid rate of change in the industry. New regulatory and reimbursement models are needed to deal with the future of a more intertwined strategy between pharma and diagnostics. The question of value, and cost (of new therapeutics) will continue to be a source of debate.

The reasons for growth of companion diagnostics:

- Low drug efficacy rates in clinical practice.
- Poor drug dosing compliance among patients.
- High cost of drug development.
- Many Phase II and III Drug development failures.
- Numerous drug recalls.
- New tools and technologies enabling the move to companion diagnostics.
- Growing significance of biomarkers in clinical medicine.
- Reducing costs of genome sequencing.

Companion diagnostics combines drug and diagnostic test development. The potential for efficient drug development is great because companion diagnostics can be used to predict drug response and treatment efficacy in the clinic. In this regard, companion diagnostics dovetail with the promise of personalized medicine.

However, the advantages of companion diagnostics are only one side of the equation. They can also be seen as disruptors of the pharmaceutical market in that they could potentially restrict the size of treatable populations. Finally, to date Roche Laboratories is the leader in this space, with the largest number of successful companion diagnostics.

