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CELL-BASED ASSAYS FOR DRUG DISCOVERY

(SAMPLE COPY, NOT FOR RESALE)

Trends, Industry Participants, Product Overviews and Market Drivers

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1. Overview

The area of drug discovery tools is one of the newest and most important sectors of pharmaceutical research and development. The term drug discovery tools usually refers to high-content screening (HCS) and analysis and is composed of those applications that require sufficient levels of sample throughput, but that also encompass the study of complex cellular events and phenotypes. Elements of drug performance such as toxicity and specificity can be established simultaneously using mixed cell types—primary cells, cell lines and cell subpopulations. HCS seeks to assess the impact of phenotypic and cellular changes that are brought about by gene modification (such as with RNA interference [RNAi] approaches) and/or drug (or compound) treatment.

1.1 Objectives of the Report

The purpose of this examination is to describe the specific segments of the global drug discovery tools market. Within this area, the report covers those segments that are highly active in terms of innovation and growth. Specifically, this study examines the markets for small lab equipment all the way up to large automated platforms, as well as accessory equipment such as reagents, supplies and additional equipment from original equipment manufacturers (OEMs).

The emphasis in this analysis is on those companies and products that are actively developing and marketing drug discovery tools for the pharmaceutical industry, including traditional pharma companies as well as biotech and bioscience companies. This study concentrates on the laboratory instrumentation industry market segment and the companion reagents sector in the U.S. and around the world. Particular attention is paid to those areas of drug discovery instrumentation/reagents that are showing the greatest growth or the most innovation. The report attempts to answer the questions:

- Which companies are key players?
- What is the market for high-content analysis (HCA)?
- What are the opportunities in drug discovery tools markets?
- What is happening with the information revolution in lab instruments?
- What are the developing trends?
- Where are the new market growth areas?
- What are the most favored technology platforms?
- Where are the drug discovery tools technologies for HCA taking us?
- How is high-content drug discovery technology blending with more established laboratory procedures?
- What are the business trends in the industry?

The analysis surveys some of the leading companies known to be marketing, manufacturing or developing products for the drug discovery instrumentation and reagent market for those sectors covered here. Each company is discussed in depth with a section on the history of the company, the product line, business and marketing analysis, and a subjective commentary on the position of the company in its market. Unique benefits of this report are:

- In-depth analysis of the major sectors of the drug discovery tools high-content sectors, their size, growth rates and major drivers.
- Presentation of some of the emerging technology platforms, elucidating the potential areas that could gain traction in this market.
- Analysis of the partnerships and alliances the various key sector players have forged, as well as descriptions of financing of these market participants, giving insight into potential market collaborations.
- Examination of new technology platforms that seek to dominate this new market, and identification of lead positions and potential future growth areas.
- An overview of the current state of cell-based assays in drug development and the numerous opportunities that exist to increase the quality of screens using HCA.
- A profile of the HCS customer and an analysis of factors influencing the adoption of HCS technology.
- Spending projections of new equipment and reagents.
- Impact of HCS on systems biology.

1.2 Methodology

The author of this report is a Ph.D. in biochemistry from the University of Minnesota, with many decades of experience in science writing and as a medical industry analyst. He has over thirty years' experience in laboratory testing and instrument and reagent development technology, as well as extensive experience in senior level positions in biotech and medical service companies. The editor has a Ph.D. in molecular and cellular biology from Tulane University, with postdoctoral work at the USDA Agricultural Research Service and the University of Leipzig in Germany.

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. Additionally, sources of information include the non-governmental organizations (NGOs) such as the World Health Organization (WHO) and governmental entities like the U.S. Department of Health and Human Services (HHS) and U.S. federal agencies such as 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 we publish annually. We extract relevant data and analytics from TriMark's 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 in TriMark Publications 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 data and proprietary databases.

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

    - 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.

- Completing a confirmatory primary research assessment of the report's findings with the assistance of expert panel partners from the industry being analyzed.

1.3 Scope of the Report

Technologies and Product Offering for HCA

This section is focused on the presentation and analysis of the technologies and associated trends in the high-content and secondary analysis space of the drug discovery tools marketplace. Specifically, in this section, TriMark presents the following:

- Definition of HCA and why HCA is so attractive.
- Key HCA application areas.
- Classes of measurements possible with HCA approaches.
- Instrumentation platforms for HCA.
- Reagent/assay platforms for HCA.

Market Analysis of the High-Content Tools Space

This section is focused on the presentation and analysis of the market landscape for HCA tools in basic research and drug discovery efforts. This chapter complements the other chapters of this report in that it provides a qualitative and quantitative framework to describe the current market trends operative in this space, as well as providing a snapshot of the emerging trends in this space. In this section, TriMark presents the following specific market parameters:

- Results from a primary market survey describing qualitative and quantitative parameters.
- Experimental/research trends in HCA.
- Instrumentation usage in HCA.
- Reagents/assays/biotechnology usage in HCA.
- Emerging trends in the HCA marketplace.
- Forecast market size and growth rate for HCA.
- Qualitative opportunities and challenges for market adoption.

Strategic Analysis of the High-Content Tools Space

This section is focused on an analysis of the landscape and strategic issues that impact the HCA space. Specifically, TriMark provides the following analyses in this section of the report:

- Description of the marketplace, definition of the field, its structure, and the key drivers in the market.
- Current challenges and leading-edge sectors and technologies in the HCA space.
- Consolidated picture of the marketplace across the different segments of this HCA marketplace.

Company Profiles and Glossary of Terms in HCA

The reader should consult other TriMark Publications reports at http://www.trimarkpublications.com for a detailed discussion of the important individual market segments that are related to drug discovery tools, including *DNA Sequencing and PCR Markets*, *Genomics World Markets*, *Microarray Markets*, *Molecular Diagnostics Markets*, *RNAi Markets* and *Stem Cell Markets*. TriMark Sector Snapshots in related areas include *Flow Cytometry* and *Protein and Antibody Microarray Markets*.

1.4 Executive Summary

High-content screening technologies use massively parallel analyses on a microscope or other equipment designed to measure intracellular events. Emerging tools and capabilities in HCS are driving a wave of new opportunities for investment on both the supply and demand sides as new hardware systems, software applications, and reagent kits enable researchers to study intracellular events on hundreds of thousands of cells per month.

HCS/HCA occupies a key market segment composed of those applications that require sufficient levels of sample throughput, yet are complex enough whereby complex cellular events and phenotypes can be studied, including toxicity and specificity simultaneously; use of mixed cell types—primary cells, cell lines and cell subpopulations; and off-target effects. HCA seeks to assess the impact of phenotypic and cellular changes that are brought about by gene modification (such as with RNAi approaches) and/or drug (or compound) treatment.

Pharmaceutical companies are performing HCA for a number of reasons, including target validation, compound-library screening, and determination of the mechanism of action of compounds. High-throughput screening (HTS) groups in the pharmaceutical and biotechnology community are increasingly adopting high-content screening and analysis.

The following biological applications are areas in which HCA finds significant current market appeal:

- Apoptosis.
- Cell cycle control.
- Cytoskeletal assays.
- DNA damage repair assays.
- Mitogenesis assays.
- G-protein coupled receptor (GPCR)-driven signaling.
- Ion channel-driven signaling.
- Kinase-driven signaling.
- Proteasome assays.
- Stress/inflammatory response.
- Transcriptional control.
- RNAi coupled with HCA.

Important drivers of HCA are:

- The ability to make many diverse measurements on biological systems using a suite of assays and one instrument.
- Higher information output compared to traditional biochemical or cell-based assays.
- Information that is derived has spatial and temporal context—*i.e.*, this information correlates various cellular parameters with the morphology of the cell and/or time post-stimulation.
- In the current era of an expanding number of pharmaceutical targets, it is crucial to be able to investigate a number of diverse parameters of drug targets related to their *in vivo* biology.
- High-content biology also enables multiple assays to be combined, different assays formats to be automated, and output data to be analyzed en bloc—*i.e.*, HCA is multiplexable.

HCA has two clear application areas:

- Basic research to characterize biological pathways and proteins therein.
- Target identification, analysis, validation and screening in drug discovery.

The instrumentation platforms for HCA are essentially high-throughput microscopes that have associated features. The largest current market opportunity in HCA is high-content imaging and sub-cellular localization and translocation events. There are a number of related market segments that have some impact on the development of HCA; an important one is HTS. TriMark presents its analysis of the opportunities and challenges in the HCA space.

Opportunities for Market Adoption

- Biologically relevant assays—gleaning of novel spatial and temporal information.
- Investigation of targets with no current drug treatments.
- Harnessing of the power of cellular networks—study of drug selectivity and toxicity across a biological system.
- Drug and target profiling, network mapping, biomarker identification and validation.
- Complementing of macroscopic assays.
- Single cell resolution leading to measurement of new cellular parameters.
- Study of heterogeneous cell populations—primary cells, stem cells, tissue cultured cells.
- Population distribution of phenotypes in cells.
- Flexible assay formats—single cell level, sub-cellular resolution.
- Quantitative measurements can be made in mixed or rare cell populations.
- Many potential applications/assays in cell biology: cell motility, fusion-division, polarity, viability, gross morphology, endocytosis, exocytosis, receptor internalization, inter- or intracellular redistribution, signal transduction, apoptosis, oxidative stress, cytotoxicity, DNA content, organelle size.
- Creation of assays based on configuration of changes in intensity or location of cellular proteins.

Challenges for Market Adoption

- HCA assays are lower throughput with more complex assay biology.
- Complex instrumentation is required, usually with a large capital expenditure and high IT infrastructure costs.
- Unprecedented data generation and storage issues.
- Needs for data visualization, mining, retrieval and archiving—image analysis.
- Huge demands on hardware/software support.
- Need for dedicated IT and statistical analysis support teams.
- Need to generate the most biologically-relevant assays, rather than any assay that can be developed.
- QA/QC steps needed throughout the process to ensure integrity of the data that is collected.
- Images—the majority of the HCA data output—are difficult to interpret.
- Lack of standardization in the HCA space—unlike the case with HTS where standards exist for data collection, QA/QC and analysis.
- Interoperability between different analysis systems across vendors does not generally exist— this slows down adoption of different platforms that have different value propositions.
- Implementation of a new technology platform—especially HCA—is exceedingly expensive. A general lack of "success stories" resulting from HCA hampers broad adoption across the pharmaceutical and biotechnology industries.
- HCA is too expensive for individual academic labs to implement—needs to be done by an institutional core facility.
- An increasing number of assays and assay formats, and their successful utilization, will enable skeptical pharmaceutical and biotechnology company customers to embrace the HCA discipline.

The initial adoption of HCA has been undoubtedly slow, but the pace is picking up rapidly. Cellomics, Inc. (acquired by Thermo Fisher Scientific Inc.) was the pioneer in this space and for many years received neither acclaim nor any traction in the marketplace. Over the past several years, however, the community—academic/basic research, pharmaceutical research, and biotechnology—has embraced HCA and this is driving industry dollar generation in this space. HCA offers a number of elements of bona fide value to end-users: it provides more biological context to screening data, enables the quantification and understanding of toxic effects, provides basic and applied researchers the ability to visualize and quantify the real effects of an experiment from a systems biology point of view versus single data points. In comparison to the other segments of the life sciences tools space, HCA is a very small marketplace (sized currently at about $[redacted], worldwide), but it offers a robust growth opportunity fueled by broader market acceptance, new applications development and integration into the "must-have" of drug discovery and development operations.

After an initial hype about HCA in the past few years followed by a lack of solid adoption of HCA industry-wide, HCA is coming back in focus and is expected to grow in size in the next few years. No doubt, currently HCA is a small market, but we and others in the industry expect good growth. HCS and secondary screening are an outgrowth of HTS, which has commanded significant attention and resources from pharmaceutical and biotechnology companies over the past decade. Currently, the challenge has moved towards analyses of sub-cellular organization and morphology, and these are major facets of HCS.

