

## Personalised Medicine – Navigating Dx/Rx Co- development

**Mr Paul Cohen, Senior Consultant Brandwood Biomedical Pty Ltd**

The US National Cancer Institute defines personalised medicine as: “the use of information about a person’s genes, proteins, and environment to prevent, diagnose, and treat disease.”<sup>1</sup>

Available information on biomarkers that indicate whether a therapy could work on a particular individual continues to grow rapidly. The anticipated success of personalised medicine depends largely on a molecular-targeted drug having a linked, or “companion,” diagnostic test designed to determine precisely whether a patient will benefit from the specific treatment.

In the strictest sense, personalised medicine diagnostics may exist exclusively of *companion diagnostics*, which are by definition intended to inform individual patient treatment decisions for a particular drug. At the other end of the personalised medicine spectrum, personalised medicine tests may also include early diagnostics, prognostics and other types of diagnostics.

This short article will focus on companion diagnostics and the regulatory challenges facing their route to market.

### What are Companion Diagnostics?

Companion diagnostics are assays (a test or measurement) intended to assist doctors in making treatment decisions for their patients. They do so by elucidating the efficacy and/or safety of a specific drug or class of drugs for a targeted patient group or sub-groups.

There are two main groups of companion diagnostics:

- Tests that have been developed after a drug has come to market
- Tests that are being developed in conjunction, or as a companion to the drug (co-development)

There are already several examples of the pairing of a diagnostic test (Dx) to a therapeutic drug (Rx) and the numbers are growing. The most widely cited example of a Dx/Rx success story is the HercepTest®/trastuzumab (Herceptin®) combination from Dako and Genentech/Roche for the treatment of certain breast cancer patients. In this combination, the benefits of trastuzumab were demonstrated to be greatest in the Her2-positive subset of breast cancer patients. For patients the advantages were clear: improving median survival and overall response rates to chemotherapy. For the

drug's developers, fast-track approval was granted by the FDA in 1998 based on the test/drug combination data; proving, in this case at least, that studying a subset of responders based on a companion diagnostic can shorten drug development and approval timelines. Importantly, the drug and the diagnostic came to market at the same time, with the drug's labeling specifying the requisite diagnostic test.

As of the end of 2009, there have been 28 Rx-Dx co-development projects identified, of which 17 are in the oncology area. The remainder has been found to cover cardiovascular, CNS, autoimmune, infectious diseases, HIV and growth factors.<sup>2</sup>

### **The Regulatory Environment:**

Despite the promise that companion diagnostics holds for personalised medicine, there are a significant number of regulatory hurdles facing pharmaceutical and diagnostic companies when developing combination products:

- Paucity of regulatory clarity-Currently there are several regulatory pathways to market authorisation in the USA, including a PMA, 510 (k), FDA clearance for IVD Multivariate Index Assays (IVDMIAs); or the CLIA laboratory certification process for laboratory developed tests. For each biomarker there may be several assays available from different manufacturers to test for the biomarker; and each of these assays may have followed different clinical development pathways and regulatory approval mechanisms.
- What is the most appropriate regulatory pathway for co-development? If it is not a combination product, is simultaneous or sequential approval most suitable?
- Co-development may cause regulatory issues to arise that would not have existed for either product in isolation. Also post-approval changes in either the drug or diagnostic may affect the safety and effectiveness of the other.
- What type/amount of data is needed to support product labeling using biomarkers?
- What are the advantages of having drug and diagnostic development based at one location?
- Why is it important to complete analytic validation of an IVD test before applying the test to specimens in clinical trials that will be used for regulatory review?

Regulatory agencies (especially the FDA and EMEA) are showing signs of addressing these issues. They are encouraging greater use of biomarkers (companion diagnostics) in informing prescribing decisions. This encouragement has been seen in various forms since 2004, including the FDA's Critical Path Initiative, the FDA's release in 2005 of its Drug-Diagnostic Co-Development Concept Paper<sup>3</sup> and more recently in the form of the FDA and EMEA mandating that biomarker testing be performed prior to prescribing certain drugs. The FDA has recently started reporting a table of genomic biomarkers that it considers valid in guiding the clinical use of approved drugs.<sup>4</sup> The regulator has decided to provide this data in response to the ever-increasing level of pharmacogenomic information contained in the labels of approved drugs. It is reported that approximately 10% of approved drugs contain such information in their labels.<sup>2</sup>

As of March 2009, there are 28 valid biomarkers listed on the FDA’s website <sup>4</sup> across a spectrum of therapeutic areas, including cancer, infectious diseases, cardiovascular disease, neurological disorders, rheumatic disease, anaemia and immunosuppression. Of the 28 biomarkers, only 4 are mandated to be tested prior to using its companion drug. These drug/diagnostic combinations are:

Biomarker	Label	Indication	Drug
CCR5-chemokine C-C motif receptor	Maraviroc in combination with other anti-retroviral agents is indicated for treatment-experienced adult patients infected with only CCR5-tropic HIV-1	HIV	Maraviroc
Epidermal growth factor receptor (EGFR) expression	Patients enrolled in clinical studies were required to have immune-histochemical evidence of EGFR expression using the DaktoCytomation EGFR pharmDx test	Colorectal cancer	Cetuximab
Her2/neu over-expression	Detection of Her2 over-expression is necessary for selection of patients appropriate for Herceptin therapy	Breast Cancer	Trastuzumab (Herceptin)
Philadelphia chromosome-positive responders	Dasatinib is effective for the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukaemia (Ph+ALL) with resistance or intolerance to prior therapy	Leukaemia	Dasatinib

Source: Adapted from <sup>2</sup>

For the remaining 24, the label makes a recommendation for testing or is for information only.

While the EMEA’s position on appropriate drug labeling requirements for use of companion diagnostics is less formalised; on the other hand it does currently name 100 approved drugs for which such labeling is applied.

From the perspective of the pharmaceutical and diagnostic company, alike, there are several major drawbacks with the FDA’s Concept Paper. Many of these are associated with the labeling of the therapeutic. These have been highlighted and addressed by the Personalized Medicine Coalition (PMC) The PMC believes that the FDA should <sup>5</sup>:

- Expand the scope of the paper to include additional Rx/Dx development models for independent development of diagnostic tests where the development takes place separately from the drug (companion diagnostic) as well as co-development models of diagnostic and therapeutic by a single sponsor or collaboration of sponsors.
- Create a transparent but flexible regulatory pathway for co-developed companion diagnostic IVDs and Laboratory Developed Tests.

- Clarify and unify the level of evidence required to validate the companion diagnostic for purposes of referencing or mandating the use of the diagnostic in the therapeutic labeling.
- Consider how it can handle the regulatory approval and labeling requirements of a broad-based diagnostic that is used to assess treatment benefits for a range of therapeutics where it is likely that all the possible treatment combinations are not included in the labeling of the therapeutic.
- Develop guidance on the timing of the development and regulatory approval of the diagnostic relative to the therapeutic and consider the associated labeling requirements and how this impacts clinical usage.
- Clarify its mechanisms for adding companion diagnostics to drug labeling for Laboratory Developed Tests (e.g. warfarin pharmacogenetic testing)
- Provide clear advice on the degree of information about the diagnostic that should be included in the drug label when a variety of diagnostic tests are available in addition to the one/s used in the clinical trial.

There is no doubt that the industry will continue to provide challenges to the regulators as personalised medicine, and moreover, the science and technology of pharmacogenomics and proteomics continue to evolve. It will be interesting to see how both industry and regulatory bodies alike adapt to the challenges posed by companion diagnostics. The FDA and EMEA both have consultation papers at the consultation stage for publication in 2010. These can be accessed at:

FDA: <http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/pharmacogenetics/default.htm>

EMA: <http://www.emea.europa.eu/htms/human/mes/emergingtechnologies.htm>

References:

1. National Cancer Institute, US national Institutes of Health:  
<http://www.cancer.gov/dictionary/?CdrID=561717>
2. Diagnostics 2009: Moving Towards personalized medicine. PricewaterhouseCoopers report (<http://www.pwc.com/us/en/healthcare/publications/diagnostics-2009-moving-towards-personalized-medicine.jhtml>)
3. Department of Health and Human Services (HHS) F, FDA, April 2005 Drug-Diagnostic Co-Development Concept Paper
4. US Food and Drug Administration. Table of valid genomic biomarkers in the context of approved drug labels. ( [http://www.fda.gov/cder/genomics/genomic\\_biomarkers\\_table.htm](http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm).)
5. Personalised Medicine Coalition, PMC RX-DX Co-Development Letter to FDA, December 9 2009