

# Why pharmacogenetics is important to Pharma

The field of genetics and its applications have seen rapid and continuing growth since the completion of the sequencing of the human genome in 2001. To understand the importance of this topic to the biopharmaceutical industry, one needs to start at the sharp end – the delivery of cost-effective new medicines of value to patients. Pharmacogenetics is the study of the genetic basis of varying individual responses to medicines (see Box). It represents a case where economics and patient benefit come together.

In an increasingly cost-constrained healthcare market, demonstrating cost-effectiveness has now become the so-called fourth hurdle of drug development.<sup>1</sup> Many countries are now putting into place flexible pricing structures, with reimbursement only being given to those patients in whom the medicine can be shown to be effective. For the biopharmaceutical industry, financial reward is being ever more closely linked with the clinical value obtained by the patient.

Pharmacogenetics is one of a number of emerging scientific fields, along with expression profiling, imaging and blood biomarkers, that offers the potential for a more 'personalised' approach to healthcare with improved predictability of response and increased confidence of reduced side-effects. This ability to provide more objective data and greater certainty in response will strengthen cost-effectiveness claims, and increase the likelihood of reimbursement and extended product lifecycles. This is exemplified by the antiretroviral treatment, abacavir.

Abacavir is an effective antiretroviral treatment against infection from the human immuno-deficiency virus (HIV). Its use has been limited by a severe skin-hypersensitivity reaction that occurs in 5 to 8% of white Caucasian patients. Two retrospective pharmacogenetic studies found a genetic variant within the HLA-B\*5701 gene to be highly associated with this severe adverse drug reaction. A subsequent prospective study evaluated the cost-effectiveness of HLA-B\*5701 screening prior to prescribing abacavir and demonstrated that avoiding prescribing the medication in HLA-B\*5701 positive patients significantly reduced the hypersensitivity reaction.<sup>2</sup> HLA-B\*5701 testing is now included as part of the drug label and required prior to prescribing abacavir in the UK and is recommended in the US.

The use of companion diagnostics and the need for diagnostic co-development as part of clinical drug development are predicted to become increasingly necessary to derive the full potential value from a pharmacogenetics approach.<sup>3</sup> Companies will need to have the diagnostic data package ready for regulatory co-approval and launch. In the case of abacavir, a test for HLA-B\*5701 has been available for some time.

Taking a step back into the clinical development path, pharmacogenetics is recognised by regulatory authorities worldwide as offering a solution for improving the effectiveness and efficiency of drug development. Both the US Food and Drug Administration (FDA) and the European Medicines Evaluation Agency have issued pharmacogenetic guidance documents and reflection papers. More papers are at the consultation stage for publication in 2010 [FDA: <http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/default.htm>; European Medicines Agency: [http://www.emea.europa.eu/htmls/human/mes/emerging\\_technologies.htm](http://www.emea.europa.eu/htmls/human/mes/emerging_technologies.htm)]. The coming together of global regulatory thinking is represented by pharmacogenetic guidance published by The International Conference on Harmonisation (see Box).

At the heart of pharmacogenetics is an increased understanding of drug response, reducing noise and increasing homogeneity in the clinical trial population. It provides another marker or another window to increase understanding of a drug response profile and the patients for whom it works best with the least side-effects. This can be particularly important at the proof of concept stage of a compound's development because it can increase confidence in a positive efficacy signal.

Application of the right pharmacogenetic strategy early in the clinical development path is essential in order to gain the value of pharmacogenetics. The question is: how does industry acquire the necessary knowledge and experience? Each company needs to decide its level of commitment for applying the emerging science to get the best out of its pipeline and meet the growing expectations of regulatory authorities and healthcare providers for the demonstration of cost effectiveness. What is certain is that no company involved in clinical drug development can afford to ignore pharmacogenetics and the potential value it offers.

**Pharmacogenomics** and **pharmacogenetics** have distinct meanings but are often used interchangeably:

**Pharmacogenomics** is defined as: *The study of variations of DNA and RNA characteristics as related to drug response.*

**Pharmacogenetics** is a subset of pharmacogenomics and is defined as: *The study of variations in DNA sequence as related to drug response.*

*Source: International Conference on Harmonization (ICH) - Guidance for Industry: E15 Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. April 2008*

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*References: <sup>1</sup>Taylor RS, Drummond MF, Salkeld G and Sullivan SD. Inclusion of cost-effectiveness in licensing requirements of new drugs: the fourth hurdle. *BMJ* 2004; 329: 972-975. <sup>2</sup>Mallal S, Phillips E, Carosi G, et al. HLA-B\*5701 screening for hypersensitivity to abacavir. *N Engl J Med* 2008; 358: 568-79. and Hughes R, Spreen WR, Mosteller M et al. Pharmacogenetics of hypersensitivity to abacavir: from PGx hypothesis to confirmation to clinical utility. *The Pharmacogenomics Journal* 2008; 8: 365-374. <sup>3</sup>Diagnostics 2009: Moving towards personalized medicine. PricewaterhouseCoopers report (<http://www.pwc.com/us/en/healthcare/publications/diagnostics-2009-moving-towards-personalized-medicine.html>)*