THE INDEPENDENT

Demolished: the myth that allows drugs giants to sell more

By Steve Connor, Science Editor Monday 08 December 2003

For years, the drugs industry has grown fat on a myth - the false belief that all drugs will work on just about everybody.

That has essentially been the rationale for a culture that has encouraged doctors to prescribe first and ask questions later - at a cost to the NHS of £7.2bn a year in medicines.

Yet it has been an open secret within the drugs industry that most drugs do not work for most patients, a secret that has now been publicly aired for the first time by Allen Roses, the head of genetics at GlaxoSmithKline, Britain's biggest drugs company.

Dr Roses, an academic with a distinguished record in medical genetics, is used to speaking his mind, especially on the benefits of a revolutionary new approach to drug development called pharmacogenomics.

That is the science of applying the results of the human genome project to drug development. In essence, it means testing the DNA of patients in order to identify those for whom a particular drug will work - the "responders".

That would enable doctors to eliminate the "non responders" who, as a result, will at least not be given a drug that at best could be useless and at worst dangerous in terms of harmful side-effects.

In the past, drug companies have developed drugs aimed at the widest possible population. That was the most profitable strategy but one that ignored a basic fact in biology - people are different.

To emphasise the point, Dr Roses likes to quote Sir William Osler, a Canadian physician who in 1892 remarked: "If it were not for the great variability among individuals, medicine might as well be a science and not an art."

Bringing a new drug to market is an expensive business costing tens of millions of pounds. It takes place in a culture of maximum possible sales for maximum possible profit - a culture that does not like to broadcast the fact that most drugs don't work for most people.

Drug testing in patients involves three phases of increasingly complex clinical trials that must be successfully completed before the drug is approved by regulatory authorities such as the mighty US Food and Drug Administration.

But even when a drug has been approved in terms of safety and "efficacy" - whether it does what the label says it should do - few people realise just how poorly they perform in real life.

Dr Roses cited a study published three years ago by Brian Spear, a senior scientist at Abbott Laboratories, a medical diagnostics company in Chicago, on the efficacy rates of a range of different drugs.

It found that drugs vary enormously in terms of how well they work, with efficacy rates varying from as low as 25 per cent for cancer drugs to 80 per cent for painkillers.

For many drugs, however, the efficacy rates hover around 50 per cent or lower, meaning that, for most people, these drugs just don't work. As Dr Roses puts it: "The vast majority of drugs - more than 90 per cent - only work in 30 or 50 per cent of the people."

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Dr Roses is one of the pioneers in a field of genetics that promises to help to identify those people who could benefit from a drug. It is called single nucleotide polymorphisms (SNPs) and it is a way of distinguishing the smallest possible genetic differences between individuals.

The use of SNPs has already led to the discovery, for instance, of a test to detect the 5 per cent of the population who inherit a predisposition to a potentially fatal side effect of an anti-HIV drug called abacavir.

Now it is possible to test HIV patients before the drug is given to them in order to weed out those patients who will suffer a severe adverse reaction - a violent rash on the body.

Scientists believe that SNPs can be used to test people not just for their vulnerability to a drug's side-effects, but also to whether it will work or not.

John Bell, the regius professor medicine at Oxford University, said that for pharmacogenomics to catch on, doctors will have to learn new ways of dealing with patients.

"One of the biggest obstacles is culture. We've all been taught to take the dose for a drug straight out of the British National Formulae and then if that doesn't work to add another drug to the prescription, and so on," Professor Bell said.

"So we can end up with lots of patients on four or more drugs where only one would do. This is a big cultural issue to overcome," he said.

Apart from the ethics of prescribing useless drugs to people who could be poisoned by them, there is also the question of costs to the NHS, which has seen a record 50 per cent increase in its drugs bill over the past three years.

As Bill Clarke, the executive vice president of research at Amersham, a British diagnostics company, said: "It's just not right to spend that amount of money on drugs that don't work." For the sake of a relatively cheap genetics test that can be carried out on the wider population of patients, it would be possible to target drugs more effectively and more safely, Dr Clarke said.

It could also lead to a revolution in the way drugs are tested, he said. If "responders" to a new drug can be identified easily, it will be possible to simplify the expensive phase 3 clinical trials which can involve thousand of people being followed over many years.

Dr Roses agreed: "You can pick out people who respond a lot to the drug, can you pick out people who do not respond at all to the drug and can you pick out people who are sort of in the middle.

"By eliminating the people that we predict will be non-responders we'll be able to do smaller, faster and cheaper drug trials."

That could be the incentive that will lead to a change in the "one-drug-fits-all" culture of the drug industry, he said.

"I can't speak for other companies but I can tell you absolutely for sure that there is a change in the culture of GSK," Dr Roses said. And the advent of pharmacogenomics will not necessarily mean a fall in sales.

"If you can determine who is going to have a response [to a drug] and who is not going to have a response, you can take your next molecule and aim it specifically at the people who haven't had a response with the first one so that you can create a set of drugs that cover the population, and then you are back to selling to everybody," he said.

Trial approach

PHASE I: These first studies evaluate how a new drug or therapy should be given (by mouth, injection into the blood or injection into the muscle), how often, and what dose is safe. A phase I trial usually enrols a small number of patients, sometimes as few as a dozen.

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PHASE II: A phase II trial usually focuses on one type of illness, continuing to test the safety of treatment and beginning to evaluate how well it works. This is the essential intermediate step that will determine whether the drug will go into bigger and more costly phase III trials.
PHASE III: These studies test a new drug, a new combination of drugs or a new therapy in comparison to the current standard treatment. A participant will usually be assigned to the standard group or the new group at random (called randomisation). Often it involves "double blind" trials, where neither the patient nor doctor knows who is being given the new drug. Phase III trials often enrol large numbers of people and may be conducted at many doctors' offices, clinics and cancer centres nationwide.

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