

4th US FDA–Drug Information Association pharmacogenomics workshop, held 10–12 December, 2007

The 4th US FDA/Industry workshop, in a series on Pharmacogenomics, was on 'Biomarkers and Pharmacogenomics in Drug Development and Regulatory Decision Making' and was held on December 10–12, 2007 in Bethesda, MD, USA, with clear objectives to continue the dialogue that began in 2002 for enabling the use of biomarkers and pharmacogenomics in drug development and regulatory decision-making. This brief commentary will highlight the major topics and outcomes discussed at this meeting that was jointly sponsored by the FDA, The Pharmacogenomics Working Group (PWG), The Pharmaceutical Research and Manufacturers of America (PhRMA), The Biotechnology Industry Organization (BIO) and The Drug Information Association (DIA).

KEYWORDS: biomarkers, drug development, regulatory decision making

Perspectives from the workshop chairs

Dr Felix Frueh opened the meeting with an introduction to the topic, a perspective of the history of genetics and the translation of the field into the realm of clinical practice. In particular, the view was expressed that we are able today to achieve great impact using novel biomarkers to make clinical decisions as we start to understand how genetics, and other factors, influence physiology and pathophysiology. This introduction was followed by an overview of the agenda, pointing out that much emphasis was put on the breakout sessions and time for providing summaries of these sessions. These sessions are also representative of the topics of this series of articles: the proceedings published here are in order of the case studies presented and the discussion that followed.

Progress of pharmacogenomics in drug development

Dr Ron Salerno opened the plenary session of this 4th workshop on pharmacogenomics by noting the challenging environment the pharmaceutical industry is now facing. He highlighted the key characteristics of a successful drug or biologic as:

- Innovative;
- Fill an unmet medical need;
- Provide a value-added label (good benefit:risk ratio) that is sustainable;
- Differentiate from competitor drugs on the market or in development.

One way to assure differentiation of a drug is to apply pharmacogenomics and pharmacogenetics during drug development to enable clinical and regulatory decision-making. This approach should include developing pharmacogenomics testing along with biological and pharmaceutical development. The combination of targeted treatment with diagnostic tests would clearly differentiate the most appropriate drug for optimal effectiveness and safety and, therefore, yield the highest benefit:risk ratio outcome.

In the overview of the previous workshops held in 2002, 2003 and 2005, the progress of collaboration between the US FDA and industry over the last five years was evident. Most significantly, the collaboration led to innovative guidance to a new process for submission of genomic data to the agency outside the review process, known as the 'Voluntary Genomic Data Submissions' process. Over the last five and half year period, a better understanding of what genomic and genetic data should be submitted and how it would be reviewed by the agency was obtained, to enable better clinical and regulatory decision-making. The challenge in 2008 is to develop a pharmacogenomic/biomarker strategy for implementation in drug development using current technology and regulations as tools. This workshop sought perspectives and recommendations from all pharmacogenomics stakeholders – drug and diagnostic industries, regulatory experts, payers, consortia and institutes, physicians and ethicists.

Pharmacogenomics – leading the way

Dr Larry Lesko (Director, Office of Clinical Pharmacology, Center for Drug Evaluation and

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Research [CDER], FDA, MD, USA) presented the keynote message on how to lead the way in incorporating and accepting genetics in drug-development and medical practice. He summarized the current environment and opportunities for drug development in the genomic age, and discussed successful drug development key drivers that include industry, regulators, politicians, payers and the public who all want safer and more effective drugs for untreated conditions. The call for personalized medicine is the way for improving drug development and treatment, and the government is providing the push, as personalized medicine is now one of the top priorities at the Human Health Services (WA, USA). Drug companies are now realizing the medical and commercial value of targeted therapy, such that they are changing their drug development paradigms to incorporate genomic biomarkers early in discovery through Phase III.

Dr Lesko reiterated the commitment of the FDA shown by continuation in generating new guidance. He also emphasized the value of diagnostic assays that improve patient's health and provide alternatives to therapy, and hence, will be reimbursed by payers as more pharmacoeconomic studies and analyses conclude that pharmacogenetic testing is cost-effective and leads to faster, safer and better drugs. For personalized medicine to become a reality, mechanism-based science needs to lead the way in finding useful biomarkers for clinical evidence, which links target–disease–drug. The FDA will lead the way in the near future to safer drugs, as new legislation (FDA Amendments Act of 2007) provides new risk evaluation and mitigation strategies for post-marketing drugs.

Regulator's pharmacogenomics guidance

Two additional key regulatory presentations were delivered on the last day of the conference. Dr Janet Woodcock (Director, CDER, FDA) discussed the agency's views on 'Biomarkers on the Critical Path to New, More Personalized Medicines'; and Dr Bruno Flamion (Chair, Scientific Advice Working Party, The Committee for Human Medicinal Products-European Medicines Agency [CHMP-EMA] and Vice Chair, Pharmacogenetics Working Party, EMA), who described pharmacogenomic guidance and activities at the EMA.

■ FDA leading the way

Dr Woodcock described the current use of biomarkers in early and late product development

and decision-making, as well as the use of efficacy and safety surrogate end points. She pointed out the current limitations of most drug-development programs, including the fact that many people who take the drug do not benefit. Dr Woodcock emphasized the need for evidence-based approaches to distinguish response subsets and at-risk groups.

Since controlled clinical trials do not predict outcomes in the market for individual patients, new diagnostics may improve predictability as new biomarkers could define who should be treated, how and with what. Therefore, Dr Woodcock believes 'it is imperative that biomarker development be accelerated along with therapeutics'. In addition, Dr Woodcock proposed scenarios for drug–diagnostic codevelopment; especially noting that a marker required to be used with a new drug should also be FDA-approved at the time the drug is approved. She also discussed the importance of natural history studies of disease that provide the new candidate biomarkers and quantitative disease models to determine the impact of drugs on disease course using trial modeling and simulation studies.

Given the importance of biomarker discovery and lack of biomarker development models, the FDA has launched several initiatives. For example, the Secretary's initiative on Personalized Healthcare includes work on genomic biomarkers, an Oncology Biomarker Qualification Initiative includes a FDA–National Cancer Institute (NCI)–Centers for Medicare and Medicaid Services (CMS) consortium to qualify new cancer biomarkers, and the first project involves fluorodeoxyglucose positron emission tomography in non-Hodgkin's lymphoma. As new public–private biomarker consortia are formed, successful biomarker qualification will move from the uncommon to the common. Thereby, all parties (government, industry, insurers, academia and patients) will greatly benefit.

■ EMEA leading the way

Dr Bruno Flamion summarized EMA's proactive and actual experience in the pharmacogenomics and biomarker areas. Dr Flamion reported that 22% of the new oncology products approved over the last 7 years had pharmacogenomic implications. Examples of pharmacogenomic labeling were discussed relative to US labeling. The EU requires testing to be performed in a specialized laboratory; whereas the FDA requires the diagnostic tests to be approved.

Dr Flamion summarized the available guidelines and position papers or reflection papers that address pharmacogenomic issues. For example, this year alone, three reflection papers were published on use of pharmacogenomics and pharmacogenetics in pharmacokinetic evaluations and in cardiovascular clinical intervention trials. The EU now requires studies on the effect of pharmacogenomics on pharmacokinetic evaluation of a new chemical entity, if the genetic variation is likely to translate to important differences in exposure or its active or toxic metabolites. The guidance further recommends that samples from the early Phase I studies be stored to allow retrospective analyses during drug development. This reflection paper addresses options for dose adjustment including genotype or phenotype dosing, and even gene-based dosing if variability in drug action is undesirable. The EMEA further recommends dedicated genomic-association studies based on follow-up of cohorts of treated patients and testing candidate genes after appropriate power calculation. Any association study would need to be confirmed in a second trial, possibly using allele-enriched designs.

Dr Flamion also summarized the positive outcomes of pharmacogenomic briefing meetings held with the CHMP and in some cases jointly with the FDA. Guidance on *post-hoc* subgroup analysis for patient stratification and *ad hoc* designs for disease stratification and enrichment design were discussed. Dr Flamion pointed out that the use of biomarkers as surrogate end points for confirmatory trials is currently determined on a case-by-case basis. In addition, the CHMP was due to launch the first quarter of 2008 a qualification process of innovative development methods for pharmacogenomics/biomarkers for a specific intended use. Further, the CHMP is collaborating with the Critical Path Institute (C-Path) and the EU's Innovative Medicines Initiative involving pharmacogenomics in an effort to lead the way for better drug development.

Payers perspectives

This workshop differed from the previous workshops in that it highlighted the important stakeholder roles of pharmacy benefit managers and healthcare plans of employers. Dr Robert Epstein (Chief Medical Officer, Medco Inc.), presented the potential benefits of pharmacogenomics to pharmacy-benefit management (PBM). Organizations providing pharmacy benefits are usually self-insured employers,

insurance carriers, health maintenance organizations, retirement systems, unions or governments. PBM services these groups to design treatment coverage policy, set pricing and utilize management programs for formularies, coverage, distribution, utilization and communication. Dr Epstein believes pharmacogenomics could potentially bring greater precision to drug-benefit management. He discussed the drug-utilization review process, which links all US pharmacies in real time and provides messaging on longitudinal drug-history at the patient level. Drug-utilization review modules look at contraindications, dosing and incorrect use of drugs. Pharmacogenomic interaction modules could be developed for new drugs to access metabolizing-enzyme activity. Drug-utilization programs decide terms of coverage – indication, dose and duration. For example, prior authorization is needed for growth hormones, oncology treatments, quantity duration of treatment and monitoring programs. Pharmacogenomics can potentially help differentiate and gain formulary status in a way similar to the trial and error antibiotic selection that is used before follow-up with culture to determine drug need.

Dr Epstein reported that patients appropriate for pharmacogenetic tests could be identified and arranged by the PBM, thereby adding value to the test results. He discussed the Medco/Mayo pilot study on warfarin usage. The study is designed to determine if testing for warfarin-metabolism rate may reduce risk for hospitalization associated with hemorrhage or thrombosis, and whether the number of dose adjustments could be reduced. A process for patient identification, contacts, intervention and follow-up was developed. Enrollment is proceeding and patient and physician feedback is very positive. The net benefit of pharmacogenetics is expected to decrease healthcare costs. However, Dr Epstein cautioned that the adoption of healthcare technology into routine clinical practice lags behind the clinical evidence by many years.

Shelly Hoffman presented on the challenges and solutions to the coverage of pharmacogenomics and biomarkers by the Health Care Plan at General Motors (GM). Ms Hoffman reported that GM spent 4.8 billion in 2006 to cover 1 million employees, and that healthcare is a competitive global issue. Retiree healthcare costs for Toyota are less than 1 cent compared with every dollar GM spends. GM relies on their vendors – healthcare plans and pharmacy benefit managers to provide rationale for

coverage. The appeal of pharmacogenomics is the potential to reduce wasteful spending on drugs. It could provide direction on predictive use of a drug, dose and duration of therapy, and on the selection of a drug. What is not useful to GM healthcare are new technologies that do not reduce overall adverse outcomes, improve efficacy or reduce costs; however, the opportunities are there to pursue.

Consortium & institute perspectives

C-Path is a nonprofit, publicly funded institute founded by FDA, Stanford Research Institute (SRI) International (CA, USA) and the University of Arizona, AZ, USA. The Critical Path Initiative (CPI) has listed identification and qualification of safety markers as an opportunity to accelerate and streamline the development of novel medicinal products.

Dr Jacky Vonderscher (Novartis) presented the regulatory considerations of the C-Path Predictive Safety Testing consortium (PSTC). The goals of the PSTC include:

- To demonstrate cross-qualification of preclinical animal model biomarkers;
- To generate and submit an FDA/EMEA qualification package;
- To provide early indicators of clinical safety in drug development and post-marketing surveillance and;
- To develop new tools to assist in regulatory decision-making.

Both the FDA and EMEA participate as advisors/observers in this process. There are working groups in five areas, nephrotoxicity, hepatotoxicity, vascular injury, carcinogenicity and myopathy. Genomic signatures are useful for assessing nongenotoxic carcinogenicity and identifying candidate biomarkers. An early success is the program for drug-induced kidney injury biomarker qualification. This was the first submission of its kind under the FDA voluntary data submission process to both the FDA and EMEA on June 15, 2007. The PSTC plan is to seek a rolling qualification process for the biomarker 'as fit for use', thereby filling the need for accessible biomarkers qualified for regulatory decision-making, which enable drug development.

Dr Raymond Woosley (C-Path) presented an update on C-Path's biomarker and pharmacogenomics projects describing potential drug development and companion diagnostic paths in 2010 for personalized medicine.

Dr David Jacobson-Kram (Office of New Drugs, CDER, FDA) presented the potential of molecular safety biomarkers to predict carcinogenicity and illustrated the promise of omics technology in improving detection of drug carcinogenicity.

Breakout session topics

Several pharmacogenomic topics and issues were the focus in the workshop breakout sessions.

Efficacy and safety case studies were presented to generate discussion for what is a sufficient evidence-base to support the effective use of novel, pharmacogenomic biomarkers. Other case studies looked at what pharmacogenomics data may be included in a US drug label, and more particularly, what sections of the label. Another session addressed the development of a new drug/biologic and a diagnostic test simultaneously to label the indication and use of the drug. The impact of both early and late development of biomarker testing on the drug company, the diagnostic manufacturer, clinical laboratories and regulators was addressed. Questions were raised on how to address label updates, surveillance, clinical practice and legal liability of post-marketing safety reports; for example, how can biomarkers be used as predictors of clinically significant toxicity of adverse event susceptibility after marketing? Post-marketing databases will need to capture drug-exposure data, biomarker testing and relevant clinical outcomes. Also, a session focused on the payer perspectives of coverage and implementation of pharmacogenomics, and the potential benefits of pharmacogenomics to pharmacy benefit management.

Potential growth of pharmacogenomics

The potential growth of pharmacogenomics in drug development and therapy remains high. More and more stakeholders are assessing and utilizing the potential strength of this tool as the foundation for personalized medicine and efficient drug-development and treatment in the future. There is a strong sense that the current paradigm of one-drug-fits-all will not sustain the changing environment in the medical community. All the stakeholders are rethinking the progress made over the last 5 years, and are looking for competitive advantages. The next wave of successful blockbuster drugs is likely to be targeted drugs with diagnostic testing that captures the majority of market share. Companies who focus on targeted

therapy now will have opportunities in the near and far future. This vision requires effective short- and long-term strategic planning for successful implementation.

Future perspective

The meeting was seen as a big success and enthusiasm was expressed about the progress made over the last few years. However, important aspects were encountered that need to be addressed in the near future. For example, consistency in clinical trials should be achieved to enable and facilitate meta-analysis of multiple small trials, it was recommended that large studies should be performed early, to learn as much as possible, and confirmed in smaller studies later, and it was mentioned that clinical trials should be performed in real-life settings rather than in artificial settings, including randomized, controlled trials. It was criticized that updates of drug labels with genetic information are not providing enough guidance on how the information should be used, and it was mentioned that only actionable information should be included in the label. A big discussion evolved around the topic of drug-test codevelopment: still, the FDA has not yet issued (draft) guidance on this topic, a highly anticipated document by

industry. Importantly, the issue of comparative information was raised as a critical aspect of future activities to ensure that such comparative information is derived based on biomarker data and not solely by comparison of two drugs without additional information.

Taken together, the two and a half days revealed insights into current and future activities that will no doubt lead to better and safer drugs that are characterized in a fashion that will allow physicians and patients to make educated treatment decisions. Until we arrive there, we have a long to-do list, and many of the items on this list have been identified and discussed at this conference. The summary articles of the breakout session published in this journal are addressing some of these findings in more detail.

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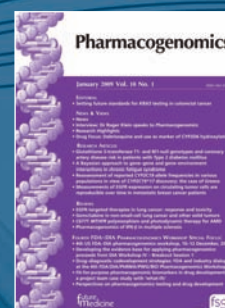
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