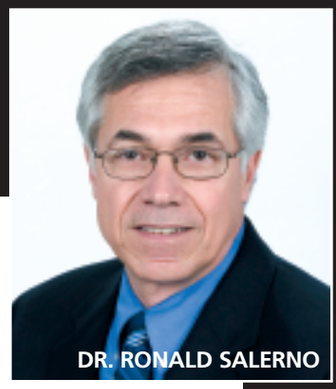
Contributed by Dr. Ronald Salerno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PHARMACOGENOMICS ADVANCING THE SCIENCE

Last spring's Drug Industry Association (DIA) workshop on pharmacogenomics reflected a much more mature, developed environment than previous workshops, paralleling the recent advances in the field. As an industry, we continue to address many concepts, such as how to use genetic information to identify biomarkers or how to validate a genetics-based diagnostic for a drug. But voluntary information sharing between industry and the FDA is helping us think collectively about how we can overcome hurdles and identify requirements. As the workshops continue, we will become even more efficient in seizing upon this new paradigm of drug development. It is a science-based approach to predictive drug therapy in individual patients. The new way will improve the benefits and reduce the risks of new drugs while increasing the rate of successful clinical trials.

RETROSPECTIVE STUDIES

One of the more interesting concepts discussed at the workshop centered on the evolving feasibility of retrospective pharmacogenomic studies. In 2003, when we raised the possibility of value in retrospective analysis, the resounding reaction was "no way."

Now questions are being asked, such as: How do we make it work to provide scientific evidence? And can it stand alone, or would we still need a confirmatory trial?

Certainly, arguments can be made both ways. Now we use retrospective analysis to generate a hypothesis for a future trial. But if a clinical trial is completed, DNA collected, and the retrospective analysis confirms a correlation between drug response and outcome, the question arises: Can the drug be labeled for the subset of patients without doing an additional trial or trials?

The sentiment among workshop participants was that a confirmatory prospective trial would probably still be necessary, but there is a good chance it would be much smaller and shorter in duration and conducted in only a subgroup with a particular genotype (and therefore would be less costly).

But what about trials for labeling changes versus for full NDAs? The value of a retrospective study is that it would likely not stand alone for a label change but, again, would be supported with shorter, smaller prospective clinical designs for statistical confirmation.

Even some retrospective analyses, however, need to be considered prospectively. For example, retrospective analyses on half of the subjects in a late-phase trial may find interesting associations that would be used to predict the response in the remaining subset of patients when the statistical plan was prospectively defined.

That raises the next question: How much evidence is needed to correlate genetic classifiers with clinical outcomes?

COLLABORATING FOR SUCCESS

Our challenge now is how to better define when a biomarker becomes a surrogate for a clinical outcome and how it will become a surrogate for a clinical outcome.

To answer that question, the workshop focus needs to be on applications and use of genomic biomarkers. This fall's DIA workshop did just that by sponsoring, with the FDA and pharmaceutical organizations, a workshop evaluating the use of safety and efficacy genomic biomarkers to transform the drug development process.

One of the presentations by the FDA highlighted the experience and value of the several voluntary genomic data submissions of genomic clinical trial biomarker data. This collaborative effort between the FDA and industry has been called an intellectual handshake; each learns from the other throughout the process for the advancement of science and, eventually, for better treatment for the individual patient.

A few years ago, the industry was very hesitant to voluntarily submit pharmacogenomic data to the FDA because of concerns about regulatory impact, privacy, and data security. While there were, surprisingly, a few workshop participants in April who still voiced wariness, the industry's level of comfort and trust in the FDA is greater now. In fact, the process allows the FDA to learn multiple ways to analyze data. While the FDA does not share specific information about companies, it does provide back to the industry a general idea about good methods for analyzing data, which is an overall benefit to the industry.

Once the next level of guidance is in place (qualification and validation of genomic classifiers and biomarkers), the next concerted pharmacogenomic effort will be to develop better diagnostics for biomarkers and bring the resulting diagnostics all the way through the process from early discovery to labeling claims. That way, patients who fit a particular genetic profile for which a drug is targeted can be identified and placed on the best therapy.

From there, physicians will need to be educated about the use of pharmacogenomic diagnostics and the details of the labeling so that these tests are used. For example, pharmacogenetic tests are available for the cytochrome p450 enzymes, but they are underused because of a lack of education on how to apply the results to existing drug therapies to determine the best dose for safety and efficacy.

Industry overwhelmingly has a goal of getting safer, more efficacious drugs to market more quickly. The old way of developing drugs is not paying off, with the oft-quoted milestone of a 50% failure rate in Phase III and now even an 80% failure rate in Phase II. Biologics, which are mechanism-based, have been succeeding at a much higher rate, which indicates that their development represents a better way. The new points of discussion and maturity of the discourse indicate that we, as an industry, are on our way to realizing this new paradigm in drug discovery and development for personalized medicine.

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