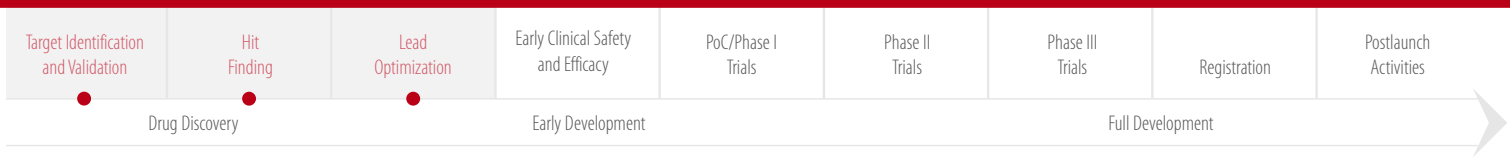

BY DENISE MYSHKO

BIOMARKERS Across Drug Development

As personalized medicine becomes more of a reality, biomarkers are becoming increasingly more important to help identify patients and develop customized therapies.

FAST FACT

THE GLOBAL BIOMARKER MARKET IS ESTIMATED TO BE $20.5 BILLION BY 2014, GROWING AT A CAGR OF 19.7% FROM 2009 TO 2014, DRIVEN BY THE HIGH DEMAND FOR BIOMARKERS IN THE FIELD OF DRUG DISCOVERY.

Source: MarketsandMarkets

Biomarkers have a multitude of applications, such as detecting disease early on, identifying potential drug targets, predicting patient response to medication, and accelerating clinical trials. The promise of biomarkers to shorten drug development time and decrease costs in the long term is likely to act in tandem to spur growth in the biomarker analysis market, which has excellent potential, according to a recent report by Frost & Sullivan.

"Biomarkers are central to an effective personalized healthcare strategy as they play an important role in determining not only the magnitude of the benefit patients will derive from a treatment, but also which patients will benefit," says Hal Barron, global head, product development and chief medical officer, at Roche.

Biomarkers: The Potential

Biomarkers can be used to evaluate the biological response of an investigational product in healthy volunteers in comparison with a target patient population, says Nagaraja Srivatsan, VP and head of life sciences, North America, at Cognizant.

"Robust use of biomarkers is useful to establish the therapeutic effect of investigational compounds in early-phase studies," he says.

The high growth potential of the biomarker market is being boosted by the demand from the baby boomer generation in the United States and from Asia's emerging IT industry, according to a report from MarketsandMarkets. The use of proteomics in biomarker testing and identification has in turn boosted the services for biomarkers. Market players are now focusing on new products and service developments to enhance their commercial portfolios. Strategic collaborations among companies are also increasing biomarker applications in the field of diagnosis and drug discovery.

"Biomarkers will play an increasing role as companies begin to appreciate their value in guiding critical drug development choices and recognize the savings — costs and resources — associated with failed regulatory applications," says Kerri Schoedel, Ph.D., scientific director, clinical pharmacology, at Kendle.

Biomarkers can impact drugs throughout the entire process from drug discovery to market introduction, says Peter Smith, Ph.D., senior VP, nonclinical development sciences, at Millennium Pharmaceuticals Inc.: The Takeda Oncology Company.

"Biomarkers have the potential to impact Phase I dosing and Phase II proof-of-concept clinical trials, as well as play a crucial role in Phase III efficacy/safety trials for early detection of drug toxicity," he says. "The incorporation of biomarkers into the drug development process will improve our understanding of how new therapeutics work and allow for more accurate identification of patients who will benefit from those therapies."

Dr. Smith says strategically planned biomarker evaluations in early-stage trials may allow for the design of more efficient Phase II trials and better screening of therapeutics for entry into Phase III development. He adds that a rational and coordinated approach to the inclusion of biomarker studies throughout the drug development process will be the key to attaining the goal of personalized medicine.

A Frost & Sullivan study found that while biomarker testing in itself is inexpensive, the process of biomarker discovery and assay development is costly. Furthermore, there is a lag between the discovery of biomarkers in the laboratory and commercialization because of major roadblocks in biomarker validation and assay development.

"The science of biomarker discovery and validation will grow as new biological disease targets are discovered," says Brian Sanderson, M.D., medical director, Chiltern Early Phase. "Biomarkers may not just be a single test or assessment but a combination of tests that, when combined, form surrogate markers for disease progression and can be used to affirm a response to therapy instead of more traditional clinical interventions."

He adds that biomarkers will be disease- and perhaps molecule-specific.

"Biomarkers can be used for applications as simple as measuring blood glucose and serum insulin in response to new anti-diabetic agents or measuring routine coagulation parameters in healthy subjects in response to new anti-coagulants targeted for thromboembolic disease," Dr. Sanderson says. "Other uses are for more complicated applications, such as in the use of forearm blood flow measurements to assess vascular response to endothelin antagonists. Newer agent models have been developed to look at anti-inflammatory effects in the skin."

Dr. Smith says a more recent challenge has been to develop biomarkers that can be used to gain earlier and more accurate readings of both drug efficacy and toxicity, as well as evidence confirming mechanism of action.

"This is an area of intense investigation within the industry and regulatory communities," he says. "Our focus on oncologic chemotherapies presents unique challenges, since cancer cells have many processes shared by normal cells."

Biomarkers: Preclinical

Biomarkers are playing an ever-increasing key role in preclinical development, says Alain Stricker-Krongrad, Ph.D., chief scientific officer at Charles River.

"For example, preclinical and clinical assays can be used as biomarkers and can be divided into two categories," he says. "The first category relates to measuring the therapeutic effects of the drug using secondary molecules. We measure effects at the RNA, protein, chemical, cellular, organ, or physiological levels, using

HAL BARRON ■ *Roche*

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validated assays that are tailored to each clinical indication. The second category relates to evaluating the safety risks associated with the drug. For each key organ and each therapeutic area, a defined list of validated assays can be used as biomarkers."

Thomas Jones, Ph.D., senior director, toxicology and pathology, at Eli Lilly and Company, says preclinical toxicology is all about biomarkers.

"A typical toxicology report includes large numbers of data points for each animal on-study ranging from noninvasive measures such as body weight and appearance to minimally invasive measures such as serum chemistries — blood sugar and liver function markers — to highly invasive tissue-level assessments requiring necropsy — organ weights and histopathology," he says. "These standard biomarkers will continue to play an important role in characterizing the effects of compounds on the preclinical test systems; there is also great opportunity in the discovery and application of new approaches to characterize and monitor compound-associated effects."

Dr. Jones says successful development, however, requires preclinical risk identification and management to be tightly coupled to the clinical activities aimed at demonstrating patient benefit.

"The key is to understand what preclinical information should drive decision-making in this regard," he says. "The majority of toxicology-driven attrition is related to findings that are, by their nature, non-monitorable and/or irreversible. While it is difficult to overcome the impact of demonstrating irreversibility of an injury, new approaches can be developed to enhance our ability to monitor adverse tissue effects. New biomarkers could have a great impact in the discovery phase if they could speed and improve compound screening and selection strategies. New biomarkers could also play an important role in drug development by enhancing the characterization of the preclinical safety profile. Even greater value can be envisioned in those cases where the utility of a novel biomarker can be translated into the clinic."

Biomarkers: Phase I Trials

Attrition rates for drugs in discovery and development are currently very high, with less than 10% of tested products entering Phase I trials, according to a report by Thomson Reuters. With increasing costs involved in the drug development process and growing concern that fewer drugs are making it through to the marketplace each year, the pharmaceutical industry is embracing biomarkers as a way of predicting a drug candidate's performance early and with a greater degree of certainty.

Biomarkers are also increasingly playing an important role in Phase I development. They can be used as a way to measure normal biological processes in the body, pathological processes, or the response of the body to a therapeutic intervention.

Jerome Bailey, VP, early phase business center, at Omnicare Clinical Research, says as this area develops, the ability to better identify specific clinical endpoints within Phase I trials will increase.

"We are seeing more trials with biomarkers, especially in the POC trials," he says. "If used correctly in POC trials, the number of patients exposed to compounds that have no beneficial advantage could decrease."

Jamie Dananberg, M.D., executive director of clinical pharmacology at Eli Lilly and Company, says biomarkers have always been important in Phase I studies even before these measures were called biomarkers.

"The fundamental premise of clinical pharmacology is the ability to assess biologic signals in humans that relate to target engagement but are short of clinical endpoints," Dr. Dananberg says. "Without question, a continued focus on excellence in the identification, qualification, and application of biomarkers to Phase I research will be absolutely essential for as long as this type of work is being done."

Murray Ducharme, Pharm.D., chief science officer for Cetero Research, agrees that biomarkers can play an essential role in proof-of-concept trials, which should be done for most compounds.

"They can help make sure that the most appropriate dosing regimens are studied in Phase II and Phase III," he says. "This is extremely important, since one hypothesis for the large percentage failure rate for Phase III trials is that the dosage regimen used in Phase II and III studies are either not efficacious or are toxic."

Mr. Bailey says biomarkers have had a positive and negative impact on the industry.

"As the number of biomarkers are identified and used in clinical trials grows, the number of validated methods required to ensure the accuracy of tests increases," he says. "This has been a positive effect as it increases the market of specialty laboratories; opens new advancement of basic science to correlate research in patient models; and allows physicians to better diagnose or treat diseases. At the same time, it has increased sample collection and the screening of subjects to identify the biomarker."

Biomarkers: Phase II/III Trials

Dr. Smith says biomarkers are potential tools for improving drug development and therapeutic decision-making across the development platform.

"Biomarkers are an objective measure or evaluation of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic, which can increase our understanding of drug, action, efficacy, and safety," he says. "Examining biomarkers may lead to better predictions of response earlier in clinical testing with the goal of reducing the reliance on longer, more costly efficacy trials to predict outcomes of drug candidates. It is believed that the application of clinical biomarkers may result in a personalized medicine approach that more closely aligns biological information —derived from molecular diagnostics — and therapy selection."

DR. JAMIE DANANBERG
■ *Lilly*

A continued focus on excellence in the identification, qualification, and application of biomarkers to Phase I research will be absolutely essential."

DR. KERRI SCHOEDEL
■ *Kendle*

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Mr. Barron says in selecting biomarkers for a clinical trial, a close collaboration between clinical scientists and translational biologists is essential.

"In many respects, identifying an effective diagnostic in Phase II is the greatest challenge facing the industry," he says. "If we are successful in this pursuit, Phase III trials can be conducted in selected patient populations, which will increase the chances of having a positive trial and maximize the benefit patients will have from any given therapeutic."

He says one of the greatest challenges in Phase III trials for the pharma industry is the need to improve the magnitude of clinical benefit and the success rates of any given trial.

"I see predictive (diagnostic) biomarkers as increasingly important factors in this pursuit," Mr. Barron says. "While advances in science should improve our ability to identify the best targets for a given disease, and thus success rates in clinical development, designing clinical trials in a targeted patient population that is most likely to benefit from a drug will also have an enormous impact on this. The successful integration of diagnostics in Phase II and Phase III trials will lead to greater success rates, provide more benefits for patients, as well as generate cost savings for the healthcare system. This is much easier to say than to do, and from an industry perspective, I am concerned that without a robust approach to personalized healthcare, the current pharma business model may not be sustainable." ✦

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KEYNOTE PRESENTATIONS

MONDAY, APRIL 19

Defining Value in Healthcare and Medical Research

MARK B. McCLELLAN, MD, PhD
Director, Engelberg Center for Health Care Reform, Brookings Institution

Former Commissioner of the US FDA and Administrator of the Centers for Medicare & Medicaid Services

TUESDAY, APRIL 20

Industry Transparency in Posting and Publishing Clinical Trial Results

DAVID VERBRASKA
Regulatory Policy and Technical Standards Committee Member, IFPMA

Vice President, Worldwide Regulatory Policy and Intelligence, Pfizer Inc

TUESDAY, APRIL 20

Delivering Value and Driving Advocacy in Medical Publications

STEPHANIE VANCE
The Advocacy Guru
Advocacy Associates, LLC

WEDNESDAY, APRIL 21

Industry and Peer-reviewed Journals: One Editor's Perspective

RITA F. REDBERG, MD, MSc
Professor of Medicine
UCSF School of Medicine

Editor, *Archives of Internal Medicine*

Topics Addressed at this Year's Meeting Include:

- The Publication Soapbox and Black Box
- The Global Outsourcing of Medical Writing—Visions of What "Value" Means in a Flat World
- Making an Impact: New Publishing Approaches to Increasing the Value of Publications
- Defining Value in Healthcare: A New Challenge for Medical Research and Publications
- ISMPP Advocacy Activities
- Advocacy Roundtable Discussions
- Reaching the Nonphysician Provider Through Publications—Insights and Advice From a Nurse Practitioner, Pharmacist, and Physician Assistant
- Journal Editors Panel
- ISMPP Metrics Survey Results

Pre- and Post-Conference Workshops:

- Publication Planning 101, 201, 301, and 401
- Global Publication Planning: Issues and Challenges
- The Manuscript: Challenges and Roadblocks
- Evidence-Based Medicine: Introduction to Principles of EBM
- The Joy of Gap Analysis
- CMPP Review Course
- Effectively Searching Online Databases: PubMed and Beyond
- Regulations & Ethics
- Health Economics & Managed Care—Impact on Publication Planning and Implementation
- Metrics: Practical Application and Experiences

Other Events of Note:

- Sunday Night Welcome Reception
- Tuesday Night Networking Reception
- Interactive Roundtable Discussions
- Member Poster Presentation Assembly
- CMPP Induction Ceremony
- Tuesday Committee Meet & Greet Breakfast
- Wednesday Abstract Presentations and Poster Awards

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