Uptake challenges

Are healthcare systems ready for personalised medicines and companion diagnostics?

Although the number of personalised medicines is increasing, many countries are not set up to jointly assess both the medicine and its companion diagnostic, leading to lower reimbursement prices and slower product uptake. In some countries, patients do not even get access to these novel drugs at all. Here we examine how pharmaceutical companies can assess levels of readiness of country healthcare systems and proactively build a case depending on the market dynamic.

Personalised medicine – defined as a medicine that uses information about a person's genes, proteins and environment to prevent, diagnose, and treat disease – is often discussed as the future of healthcare, but it is very much a reality today, particularly in the field of oncology. Personalised therapies such as Iressa for lung ➡

cancer and the well-known Herceptin for breast cancer, are helping physicians to provide the right treatment to the right patient at the right time.

Since 1999, at least 23 personalised medicines with safety or patient selection benefits based on genomic biomarkers have been authorised via the centralised EU procedure.

And this is just the tip of the iceberg. The size of the personalised medicine market is expected to experience substantial growth in the next few years, at 12 per cent annually over the period 2012-2016, driven largely by targeted biologics. The EU is also increasingly recognising the importance and value of personalised medicine - since 2007, it has committed over €1bn of health research funding to the development of personalised medicine.

€1bn

EU health research funding for personalised medicine

Companion diagnostics are a vital but often overlooked element of personalised medicine. In 2004, the AmpliChip CYP450 - the first ever pharmacogenetic test using a DNA microarray – was approved by the FDA, and hailed as "a major step in ushering 'personalised prescription' into the clinical environment". The test aims to find the specific gene types (CYP2D6 and CYP2C19) of patients to determine how they metabolise certain medicines.

Diagnostics are largely unheralded compared to medicines, but personalised medicine is entirely reliant on companion diagnostics. The original and arguably still most compelling application of diagnostics in this field is efficacy-based patient stratification (eg testing patients for HER2 gene amplification to gauge their suitability for Herceptin). In addition, safety-based patient stratification (eg testing for the JC virus to assess risk of progressive multifocal leukoencelopathy in multiple sclerosis patients prescribed Tysabri) or ongoing monitoring to assess treatment strategy (eg measuring peripheral blood BCR-ABL transcript levels in patients on Glivec to identify patients likely to achieve better long-term outcome if they are switched early to second-line therapy) have also demonstrated their practical merits.

Most healthcare systems have no holistic approach to assessing personalised medicines. While there are on-the-ground challenges in terms of implementation of personalised medicine – such as low widespread availability of '-omics' tests, gaps in physician knowledge and issues with data collection and sharing – the case for personalised medicine is compelling for all stakeholders. For patients, personalised medicines mean better outcomes and improved confidence; for healthcare professionals, improved predictability of outcome; for policy makers they inform guidelines and policy; for payers, they mean improved cost-effectiveness leading to long-term sustainability of healthcare systems, while for the pharmaceutical industry, they come with a ready-made case for market access with a compelling cost-effectiveness argument.

But despite all this, many healthcare systems across Europe are not set up to manage the drugs and their companion diagnostics in the holistic manner so essential to their success.

One issue is that current healthcare models are organ, system or disease-oriented, but personalised medicines do not necessarily fit into these definitions, requiring a focus on biological pathways and unravelling the differences between healthy and diseased conditions. For example, KRAS mutations can play a vital role in drug efficacy beyond colorectal cancer, such as non-small cell lung cancer. With personalised medicine, molecular data will increasingly need to be integrated with clinical data, leading to a need for new molecular definitions of disease.

Another issue is a degree of scepticism among payers - including one of the leading statutory health insurances in Germany - and policy makers, that manufacturers use personalised medicine to disguise higher pricing. They may also be sceptical of unfamiliar clinical data evidence used to justify economic value.

But perhaps the most fundamental issue is a lack of holistic view within healthcare regulatory systems. Current systems largely consider drugs and diagnostics via separate evaluation and payment processes; this can lead to significant challenges, such as successful reimbursement of the drug but not its companion diagnostic, or vice versa.

For example, while Herceptin is widely reimbursed across the EU, reimbursement for the HER-2/neu companion diagnostic test varies across Europe. In the UK and Germany the HER-2 test is publicly funded, in France it was authorised in 2000 but only reimbursed since 2007, and in Spain the pharmaceutical company funds the majority of testing.

Three categories of healthcare system

As with many aspects of healthcare in Europe, the local country systems vary quite significantly. Many EU countries – such as Germany – have separate submission and review processes for medicines and their companion diagnostics.

Other countries are becoming more coordinated. In France, for example, there is a trend towards further synchronisation between treatment and diagnostic evaluation. The ideal is to see the cost-effectiveness case for a new personalised medicine and its companion diagnostic compared to other treatment / diagnostic alternatives, but this will represent an ongoing challenge for pharmaceutical companies to provide.

The gold standard example however, comes

Assessment type	Country	Challenges
Separated P&R assessment	Germany	possible scenario of Rx funded & CDx unfunded / funded with delay
Coordinated P&R assessment	France	requires highly aligned Rx & CDx departments
Joint P&R assessment	Australia (the UK currently pilots a similarly joint approach)	requires highly aligned CDx & Rx clinical data / economical data

from outside Europe. In Australia, a national framework for reviewing 'co-dependent' technologies and recommending national coverage or reimbursement decisions is currently being developed.

> "Perhaps the most fundamental issue is a lack of holistic view within healthcare regulatory systems"

To determine whether the biomarker test, the drug, both, or neither should be subsidised, the framework states it is crucial to identify whether the biomarker is a treatment effect modifier or a prognostic factor. To aid in this determination, the framework explicitly allows the linkage of different types of evidence to examine whether targeting the biomarker varies the likely clinical benefit of the drug, and if so, to what extent. This kind of flexible, coordinated review system is ideal for the assessment of personalised medicines. The challenge is that it requires direct or linked clinical evidence for the treatment and diagnostic, and requires economic evidence along the treatment path including alternative diagnostics. Within Europe, the UK is currently piloting a similar approach.

Broadly speaking, countries in Europe will start to fall into one of these three categories – a separate assessment such as in Germany, a more coordinated assessment such as in France, or an entirely joint assessment such as that in Australia / the UK (see diagram).

Formulate entry strategies accordingly

Once the type of regulatory environment for personalised medicines in each country is known, pharmaceutical companies can take proactive steps to assist the assessment and reimbursement of personalised medicines accordingly.

Based on our extensive project experience, each case can be evaluated on its own merits. For example, a recent evaluation of a new molecular diagnostic in Germany assessed several factors, including the business case for the test (including its budget impact and cost-effectiveness), its level of support from the medical community to approach the national hospital remuneration system directly, and its reimbursement potential in the current environment, and concluded there was an optimum type of contract it could hope to achieve. In another assessment of an *in vitro* diagnostic in oncology, the main value drivers influencing the funding / reimbursement were identified, which included the predictive value of a test, its reproducibility and positive effects on patient outcome.

After the evaluation process, companies can conduct public policy efforts to encourage joint assessment and adequate assessment methodology, bridging strategies to improve market access through programmes and tools that demonstrate value, or develop joint data by adapting the evidence generation process early in the treatment pathway. Ultimately for coordinated and joint assessments, frameworks are required which allow the linkage of different types of evidence and provide policy makers with fewer evidence gaps to reduce decision-making uncertainty.

Challenges ahead

Although personalised medicine represents a positive development for all stakeholders, many healthcare systems across Europe are not set up to evaluate treatments and their companion diagnostics in the holistic manner so essential to their success. Hence, pharmaceutical companies and diagnostics producers need to collaborate tightly to generate the necessary evidence and obtain adequate reimbursement. It is therefore important to assess individual markets early enough before submission and identify potential entry strategies which will maximise the chance of market access.

Andrea Sobrio is managing partner; **Aleksandar Ruzicic** is partner; **Klarissa Hoday** is manager at specialist healthcare consultancy Executive Insight