

CUSTODIANS IN CRISIS

the impact of genomics on regulation

Within minutes of his birth, Adam's genome is scanned for signs of any disease or particular susceptibility to disease. The data is simultaneously transmitted to the National Gene Bank and embedded on a smart card, which the doctor gives his mother. "Congratulations," she says. "You've got a healthy little boy. He should live to a ripe old age." It's October 2010 and these days every newborn baby in the Western world is automatically issued with a GeneCard – an electronic record of his individual genome. Within another 20 years, that data will be used to provide Adam with the sort of healthcare we can only imagine: drugs that are tailored to his specific genotype, drugs that are designed to stop him falling ill in the first place.

Advances in science and technology are enabling us to understand physiology and pathology at a totally new level; to define, subtype and track diseases much more accurately; and to treat patients far more effectively, using novel delivery mechanisms and devices. As our knowledge grows, we are also increasingly able to model physiological and pathological processes on computers rather than having to rely on old-fashioned trial and error.

Moreover, the preliminary evidence suggests that the public will welcome such advances. In a survey conducted by Time/CNN in June 2000, 1,218 people were asked whether, if they had access to their genetic code, they would want to know to what diseases they were predisposed. Sixty one percent said yes¹.

So what are the regulators of the pharmaceutical industry doing to prepare for that revolution? Not nearly enough: genomics², simulation and modelling will collectively transform drug discovery and development. That will, in turn, have a massive impact on the regulators – both in-house functions and government-appointed agencies. But many of them will be ill equipped to cope.

The starting point

The completion of the first draft of the human genome, and the identification of the variations within it, are the initial steps on the road to a totally new

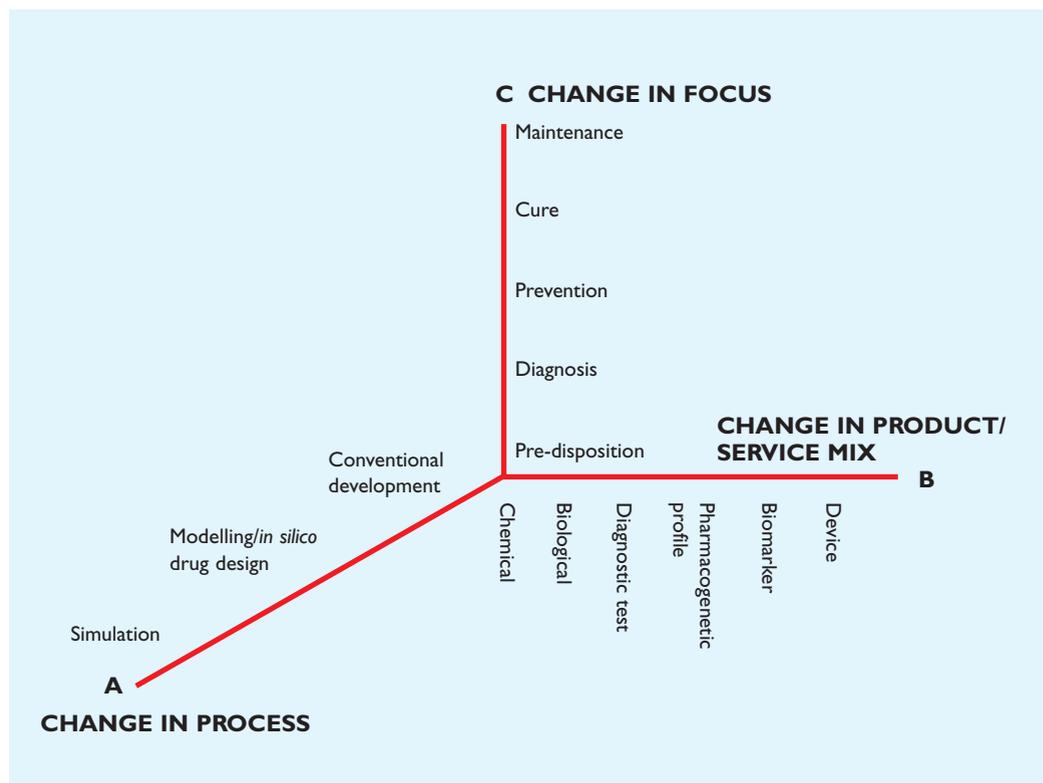
form of healthcare. As we learn more about the way in which genes and proteins behave as dynamic systems that interact with each other and with their environment, so we shall be able to identify new genes as targets for innovative medicines that work with greater specificity and efficacy, and fewer side effects. And as we identify the genetic variations that correlate with specific diseases, so we shall be able to determine why particular people suffer from those diseases. We shall ultimately be able to predict which people are pre-disposed to suffer from a specific disease, and then prevent them from developing it rather than curing them once they are sick.

Of course genetic variation in the individual is not just responsible for almost every disease; it is also responsible for individual responses to medication. Pharmacologists have long known that, on average, only 60% of patients taking a particular drug derive any benefit from it. Some actually get worse. Research recently conducted at University College, London, suggests that every year more than 800,000 patients using the National Health Service experience adverse effects. As a result, about 68,000 patients die and 50,000 are permanently disabled³. Another study conducted in 1994 estimates that adverse drug reactions are between the fourth and sixth leading cause of death in the US⁴. So the ability to understand how genes influence the way in which different people metabolise

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Figure 1



drugs and, ultimately, to prescribe drugs based on individual genotypes has enormous value.

The new *in silico* technologies promise to deliver huge benefits, too. Simulation of biological and disease processes, protein modelling and the science of chemi-informatics and rational drug design – using models of ligand and target – will accelerate the drug discovery and development process. Indeed, simulation and modelling may even replace parts of the traditional process altogether. They will also make it easier to decide which drugs to concentrate on and reduce costs in the most cash-hungry phases of development.

In short, we are still some way from winning the big prize: predictive and preventative medicine on an individualised basis, as distinct from palliatives and cures for the masses. Nevertheless, that prize is now in sight – and the new sciences and technologies that are needed to secure it will radically alter the way in which the pharmaceutical industry works.

Impact on R&D

Genomics will massively increase the number of targets on which the industry can focus, just as high throughput screening will massively increase the number of compounds the industry can screen. This will relieve the traditional bottlenecks, but it will make target validation and lead validation a much

bigger task. Genomics will also transform clinical trials. At present, drugs are tested on the entire population. But when a drug is designed for patients with a specific genotype or disease subtype, it will clearly need to be tested on trial patients with that same genotype or disease subtype⁵.

All in all, then, genomics will make drug discovery and development a much more innovative and accurate process – but one that is also much more complex. It is likely to have an even bigger impact on the sort of products the industry makes. The portfolios of pharmaceutical companies consist largely of traditional ‘white powders’ and some products from the biotechnology sector such as antibodies. This is not surprising, given that the medicines currently on the market were in development as long as seven years ago. But genomics could transform the portfolio from a collection of products into a service package based on mass customisation to deliver personalised medicines.

Figure 1 depicts this transition. Axis A shows the change in the processes the industry uses; axis B shows the change in its remit; and axis C shows the change in the sort of treatments it provides.

Effect on the drug dossier

What are the consequences of these changes for pharmaceutical regulation? They will transform

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every aspect of regulation, except one: the emphasis on safety and efficacy.

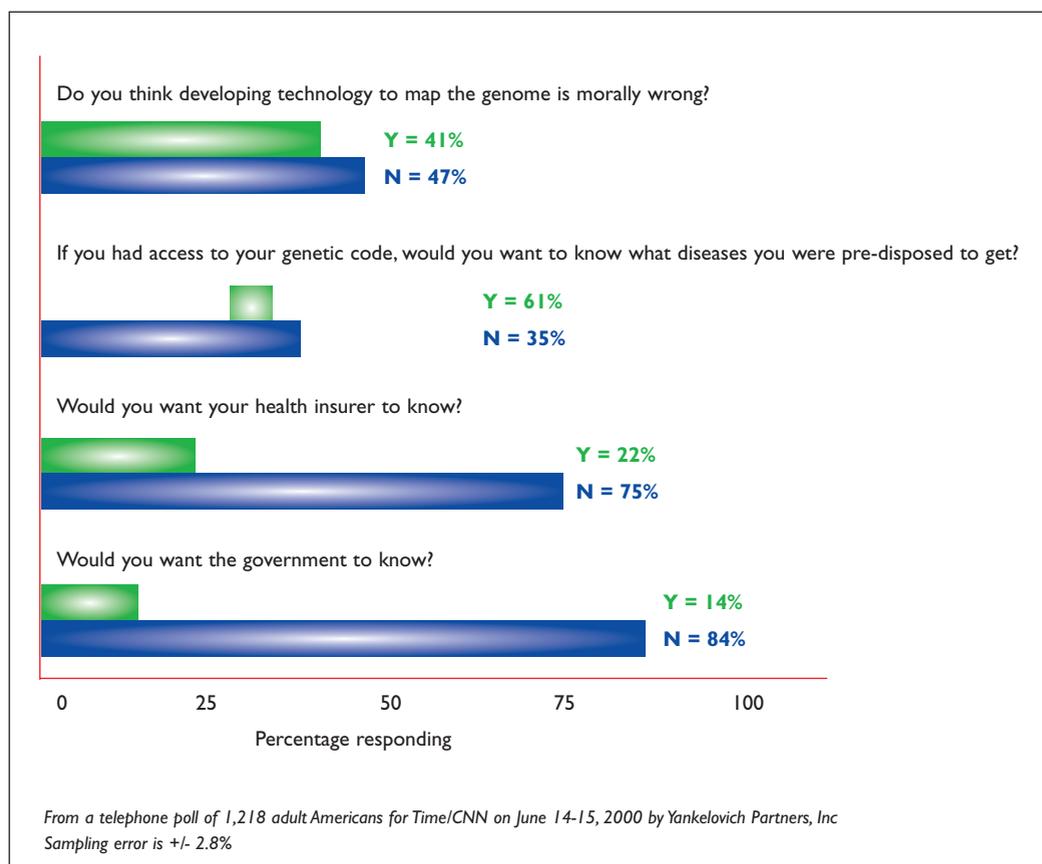
- The contents of the drug dossiers submitted to the regulators will cover totally different kinds of drugs, diagnostics and devices. So, for example, a single dossier might contain filings for a new chemical or biological drug aimed at a specific disease subtype. It might also include, as part of the same service package, a test for diagnosing people with a pre-disposition to the same disease subtype; a validated biomarker for use as a surrogate clinical endpoint; a device for monitoring the progression of the disease; and a device for monitoring drug concentrations in a patient's serum. In short, the range of products and services included within any one dossier will become very much greater than before.

- The nature of the information required to support the dossier will be very different. Most of the drugs currently on the market are based on an understanding of chemistry and pharmacology. But many of the products and services which genomics enables the industry to produce will span a much wider range of disciplines – and entail much greater volumes of data. A drug that is designed for patients with a specific genotype or disease subtype, for example, will need to be supported by

data on the individual genomes of trial patients and data on the pharmacogenetic profile of the drug itself. The dosage details will also become much more complex. Today, product information leaflets typically indicate two dosages at most: that for adults and that for children. In future, however, the dosage instructions will probably vary in line with a patient's particular haplotypes.

- Verification of much of the data contained in the dossier will be totally different, as simulation and modelling become much more common. This is especially likely with treatments for the prevention of chronic disorders that may not manifest themselves in individual patients for many years, and which would therefore require very lengthy clinical trials. Some of the information required to support the dossier is also likely to be available very much earlier in the discovery and development process. Data that is typically collected in the pre-clinical phase may be produced in late-stage discovery, limited haplotyping being one such instance.

- Assessment of the risks and benefits associated with some treatments will be much more difficult. Any drug that is sufficiently powerful to do its job carries a risk. It is relatively easy to justify that risk when a drug alleviates an existing condition. It is far harder to



do so when a drug is designed to treat someone who is not even sick, but whose genetic profile suggests that he may develop a particular disease later in life.

● The number of ethical challenges will increase. Some of these challenges will be evidential: certain drugs will be so specialised – either because they treat very rare conditions or because they treat rare subtypes of common conditions – that the patient population on which they can be tested is too small to provide statistically conclusive results. Others have to do with the danger of ‘genetic discrimination’. Suppose, for example, that there are four subtypes of a particular disease and that three are relatively common, while the fourth occurs in only 5% of cases. Should the regulators approve a medicine that treats the first three subtypes but not the last, or insist that a company develop medicines for all four?

It is this environment in which the regulatory affairs departments within pharmaceutical companies will need to work and in which the external regulators will need to devise new guidelines. For safety must remain the paramount concern.

Internal regulation

The advent of genomics has major implications for internal regulation. The regulatory affairs staff will need to understand genetics and bioinformatics, subjects now substantially outside their domain. They will also need to develop protocols for testing drugs, diagnostics and devices that are tailored to specific genotypes and secure permission to collect genetic data from the patients participating in those trials. They will therefore need to develop ethical policies and effective internal procedures for ensuring that the vast number of genetic samples obtained during clinical testing is safely managed and stored.

That will, in turn, require much closer collaboration between the regulatory affairs staff and those from the clinical, legal and information technology functions. The task will be even more onerous when a clinical programme is global and entails the collection of genetic samples from patients in many different countries with different rules on data protection. In short, the people responsible for internal regulation will have to take a much more cross-disciplinary approach – both in terms of the content they cover and the skills they require to manage the supporting data.

They will also have to communicate more effectively, both with trial patients and with the external regulators. Any company that wants to obtain genetic data from patients will need to assure them that the data will be accorded the utmost privacy. Similarly, any company that wants to produce pharmacogenomic products and services, and to

support its applications using simulation and modelling, will need to understand precisely how the regulations are changing.

But though both genomics and simulation will make internal regulation more demanding, they will also bring some advantages. There should be less risk of a drug failing to secure approval when the dossier is submitted, for example, precisely because pharmacogenomic products will be tailored to specific genotypes. So the danger of falling foul of the external regulators should ultimately diminish.

External regulation

If the challenge is big for internal regulatory functions, it is even bigger for external regulators with far fewer resources than Big Pharma can command. The most obvious dilemma is the ethical one – and most governments have already recognised the scale of the problem by setting up advisory committees. The US Government, for example, has established the Advisory Group on Genetic Testing to report on ethical issues and help the Food and Drug Administration (FDA) draft suitable guidelines. But so many stakeholders are involved that developing appropriate regulations is likely to be a long and difficult process, says Dr Larry Lesko, Director of Clinical Pharmacology and Biopharmaceutics at the FDA's Center for Drug Evaluation and Research.

The practical problems are equally daunting. The regulators will have to grapple with a massive increase in data, new forms of data and data about a much wider range of treatments. Most agencies have substantial expertise in assessing conventional medicines based on chemistry and pharmacology; however, they do not have, and cannot be expected to have, expertise in every science, let alone diagnostics and devices as well.

Advances in the emerging electronic infrastructure could compound this challenge. At present, information about a drug, biological product or device is mainly collected through clinical trials. Much less information is gleaned once a product is on the market – largely because of the limited tools available for assessing products in the context of the ‘real world’. But participants in a recent forum on innovation and regulation of medical products, jointly organised by the US Regulatory Affairs Professionals Society (RAPS) and Institute for Alternative Futures (IAF), predicted a substantial increase in the use of electronic tools to conduct post-marketing studies⁶.

With electronic medical records, more sophisticated biomarkers and biomonitoring devices, it will be very much easier to track the way in which products perform and develop a better understanding of their safety profile. However, unless such

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References

- 1 Mapping the Genome: The Race is Over, *Time Magazine* (July 3, 2000) 23.
- 2 For brevity and ease of reading, we use the term genomics in its broadest sense here to encompass genomics, genetics, proteomics, metabolomics, pharmacogenetics and pharmacogenomics.
- 3 Reported in *The Daily Telegraph*, March 2, 2001.
- 4 Lazarou, J, Pomeranz, BH and Corey, PN. (1998) Incidence of adverse drug reactions in hospitalized patients. A meta-analysis of prospective studies. *JAMA* 279, 1200-1205.
- 5 For a fuller discussion of the impact of genomics on clinical development, please see our article on 'Putting the Code to Work: The Promise of Pharmacogenetics and Pharmacogenomics', *Drug Discovery World* (Winter 2000-2001) 35-41.
- 6 Report on Co-evolution: Innovation and Regulation of Medical Products (June 8 2001). Available from IAF at <http://www.altfutures.com/news/whatsnew.htm>

studies are properly designed and managed, there is a danger that the demand for more information will simply boost research costs and flood the agencies with yet more data.

The regulators will also have to rely to a much greater extent on external sources of knowledge, including the very companies that have developed the drugs they are trying to regulate, since those companies may well be the main experts. But when much of the knowledge about a novel therapy resides in the company that has produced it, there are clearly potential conflicts of interest. So most regulatory bodies will want to call on other sources, too.

Academia has traditionally provided supplementary expertise to the agencies and industry alike. But the number of academics with the right sort of expertise is also likely to be very small, so the existing model – in which both parties use expert witnesses to bolster their arguments – will no longer work. The need to assess complex new service packages rooted in pharmacogenomics may ultimately force the regulators to pool resources, although it is difficult to envisage that this will result in a single set of global regulations, given the different legal, social, religious and ethical practices in place throughout the world.

It may also foster a more positive relationship between the industry and its regulators. In fact, participants at the forum organised by RAPS and IAF identified greater 'grass roots international co-operation' among regulatory agencies, companies and other stakeholders as one of the most important opportunities for accelerating and improving the contribution innovation and regulation can make to healthcare.

Even if genomics does not alter the nature of the relationship between the industry and its regulators, though, it will certainly alter the concept of regulation. When large amounts of data on tiny samples of people with very rare conditions are all that is available, for example, the agencies will have to rely increasingly on evaluation of the risks and benefits of a particular treatment, and less and less on corroboration of the facts. The application of genotype-specific medications in daily clinical practice will likewise produce new complexities, and greater use of post-marketing studies will blur the traditional distinction between clinical trials and real life.

All these developments may be grounds for changing the concept of the dossier itself. Under the current system, an application for a new drug gets approved and then closed. Why not replace it with a 'living' document – a continuous record that includes post-marketing studies, adverse event reports and feedback from patients? They, after all, are the industry's ultimate customers.

Whether or not this happens, one thing is cer-

tain: the regulators will have to move fast. Several new molecular entities based on genomics are already in Phase 2b trials – which leaves little time for hammering out another set of rules. And those rules will surely be needed if we are to reap the rewards of genomics without jeopardising the health of the human race. **DDW**

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