

From philosophy to patient benefit

Speakers at a session entitled drug evaluation in the 21st century looked at the successes of drug development. **Olivia Timbs** and **Ann Lewis** report

Is there a hiatus in drug discovery, asked Michael Walker, emeritus professor from the University of British Columbia, Canada, who spoke about current approaches in research and questioned whether or not scientists were taking the best one.

"I am taking a philosophical view rather than a factual one," he added, and then listed some of the problems faced by pharmaceutical companies.

Professor Walker argued that there is a school of thought that, after so many mergers, companies are now too bloated to be innovative. However, he noted that the investment in research and development is at least matched by the number of compounds going into Phase I trials. "The problem seems to be failure in Phase II," he said "so there are far fewer entries into Phase III."

The fundamental error, Professor Walker believes, is that research focuses on molecular targets and that, theoretically, if a disease process can be corrected at that level it will easily translate into a medicine. Taking such a reductionist view, however, misses the point.

Biological systems are complex. "We need to understand physiology and disease processes at the tissue level," he said. This was the approach adopted between the 1940s and 1980s and it "was slow and inefficient and required a lot of dogged research" but it was successful.

He understands why the reductionist approach is attractive: "You can screen millions of molecules to find likely candidates. The technofix is appealing — find the molecule and switch it off so all we need to do is to identify the molecule. It is fast and focused and more efficient." And he added: "We don't need creative geniuses to do it." He also suggested that unravelling the human genome had been seductive but genomic strategies do not mean that the right targets have been found.

Wrong paradigm adopted

"I think the wrong paradigm has been adopted," he explained. "The infectious disease paradigm is suitable for parasitic infestations and bacterial infections [but] it is no good for cancer. Neither is it any good for hypertension," he continued. He added psychiatric diseases and asthma to his list. "These are all complex diseases and the infectious disease paradigm leads researchers to aim at the wrong targets."

He also wondered whether the old fashioned approach to understanding what is going on at the tissue level still has value. Using the example of the treatment of ventricular fibrillation, incidentally the main cause of immediate death, he suggested it does. "For a start, there is no key molecule, there is no single molecular action that can be

targeted. The underlying problem is that damaged cardiac muscle cells go crazy after an infarction. If these cells can be quietened there is a chance that the heart will not go into VF"

Professor Walker explained that the research programme was slow and inefficient, but there is now a novel anti-arrhythmia drug waiting for approval from the US Food and Drug Administration. And he added: "The true nature of this may only appear after widespread clinical use. It wasn't a technofix; we have been building a Formula One car, not a Ford."

Sobering presentation

In a sobering presentation, Tim Mant, director of the Guy's Drug Research Unit, London, and employed by clinical trials company Quintiles, spoke about the impact of the disaster of the clinical trial into TGN 1412 at Northwick Park Hospital in March 2006 that led to six young men being admitted to intensive care with multi-organ failure.

Dr Mant pointed out that it had really shaken the clinical trials community the world over. As far as the disaster itself was concerned, the ongoing problems facing the victims themselves and the ultimate outcome for them was unknown. "Not everything is yet in the public domain as it is in the hands of lawyers," he added. Nevertheless there were aspects that could be discussed and indications given to show how the clinical trials community is doing its best to ensure that nothing like that happens again.

Dr Mant pointed out that the trial had been approved by the Medical and Healthcare products Regulatory Agency, the German authorities and the regional ethics committee. "No errors were found in the formulation, dilution or administration of the drug. There are 20 approved monoclonal antibodies in clinical use, from which over one million patients have benefited." There was little reason that the disaster could have been predicted — whatever some people claim.

There were many lessons that had been learnt from the Northwick Park experience and which were now enshrined in new regulation and guidance, Dr Mant explained. He said that one fundamental issue revolved round the testing of "high risk molecules". "It is not so much the molecule that is high risk but the way it is used," he said. "The main lesson is that trials must be designed to be low risk."

That lay behind the recent introduction of assessment by the Committee for Medicinal Products for Human Use (CHMP). "When planning a first-in-class trial, the risk mitigation strategies are laid down in this." Among the most important points Dr Mant drew at-

tention to was the need to be careful to estimate the first dose to be used in humans with the lowest risk. He acknowledged the difficulties when using biologics where there is no parallel in the animal world. That is why it is essential to do a proper scientific review.

It is also important to have trial stopping rules fully understood and to have staff who are experienced in dealing with medical emergencies. "Don't rely on technology — use experienced staff," he stressed. The Association of the British Pharmaceutical Industry Guidelines for Phase I clinical trials were invaluable.

Investigators need to be properly qualified and, he claimed, the shortcoming was partly the responsibility of the medical establishment, which had downgraded the place of clinical pharmacology in the final medical examination.

However, the Royal College of Physicians is on the point of launching a diploma in human pharmacology for doctors working in clinical research and this qualification should be essential for principal investigators.

There would also be a certificate in human pharmacology available for other health care professionals working in Phase I trials, he said.

"We need to reassure the public that everything has been done to protect volunteers. Ticking boxes is not enough. All data on trials need to be published and shared as early as possible," he emphasised.

Are patients asked what they want?

Trevor Jones, of King's College London, asked whether research was better over 20 years ago — in 1984 — and he used the example of the emergence of HIV/AIDs and the development of retrovir to make his points.

At the time, retrovir was the most underdeveloped drug to hit the market but it was urgent to find a drug treatment. The risk/benefit was in favour of getting the product to market. Since then researchers still have not solved the problem, and the virus continues to outwit scientists.

In the 1980s, it took on average of 12 years to get a medicine to market but from 1998 onwards it has taken up to 14 years.

Do we take enough account of what patients want? They should be taken into the confidence of both the regulator and the manufacturer to find out what risk-benefit balance they will accept, Professor Jones argued. "Most drugs produce side effects and have a variety of active sites. The truth is we do not really understand where most drugs act," he added.

There is much emphasis on pharmacovigilance in clinical trials, but where is the emphasis on benefit?