Personalised medicine: paradigm shift in the pharma business

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IP Value in the life sciences industries

Key issues for senior executives
We are on the brink of a new era in pharmaceutics – personalised medicine – and the change is likely to shift the balance of power in the pharmaceutical industry. The promise of personalised medicine is made possible by a convergence of major technical advances. Understanding diversity in the human genome, identification of biomarkers for diagnosis and predictive therapeutic outcomes, and the ability to sample, analyse and manipulate data in useful time periods create real opportunities for efficient development of personalised therapies. Use of molecular analysis to predict and manage an individual’s disease not only offers more efficient treatment for the individual, but also provides drug companies with better models for designing and testing drugs, predicting specific populations likely to benefit from a therapy, and combining diagnostic and therapeutic products for maximum efficiencies.

Sequencing the human genome
The impetus for personalised medicine began with the bold decision to sequence the human genome. This undertaking engendered controversy and scepticism. How would large amounts of DNA be efficiently sequenced using 1990s technology? Could such vast amounts of data be stored and manipulated? Who would pay for the effort and own the results? The project stimulated innovations in DNA sequencing technology such as ESTs (expressed sequence tags) that made the seemingly impossible possible and drove the project to an early completion date.

Completion of the Human Genome Sequencing project created an expectation that diseases would be better understood and that genome-based therapies would quickly follow. Gene sequence data alone, however, was not enough. Functional correlations between genes and diseases were needed.

Gene chips
Given the large numbers of genes identified in the Human Genome Project, analysis of individual genes was time consuming. An individual gene could be identified by hybridisation in diseased versus normal tissues to establish a correlation between that tested gene and the tested disease. At the pace of this standard one by one methodology, the discovery of potential therapeutic targets seemed unreachable. However, advances in gene expression analysis accelerated the discovery process.

Microarray technology provided the means for rapidly analysing thousands of genes from many tissues and many diseases. Differential analysis of genes turned on or off in diseased versus normal tissues led to identifying biomarkers associated with a particular disease. Numerous diagnostic and therapeutic targets were identified but significant variations in the data raised questions.

Bioinformatics
In order for the biological data, with its variations, to be understood and correlated with diagnostic and therapeutic outcomes, informational systems were needed. The software and statistical methodology were developed to handle large amounts of biological data. Use of large-scale computerised statistical methods reduces error, validates results and manipulates genomic data on multiple levels.

The convergence of all these developments permits application of large-scale data to individual diagnosis and therapy. Gene expression profiling now allows the classification of subgroups of patients that may have different biomarkers, different prognosis or different treatments.
based on that profile. Individual variation in disease prognosis and in responses to drug therapies can now be tracked and correlated with genomic profiles, permitting more effective, personalised therapeutic approaches.

**Personalised diagnosis and therapy**

Examples of great advances in personalised therapies include the diagnosis and treatment of specific cancers. Biomarkers such as mutations in breast cancer genes BCRA-1 and BCRA-2 and the prostate cancer marker PSA-1 permit diagnosis of predisposition to these cancers and allow patients to be monitored for more effective preventative therapies. Monitoring specific markers on diseased cells, such as the oestrogen receptor in some types of breast cancer allows efficient therapy with anti-oestrogens given only to those patients showing the marker.

Genetic profiling of large numbers of patients’ data allows classification into subgroups of patients not only into those likely to develop specific diseases, but also into those likely to respond to specific therapies. For example, profiles are available for predicting diagnosis and treatment outcomes for breast, ovarian, colon, lung and brain cancers. Many of these tests are already commercially available and others are in development.

**A power shift?**

Personalised medicine requires the application of individual diagnostic gene profiling in combination with selection of tailored drugs or treatment options. Early genomics companies mined the data provided in the Human Genome Project to identify biological relationships and sort groups of genes that were differentially expressed in known diseases. Such companies also identified genes that were characteristic of a biological mechanism, such as proliferation, cell cycle or apoptosis, providing these to pharmaceutical companies for drug development. Many companies grew around proprietary drug discovery platforms, with novel algorithms and software making a first selection of potential diagnostic and therapeutic targets. The genomics companies did not generally have the expertise or resources to develop and market pharmaceuticals.

Big pharmaceutical companies were not at the forefront of the genomics movement. With a historical focus on small molecule drug development, a big investment into the largely academic science of genomics was not initially practical. As the genomics industry developed, the traditional pharmaceutical companies acquired or established relationships with one or more genomics company. Identification of new therapeutic targets provided by the genomics companies and prioritisation of these targets for development using the expertise of big pharmaceutical companies is just beginning.

Following the traditional model of blockbuster drugs for treatment of large patient populations, the pharmaceutical industry will perhaps need time to shift strategies to more targeted therapies for small patient subpopulations.

Whatever business models evolve to deliver personalised medicine, they are likely to target fewer patients but be faced with high costs of development. Creative cost-sharing strategies, royalty-generating licensing programmes and continued investment in research are some ways that these new companies may achieve a return on investment. Strategic partnering between companies with a new and useful diagnostic and those developing the companion therapeutics can also create a synergistic system.

**Intellectual property issues**

Strong intellectual property strategies, as well as a good understanding and use of regulatory procedures, are essential to the successful commercialisation of these new pharmacogenomic products. Creative IP and FDA planning and execution can make a difference in a company’s success, particularly when value is derived from the analytic test and not the therapeutic drug.

Patenting products and methods useful to protect new developments in personalised medicine poses unique challenges to the drug industry. Many of the advances are made in understanding the interactions of known drugs with known disease targets. Patents may be of limited scope due to prior art knowledge about the disease, biomarker or drug. Novelty can be found in the identification of a specific genetic subpopulation, for example, that is diagnostic or correlates with a specific drug response. During research and development, gene profiles are determined using commercially available chips and arrays that contain known genes. Many gene expression profiles are already published in large public databases. One or more genes in the identified gene profile may already be correlated with the disease, limiting patents to combinations of...
genes easy to design around. The desired patent protection for a chip or other diagnostic device containing the specific genomic profile may not be available.

To support the desired broad coverage of personalised medicine inventions, patents must be drafted with sufficient information to allow the reader to make and use the products and methods. Because the number of genes and patient samples analysed to develop the biomarkers or predictive genetic profiles is generally large – for example a common array may include more than 10,000 genes and very large numbers of patient samples may be required for validation and testing – meeting what is yet an undefined disclosure requirement for this technology can be challenging. How much of this data, the algorithms and program code used to manipulate the data, the sequence of each gene used and the individual patient profiles must be provided in the patent application?

The road to bringing a therapeutic product through FDA approval to market is arduous and expensive. Getting the diagnostic to the marketplace as early as possible may provide revenue as the company progresses through clinical trials. Companies can also look for other existing drugs matching the therapeutic target that might be approved for other indications. For example, a known drug may be effective for treating cancer in only 30% of the cancer population. Identifying via genotype or biomarker a subset of cancer patients where the drug is more than 90% effective can permit re-labelling of the use tied to the identified subset. Opportunities for re-labelling also can be present in preventative and/or maintenance uses identified by genetic predisposition profiling, and can provide additional sources of revenue.

**Patent strategies**

Although desirable, broad patent claims may not be easily achieved. Competition for similar disease targets, prior publication of gene sequences, expression data and disease relationships, as well as extensive proofs that may be required, are real barriers that must be crossed to attain broad patent claims. Worldwide protection in the major markets is essential, but can be costly and must account for those countries that deny patents in the area of medical treatments or diagnostics.

A well-planned intellectual property programme should focus on those innovations that can make use of known genomic relationships to provide a unique solution to a problem. To this end, knowing what is in the public domain, what products competitors are developing and need in the marketplace are all keys to success. Continued research of new developments are essential to this type of knowledge-based company, as well as driving the fruits of the research into commercial products.

Publications and patent filings should be carefully timed to capture technology advances for the company and to limit the potential for competition. Strong patents are supported by complete and extensive experimentation, with claim scope directly related to the breadth of the disclosed information. While it is important to file early to beat the competition, this must be balanced against the reality of the time required to support fully and demonstrate the usefulness of the invention.

Where the products and array chips are known, method claims can protect the new diagnosis or outcome predictive correlation. Many non-US countries prohibit patenting of therapeutic and diagnostic methods. Consideration of alternative patent claims and strategies when drafting the application can help ensure worldwide exclusivity. In the United States, where “everything under the sun made by man” is patentable subject matter, “laws of nature, natural phenomena, and mathematical algorithms” are excluded.

Current US patent law interprets the application of these to a useful purpose, for example, to a diagnostic assay or therapeutic determination, as made by the hand of man, and therefore patentable subject matter. Method claims drafted to maximise the application steps can direct attention to the specific, credible and substantial use. Claims can be drawn to new and useful products, methods of diagnosis and treatment, screening methods used to find new therapeutics, data analysis methods leading to the identification of a new and useful biological relationship, diagnostic method, or therapeutic.

For patents in personalised medicine, it is the combinations that are key. Identifying the minimum combination useful for the diagnosis and treatment can yield broad, useful protection. Narrow claims should also be included to protect the product or therapy the company is developing. Narrow claims can protect the product and also exclude others from using the claimed relationship. In the focused diagnostic-therapeutic technology of personalised medicine, this may be enough.

**Access to your genetic profile**

Progress towards personalised medicine is not without cost, in dollars and in potential
loss of privacy. Recouping development and actual assay costs for life-saving diagnostic assays such as the BCRA-1 and BCRA-2 test, results in a per assay charge of about US$3,000. Often payment for these tests by insurance providers is limited to only identified high-risk individuals. Individuals can opt to have their entire genome sequenced and mapped at a cost of about US$100,000. Organisations are working to reduce this cost to a targeted US$1,000, believing that personal genomic profiling will become standard practice in the near future.

The question of access to this new medical information has yet to be resolved. Concern that employers and insurance providers may discriminate against individuals having a profile that predicts cancer, brain dysfunction, Alzheimer’s or other chronic disease is legitimately raised. The potential for preventative measures signals a desire to obtain genomic information, yet for some may provide diagnostic information without hope of therapeutic intervention.

Personalised medicine is emerging as a commercial reality. Along with amazing technical advances and tremendous human benefits, personalised medicine also brings challenges in costs, commercialisation, intellectual property protection and ethical use. Expensive R&D and analytical costs are passed on to the consumer and may hinder translation of life-saving innovations to the hospital bed. As with other innovative products, strong intellectual property rights are needed to reward developers. The boundaries and requirements for patent coverage are being developed. Proper safeguards and guidelines for use of the personal data generated will be needed.
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Denise Kettelberger chairs the Chemical/Biotechnology Practice Group of Merchant & Gould and leads major client teams responsible for strategic management of complex, worldwide intellectual property portfolios. Her practice encompasses procurement, creative enforcement and proactive strategies in the management of intellectual property portfolios, as well as diligent review and analysis of intellectual property matters, opinions, licensing and litigation support, particularly for chemical and biotechnology clients.

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Katherine Kowalchyk practises intellectual property law, particularly counselling clients in the chemical and biotechnology practice areas. With more than 14 years’ experience, Dr Kowalchyk specialises in strategic portfolio management, including worldwide patent prosecution matters, patentability searches and opinions, and infringement and clearance opinions. She also has experience in assisting clients with transactional matters such as technology transfer and licensing agreements. Dr Kowalchyk enjoys partnering with clients to develop their intellectual asset portfolios and business strategies.

Dr Kowalchyk holds a PhD in microbiology and conducted postdoctoral work at the University of Minnesota. She has extensive experience in patent prosecution in the biotechnology and chemistry areas, and has prosecuted patents in the areas of pharmaceutics, antibodies, proteomics, genomic and bioinformatics. Katherine currently teaches intellectual property law as an adjunct professor at the University of St Thomas Law School.