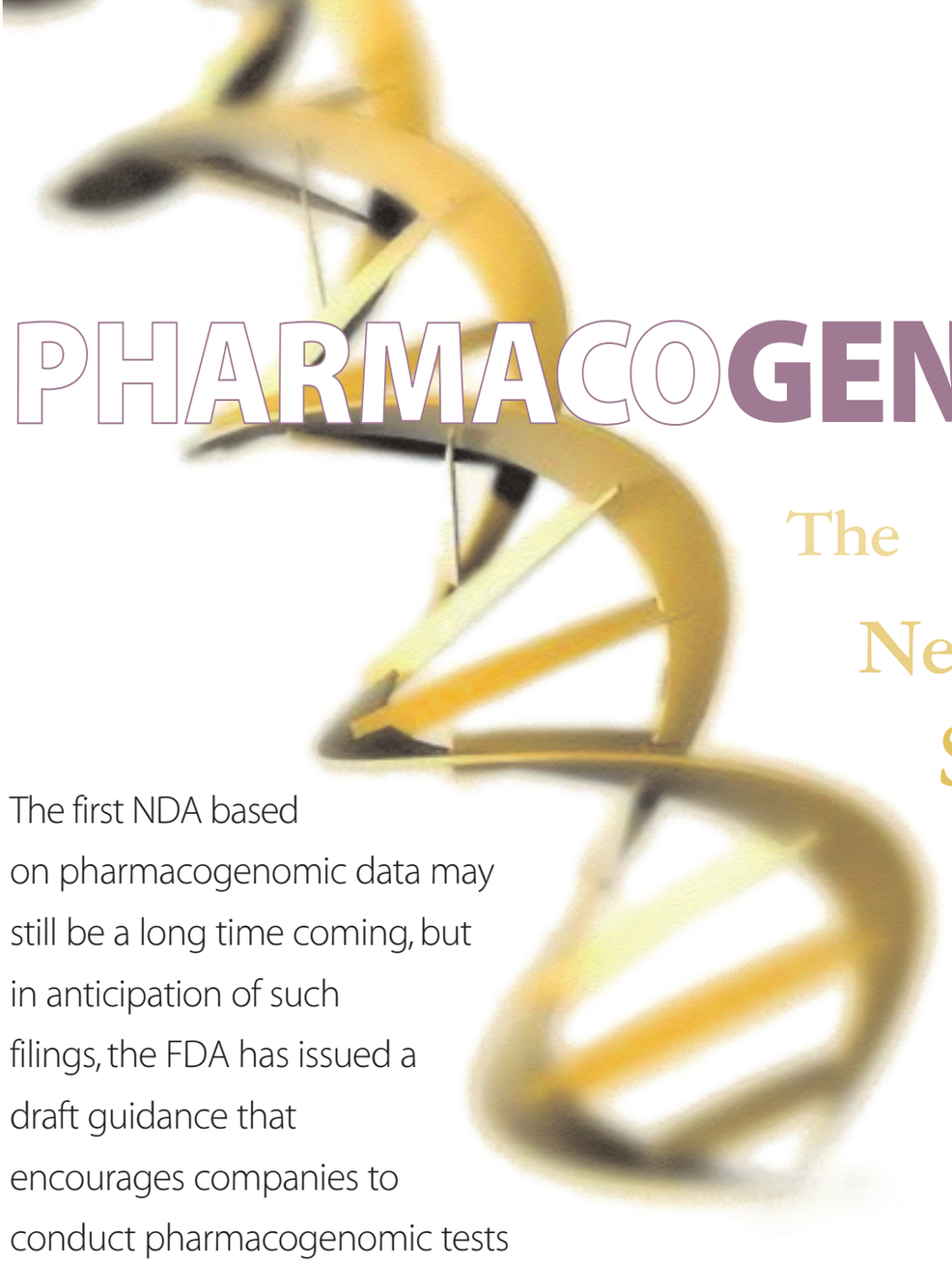


BY DENISE MYSHKO

PHARMACOGENOMICS

The Next Step Forward

The first NDA based on pharmacogenomic data may still be a long time coming, but in anticipation of such filings, the FDA has issued a draft guidance that encourages companies to conduct pharmacogenomic tests during the drug-development process.

Pharmacogenomics will facilitate drug discovery and allow pharmaceutical companies to produce therapies more targeted to specific diseases. Based on pharmacogenomic technologies, companies will be able to create drugs based on the proteins, enzymes, and RNA molecules associated with genes and diseases. Companies will be able to discover potential therapies more easily using genome targets. Previous failed drug candidates may be revived as they are matched with the niche population they serve. The drug-approval process should be facilitated as trials are targeted for specific genetic population groups. This provides a greater degree of success. Targeting only those people capable of responding to a drug will reduce the cost and risk of clinical trials.

But to be able to evaluate anticipated future submissions based on genomic markers and pharmacogenomic data, the Food and Drug Administration needs to develop an understanding of the data implications of this field of research and related scientific issues. On Nov. 3, 2003, the FDA issued a draft guidance for pharmacogenomic data submissions, which is intended: to ensure that regulatory policies and study designs are based on the best science; to provide public confidence in this new field where scientifically appropriate; to facilitate the use of such tests during drug development; and to clarify for the industry what types of pharmacogenomic data to submit. The guidance stresses that submission is voluntary, except in certain cases where test results constitute a known valid biomarker or where the pharmaceutical company will be using such data to conduct trials or for labeling. (See box on page 26 for more information.)

"All of the basic ideas in the guidance are consistent with statements that the FDA has been making for the past year," says Richard S. Judson, Ph.D., senior VP and chief scientific officer at Genaissance Pharmaceuticals. "The agency believes that pharmacogenetics will improve the safety and efficacy of drugs and will be beneficial in the practice of medicine. But the agency recognizes that the technology is still in its early stages and that much work is needed to move the data into routine drug-development practices."

To encourage pharmaceutical companies to start using pharmacogenomic technologies, the

FDA is minimizing the regulatory requirements surrounding its exploratory use.

"We believe that this is a very positive development because it will reduce the uncertainty about the FDA's position on pharmacogenetic data," Dr. Judson says. "Companies are free to test new technologies in programs without the fear of adverse regulatory impact. The FDA benefits by having more companies using technology in more programs and reporting back at least limited information."

Because of the tremendous potential that pharmacogenomics has in the drug-development process, the industry and the FDA are collaborating to better understand the data and the science behind the technology.

"The industry has been looking for an appropriate environment and that's what this document is dedicated toward," says John L. Ryan, Ph.D., M.D., senior VP of experimental medicine at Wyeth Research. "I expect the draft to be positive, but I'm sure there will be some details where there are problems. From all of my discussions with the FDA, regulators are extremely interested in working cooperatively with industry."

According to some experts, while the agency has been looking at pharmacogenomics for about five years, it recognized that the industry was a bit ahead.

"The FDA is now coming up to speed," Dr. Ryan says. "It is my impression that the FDA really wants to learn and is being extremely cooperative."

According to Lawrence J. Lesko, Ph.D., director of the Office of Clinical Pharmacology and Biopharmaceutics, Center for Drug Evaluation and Research at the FDA, the only way to realize the potential of the new technology is to start at the ground floor and share views, encourage informal meetings with the agency, and have workshops.

"It's only through these types of mechanisms that we're able reduce uncertainty," he says.

COMPANIES HAVE BEEN RELUCTANT TO PERFORM TESTS IN WHICH THEY DON'T UNDERSTAND THE SIGNIFICANCE OF THE DATA because there may be unexplained results that cast a shadow on the drug.
Dr. Bruce Seligmann

Dr. Lesko says in November 2003, the clinical pharmacology subcommittee held a meeting to address the integration of pharmacogenetics into new drug development.

"We had presentations from industry, academia, and clinical practice," he says. "The agency is going to use that information as part of another draft guidance."

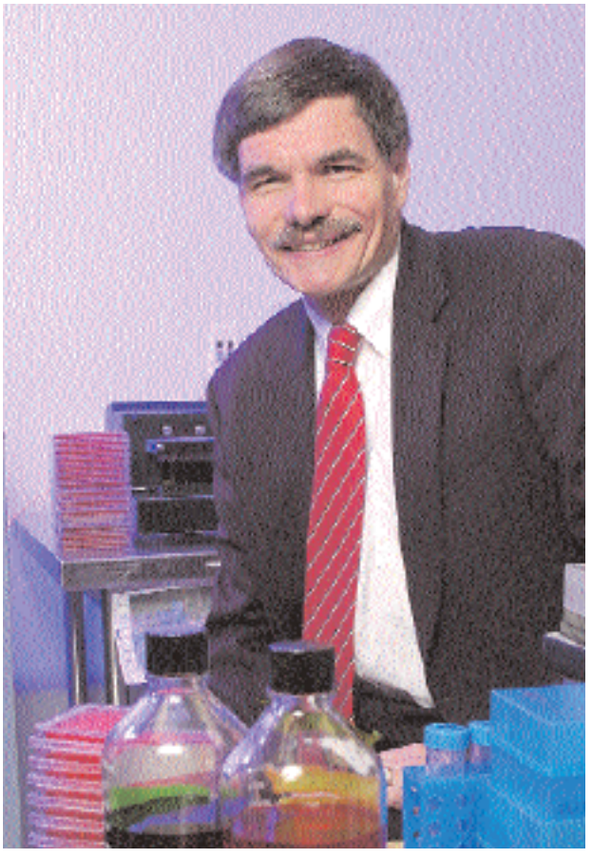
Dr. Lesko estimates that a draft of this second guidance will be issued by June 2004 and will be a general pharmacogenetic guidance that primarily covers new drug development.

"This guidance will address the FDA's thinking about how pharmacogenetics will play a role in the areas of preclinical, clinical pharmacology, and clinical safety and efficacy," he says.

Questions Remain

In the meantime, according to Lee Evans, VP of pharmaceuticals and biomedical informatics at Intrasphere Technologies, there is a lot of science stacking up in the pharmaceutical industry and a great deal of confusion remains about how to make these data work within the constructs of clinical submissions and reviews in the future.

UNTIL THERE IS ENOUGH DATA OUT THERE, WE'RE NOT GOING TO KNOW HOW THIS TECHNOLOGY IS GOING TO HELP PEOPLE. What the FDA wants is for pharma companies to do the experiments and share the data. Then, collectively the industry, the physicians, and the patients can understand where data help or don't help.
Dr. Richard S. Judson



"The November guidance is going to help," Mr. Evans says. "Will it help enough? No. But it gets the ball rolling and provides a forum for industry to get more involved in this important matter."

According to industry experts, one issue that is causing concern for pharmaceutical companies is that in the future the agency might change its mind about how data are to be considered or have a different, independent interpretation of the data.

"The draft guidance raises some questions regarding data submitted but not used as part of the regulatory submission," says Doug Dolginow, M.D., executive VP of pharmacogenomics at Gene Logic. "The way I interpret the guidance is that in the future if a biomarker becomes established or known, then the FDA could go back to the data and determine that the biomarker was relevant to the study."

Dr. Lesko says the FDA guidance will not require additional tests in a case such as this, although regulators will recommend that companies consider additional testing.

"Additional testing would be the company's responsibility," Dr. Lesko says. "When a sponsor submits data through the voluntary path, that's where these data stay. We don't move data out of that path. But once a company recognizes that it has a marker that is important either for efficacy or safety, it's the company's responsibility from a regulatory standpoint, as well as a moral standpoint, to report that data."

"Currently, most pharmaceutical companies are doing exploratory studies," Dr. Ryan says. "The FDA has been clear that as long as a company doesn't try to use pharmacogenomic information to craft a label, the agency will treat the data totally separate from its other regulatory requirements. But if a company wants to design a trial using pharmacogenomic information, it should expect a higher level of scrutiny from the FDA. This is not the case at most companies."

Wyeth does plan to submit pharmacogenomic data, but Dr. Ryan stresses that the information will be for research only.

"We don't have any plans at the moment to submit pharmacogenomic data as part of a package to craft a label," he says.

Another significant issue of concern for pharmaceutical companies is possible liability, says Michael Liebman, Ph.D., chief scientific officer at The Windber Research Institute and former director of computational biology and biomedical informatics at the University of Pennsylvania.

"What happens if later there's some negative effect in the general population and it turns out that the company had information from the experimental data set that suggested that there could be a problem, even if it couldn't be recognized at the time of original data collection?" Dr. Liebman asks. "I don't think the FDA wants to bring this topic up. But this is an area of concern. This voluntary information could potentially hurt companies later on. If I were a pharmaceutical company lawyer, I would say that there is no reason to give the FDA genomic data, even though I think it is for the betterment of society."

James N. Czaban, a shareholder in the FDA practice group at Heller Ehrman White & McAuliffe, says if companies have data that reflect risks that ought to be known by patients and prescribers and they don't put the information in the label they are facing a liability concern.

"The fact that data are from a new and exciting category of pharmacogenomics really doesn't change the baseline consideration: if a company has evidence relating to the safety of a product, it has to decide whether to put it in the label or not," Mr. Czaban says. "Companies that keep information out of the labeling, which could later be argued to be important safety information, run a risk. It doesn't matter if the information stems from a pharmacogenomic study or a study with no genetic component."

A third concern according industry experts, is that the draft is too general.

"What's missing from the guidance are the technical specifications or requirements that a submission should have," Dr. Dolginow says.

Dr. Lesko points out that the final 2004 draft is likely to include more details to clarify certain points. He says there is likely to be better clarity on the definition of biomarkers. In addition, the final guidance is expected to address the decision pathways necessary for submission. The final guidance also will discuss what the agency will do with the data and how it will analyze the data.

"What we intend to do is look at the analysis of the data within the submission to gain experience," Dr. Lesko says. "We will look at the data from a statistical and informatics standpoint and begin to get some idea of what the format of

The Pharmacogenomic Draft Guidance

THE FOOD AND DRUG ADMINISTRATION ISSUED ITS DRAFT GUIDANCE FOR THE INDUSTRY ON PHARMACOGENOMIC DATA ON NOV. 3, 2003. THE AGENCY IS ACCEPTING COMMENTS THROUGH FEB. 2, 2004.

The draft guidance addresses pharmacogenetic or pharmacogenomic tests, including drug absorption, disposition, pharmacodynamics, and response. It does not cover use of genomics in drug discovery or product characterization or use of proteomic data. The guidance explains regulators' current thinking on how pharmacogenomic data fits into the regulatory scheme, especially as regulations were written before the advent of pharmacogenomics.

THE KEY CONCEPTS BEHIND THE DRAFT, ACCORDING TO JANET WOODCOCK, M.D., DIRECTOR OF THE CENTER FOR DRUG EVALUATION AND RESEARCH, WHO LED A WORKSHOP IN NOVEMBER, INCLUDE:

- Pharmacogenomic data submission policies must conform with regulations
- Much of the pharmacogenomic data currently available are not well-enough established scientifically to be suitable for regulatory decision making
- There needs to be a threshold definition of what is a valid biomarker

THERE ARE THREE SITUATIONS IN WHICH SUBMISSION OF PHARMACOGENOMIC DATA ARE REQUIRED FOR AN INVESTIGATIONAL NEW DRUG (IND) APPLICATION:

- Test results will be used for decision making in a clinical trial or in an animal study
- Sponsors are using the test results in an IND to support scientific contentions about a drug
- Test results constitute a known valid biomarker in humans or a known valid biomarker for safety in animals

FOR A NEW DRUG APPLICATION (NDA), SUBMISSION OF PHARMACOGENOMIC DATA WILL BE REQUIRED:

- If data are part of a database to support approval
- Or where results are intended to be part of a product's label

VOLUNTARY SUBMISSION OF PHARMACOGENOMIC DATA IS ENCOURAGED:

- For data that are exploratory
- When results are from test systems where validity of biomarker has not been established

Dr. Woodcock stresses that pharmacogenomic information is for FDA knowledge building. The information will not used for regulatory decision making and will be kept confidential. But, she says, if the FDA learns through multiple submissions that a particular test results in a valid biomarker, additional tests may be required.

"We have an obligation to inform companies if they need to perform additional tests, but it would be through a formal process," Dr. Woodcock said during the workshop. "This is part of our societal obligation. If we find a biomarker that results in a toxicity, part of our obligation is to tell people about it."

Source: The Food and Drug Administration, Rockville, Md. For more information, visit fda.gov.

WITH PHARMACOGENOMICS, THERE IS AN OPPORTUNITY TO INDIVIDUALIZE DRUG TREATMENT. We will start to see a biosignature, similar to a bar code, using the gene of what's happening in a particular patient.

Dr. Scott R. Magnuson

these data ought to be. Eventually, we would like to recommend a format for submitting these data as part of an NDA that is best for the sponsors and that is easiest for us to handle and review."

Over time, he says, the agency plans to look at a number of submissions to find associations between genomic data and other information, for example outcomes data from preclinical or clinical studies.

Finally, the FDA will evaluate how sponsors validate microarrays before making recommendations. Microarrays are sets of miniaturized chemical reaction areas that also may be used to test DNA fragments, antibodies, or proteins. Microarrays are the "gene chips," the tools to determine genomic expression. They allow scientists to analyze the expression of many genes in a single experiment quickly and efficiently. But a standard protocol for microarray data analysis has yet to be established.

At this point, submission of pharmacogenomic data is voluntary because regulators recognize that microarrays are not yet a stable clinical instrument.

"Microarrays haven't gone through any regulatory analysis but they can lead to additional information for research and ideally can protect patients," Dr. Liebman says. "Because of this uncertainty, I suggest that the original data collected be archived because the methods for data analysis are constantly evolving."

"Because arrays are manufactured in different ways, there is little consistency and reproducibility," says Scott R. Magnuson, Ph.D., president and founder of GenUs Biosystems. "I think the FDA will require certain levels of reproducibility. This will put pressure on the various array manufacturers to meet these standards, and it underscores the importance of conducting the experiments properly."

Bruce Seligmann, Ph.D., president, CEO, and chairman of High Throughput Genomics, says because the results from various high-density commercial arrays are not concordant drug companies may be reluctant to perform tests when the data are still very unreliable and difficult to repeat.

"In fact, there may be only a 10% concordant agreement between two arrays from different commercial sources, so out of 500 genes only 50 may be shared between the two methods," he says. "It is not known whether this is because one or both of the methods identify genes erroneously or if they each measure successfully only a subset of affected genes, and thus all genes are relevant and both methods must be used to identify all relevant genes. Thus, high-density array data are unreliable or are certainly very discordant at the very least, requiring careful validation and making comparison of results between methods and labs problematic."

IN THE FUTURE, THE CONCERN IS IF IT TURNS OUT THAT A BIOMARKER BECOMES ESTABLISHED OR KNOWN, then the FDA could go back to the data and determine that the biomarker was relevant to the submission.

Dr. Doug Dolginow

Down the Road

Dr. Lesko says the agency is just beginning to hire additional staff members who will be part of a new interdisciplinary group dedicated to working with pharmacogenomic data. The staff will interact with sponsors; help develop standards for validating genomic assays; and when voluntary submissions come in, lead the review of those submissions from an exploratory standpoint.

"With pharmacogenomic data, there is an opportunity to individualize drug treatment," Dr. Magnuson says. "In a standard trial, there usually is only one way to look at the drug, and this can be very subjective. If we were to have 50 genes that reflected a particular change quite accurately, then instead of having one subjective data point there could be 50 very exact sets of data that contribute to a signal. This is where companies can start to individualize various treatments. Pharma companies can begin to characterize and clarify patient populations."

Additionally, Dr. Judson says pharmacogenomics could address a major problem in drug development: not all patients respond to a drug in the same way. There are varying levels of efficacy for all drugs, and many drugs cause side effects in an unpredictable fashion. A sizeable fraction of this response variability is due to genetic variation between individuals.

"Trying to identify the variance of clinical outcomes based on the genomic profile of patients coming into a hospital is the nirvana of pharmacogenomics," says Vijay Pillai, director, life sciences industry, at Oracle. "The real challenge is to determine, for example, why clinical outcomes are different for two people with very similar profiles."

Pharmacogenetics studies provide data showing how particular genetic markers correlate to varying results, Dr. Judson says. More generally, he says pharmacogenetic data can be used to: understand the reasons for variability in efficacy; understand the reasons for variability in side effects; understand the detailed mechanism of the action of a drug; and better understand the underlying cause of the disease being treated.

"Pharmacogenetic data can be gathered relatively easily as part of trials already being run," Dr. Judson says. "A development team needs to add a few pieces to the trial design, at least for exploratory studies. Trial participants need to give informed consent for genetic analysis, and a small blood sample is needed from each subject. Because blood already is drawn in most trials, this is usually not a problem. More importantly, a set of hypotheses needs to be developed that will

WE INTEND TO LOOK AT THE ANALYSIS OF THE PHARMACOGENOMIC DATA within the submission itself to gain experience.

Dr. Lawrence J. Lesko

guide the gathering of genetic data. Genotyping and statistical analysis of genetic data can be carried out using procedures that are coming into wide use."

Dr. Magnuson says pharmacogenomic testing could reduce drug-development times because pharmaceutical companies will get a much clearer answer about how a drug works, how effective the drug is, and what patient segments the drug can be applied to. All of these factors provide a much better profile in terms of how a drug is metabolized.

Dr. Lesko says the agency has other initiatives in the works, including evaluating how pharmacogenomics can be applied to drugs on the market. As for already-approved drugs, Dr. Lesko says there won't be a guidance issued.

"We're going to continue to look at drugs that have a high incidence of adverse events, that are widely used, and that have narrow therapeutic ranges," he says. "If a drug has those attributes, then there is a possibility that genetics can guide therapy."

But he stresses in these cases genetic testing would not be done to define a product's patient population but as a tool to appropriately adjust the dose for patients.

"We're trying to avoid adverse events by lowering the dose in the appropriate case and keeping the dose tailored," he says. "In other words, this is about developing testing for drug dosing. And this shouldn't frighten the industry at all."

Mr. Czaban predicts that the FDA may, with experience, eventually develop more specific guidances in relation to genetic data for particular indications or particular classes of drugs.

"The FDA's November guidance is a measured first approach to an interesting and potentially promising area," he says. "There was a large degree of excitement about the mapping of the genome and many discussions about how this was going to revolutionize modern medicine. The reality is that while it may do that, it's not going to be as soon as people once thought. Science can move slowly." ✦

PharmaVoice welcomes comments about this article. E-mail us at feedback@pharmavoice.com.

Experts on this topic

JAMES N. CZABAN. Shareholder in the FDA practice group, Heller Ehrman White & McAuliffe LLP, Washington, D.C.; Heller Ehrman White & McAuliffe is a law firm with more than 700 attorneys and professionals in 12 offices nationwide and abroad. For more information, visit hewm.com.

DOUG DOLGINOW, M.D. Executive VP of pharmacogenomics, Gene Logic Inc., Gaithersburg, Md.; Gene Logic is a contract service provider to pharmaceutical, biotechnology, and institutional researchers worldwide combining experience in sample collection and data analysis of gene-expression information and expertise in preclinical safety and pharmacology studies and clinical-trial consulting. For more information, visit genelogic.com.

LEE EVANS. VP, pharmaceuticals and biomedical informatics, Intrasphere Technologies Inc., New York; Intrasphere Technologies is a technology consulting, software development, and systems integration firm that provides enterprise solutions in the areas of business intelligence, document and content management, IT strategy, enterprise integration, and enterprise portals. For more information, visit intrasphere.com.

RICHARD S. JUDSON, PH.D. Senior VP and chief scientific officer, Genaissance Pharmaceuticals Inc., New Haven, Conn.; Genaissance is a leader in the discovery and use of human gene variation for the development of a new generation of DNA-based diagnostic and therapeutic products. For more information, visit genaissance.com.

LAWRENCE J. LESKO, PH.D. Director, Office of Clinical Pharmacology and Biopharmaceutics, Center for Drug Evaluation and Research, Food and Drug Administration, Rockville, Md.; the FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, food supply, and cosmetics. For more information, visit fda.gov.

MICHAEL LIEBMAN, PH.D. Chief scientific officer, The Windber Research Institute, Windber, Pa.; WRI is a state-of-the-art biomedical research facility that has taken on the challenge of finding cures for genetic and metabolic diseases. For more information, visit wriwindber.org.

SCOTT R. MAGNUSON, PH.D. President and founder, GenUs Biosystems Inc., Chicago; GenUs BioSystems provides outsourced gene expression experiments using bioarray technology in the emerging field of systems biology. For more information, visit genusbiosystems.com.

VIJAY PILLAI. Director, life sciences industry, Oracle Corp., Reston, Va.; Oracle, with headquarters in Redwood Shores, Calif., is an enterprise software company and offers life-sciences solutions for discovery, clinical trials, manufacturing, and sales and marketing. For more information, visit oracle.com.

JOHN L. RYAN, M.D., PH.D. Senior VP of experimental medicine, Wyeth Research, Cambridge, Mass.; Wyeth, based in Madison, N.J., is a research-based, global pharmaceutical company responsible for the discovery and development of some of today's most innovative medicines. For more information, visit wyeth.com.

BRUCE SELIGMANN, PH.D. President, CEO, and chairman, High Throughput Genomics Inc., Tucson, Ariz.; High Throughput Genomics discovers and develops molecular biology-based processes that improve the efficiency and productivity of drug discovery. For more information, visit htgenomics.com.