Dr Elizabeth Foot, CEO of London Genetics, argues that biomarker-driven drug development is the only way for biopharmaceutical companies to survive the changing face of healthcare, and outlines the three essentials for the successful development of targeted drugs. Comments are based on a paper given at the BioStorage Technologies first annual Global Sample Management Benchmarking Symposium, Germany, September 15 2010.

The idea that pharma will lose revenues as it turns away from the blockbuster model towards the development of nichebusters has undoubtedly caused fear for the industry, but this change should be seen for what it truly is – an advance in the science of drug development that will not only significantly improve patient care, but also bring economic rewards.

The goal of clinical development has always been to identify those patients likely to derive most benefit from a given drug with a particular mode of action, and with the development of biomarkers, the tools are now available to predict more effectively who these patients will be.

The drivers to identify biomarkers and develop targeted medicines are getting stronger. Regulatory approval may still be the key milestone for any new medicine, but the final hurdle to market increasingly lies with the payors and reimbursement authorities. In a move away from free market pricing, flexible pricing structures are now being put in place or are under discussion in many countries, with reimbursement only being given for those patients in whom medicines are shown to be cost effective. The result for the biopharmaceutical industry is that financial reward is ever more closely linked with the clinical value obtained by the patient.

Regulators have also been pushing this approach and encouraging and guiding pharma companies on how to incorporate biomarker approaches into clinical development plans. Their willingness to discuss outside the main regulatory path is shown by the Voluntary Exploratory Data Submissions for the FDA (VXDS), and Scientific Advice Working Party and Pharmacogenomic Working Party for the European Medical Agency. The VXDS and PGxWP further offer the opportunity for a common forum across agencies including the Pharmaceuticals and Medical Devices Agency in Japan.

Indeed there are increasing numbers of guidances and white papers now available or currently out for consultation (see Table 1), the most recent being from the FDA, which earlier this year released for comment guidelines for the development of targeted drugs and diagnostics, further supporting the central role of stratified approaches into the clinical development process right from the earliest days of clinical planning.

The Three ‘Cs’ of Biomarker Development

No Samples, No Science

Pharma should take these opportunities and work with regulators early in development to discuss and gain advice on issues such as biomarker strategy, clinical design, what kinds of tissue samples they should be collecting, and which analyses should be conducted. The big questions under discussion are how to identify robust biomarkers efficiently, how to build accurate biomarker hypotheses, and how to do so early enough in development to incorporate into the development plan. And all this needs to be considered alongside the development of a companion diagnostic, ready for approval at the same time as the medicine.

While the details are debated, it is clear at least that in the meantime, the consideration of, and planning for, the use of biomarkers...
must start very early in the development path of the drug.

Most fundamentally, it is vital that the appropriate samples are collected, handled and stored in a robust manner to ensure the conclusions made based upon the derived data are reliable. If there are no samples, there is no science – no way to identify the responding populations and a lost opportunity to investigate unexpected and otherwise unexplained responses and adverse events arising during development or beyond (see Mills FJ (2009). The Need for Good Storage Practice, Biopreservation and Biobanking, 7 (2), pp 115-117).

For the best chance of success in developing targeted drugs with proven biomarkers, companies must use as their starting point in all their clinical programmes the three ‘Cs’ of biomarker sample management – Consider, Collect and Conduct. Using this formula, pharma can apply the emerging science to its development programmes and be more confident that they are on the right road for future success.

For every clinical development programme it is essential to:

1) Consider the impact of emerging data and build a robust biomarker hypothesis and strategy to better define the patient population and evaluate the drug response profile.

This should be based upon prior knowledge of the drug target, signalling pathways and disease. For example, is there a genetic hypothesis? Are there gene variants with high likelihood of modulating drug response within the drug target, drug signalling pathways or genes involved in how the drug is metabolised? Are there data from a drug in a similar class already in development? In some cases candidate genes will be known that can be investigated, but in others, particularly when predicting adverse safety events, data may be limited or completely absent.

Developing technologies now afford greater opportunities to start exploration and build hypotheses, and play an important role at this hypothesis generation stage by investigating expression changes across tissue types (Bilello JA, 2005 The agony and ecstasy of “omic” technologies in drug development. Current Molecular Medicine, 5: 39-52.). Taking both tissue and biological samples from the preclinical stage and onwards and conducting exploratory analysis is a first step to start building these hypotheses.

One success in this area – from the Predictive Safety Testing Consortium, a collaboration between pharmaceutical companies, biotech and academia as well as regulatory authorities (FDA and EMA) – has been the identification and subsequent qualification (establishment of utility) of seven biomarkers for the detection of renal injury in preclinical studies. These markers have subsequently been accepted by the Japanese regulatory authority, the PMDA, as useful in assessing the safety of new drugs. To guide thinking in this area of biomarker discovery and validation, the EMA has developed a Biomarker Qualification process and issued guidance to help guide industry in the use of biomarkers within drug development. In July of this year it issued for comment (deadline 25 November 2011) a draft reflection paper on the use of pharmacogenomic biomarkers as patient selection and treatment stratification tools in drug development.
2) Collect samples either for prospective analysis or for storage for retrospective analysis in response to data arising during clinical development.

As part of any risk management strategy, it is imperative to ensure appropriate samples are collected as part of clinical development. These can range from a single DNA sample to a broad spectrum of samples to look at RNA expression and/or biomarkers from a range of different tissues that may hold the key to understanding the effects of investigational drugs in different populations. At the very minimum samples must be collected and appropriately stored to allow analysis either for an individual study or collectively across studies as appropriate in the light of arising data.

With the increasing number of samples being collected within a clinical programme it is also imperative to ensure samples are handled appropriately, shipped under the right conditions and stored to ensure their integrity and quality together with a fully documented trail of custody, all factors that will be required if samples are used for analyses included within a regulatory submission.

Sample integrity is of paramount importance in order to make robust conclusions from the data – from the point of collection, through handling and shipment, storage and sample management (to ensure efficient retrieval of the correct sample and ability to link with relevant clinical data), together with a detailed and complete audit trail. A number of recent studies have demonstrated the adverse impact of poor storage on the quality of samples and ultimately on the reliability of the data derived from their analysis.

Balasubramanian et al. presented recently simulation data quantifying the loss in statistical power to detect true biomarkers owing to diminishing concentrations of measured analytes in the samples, together with the impact of poor sample handling and storage conditions (Balasubramanian R, Muller L, Kugler K, Hackl W, Pleyer L, Dehmer M, Graber A (2010) The impact of storage effects in biobanks on biomarker discovery in systems biology studies. Biomarkers, 15: 677-783).

More recently, Kugler et al. provided further data, presenting estimates of bias for association of biomarkers in discovery studies (Kugler KG, Hackl WO, Mueller LAJ, Fiegl H, Graber A and Pfeiffer RM (2011) Journal of Clinical Bioinformatics, 8: 1 doi:10.1186/2043-9113-1-9). Ensuring the highest quality sample management processes are adopted as part of a clinical study is of vital importance to ensure the robustness of the data, decision-making and conclusions from these studies.

3) Conduct appropriate studies and analysis

The need for prospective versus retrospective analysis of samples collected in order to achieve regulatory approval is not clearly defined and data obtained from both retrospective and prospective studies have been approved by the FDA for inclusion on drug labels. For example, there is the case of GlaxoSmithKline’s antiretroviral Ziagen (abacavir, now marketed by the GSK/Pfizer joint venture Viiv healthcare), which was initially launched without a test to predict the incidence of serious hypersensitivity (approximately 8%), instead relying on clinical characteristics to determine those most at risk. However, later extensive pharmacogenetic studies identified and validated the utility of the HLA-B*5701 allele in predicting patients most at risk. This led to a drug label change, and genotype testing for this risk allele being incorporated into clinical guidelines with a resultant decrease in the incidence of abacavir hypersensitivity, and for GSK, an increase in Ziagen’s sales.

The marketed neurological drug carbamazepine had its US label changed in 2007 to include a recommendation that, before starting therapy, patients with Asian ancestry get a genetic blood test that can identify a significantly increased risk of developing rare, but serious, skin disorders including Stevens-Johnson syndrome and toxic epidermal necrolysis. It was found that patients who have an inherited variant of the immune system gene, HLA-B*1502, seen almost exclusively in people of Asian ancestry, run a greater risk of developing the rare skin diseases.

Abacavir’s labelling was based upon prospective testing, whereas the label change and black-box warning for carbamazepine was based upon retrospective analysis of a relatively small sample set.

Factors such as strength of the association and seriousness of the adverse effect will all impact upon the conclusions made.

Table 2 provides examples of genetic data in labels and whether they are based upon retrospective or prospective data. Study and analysis design are issues that may be, and should be, discussed as part of a VXDS or PGxWP discussion and will depend upon factors including strength of association, clinical impact and utility.

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