

# Pharmacists must embrace science

Our coverage of the British Pharmaceutical Conference 2004 continues. **Harriet Adcock** reports sessions on the changing face of science and practice (p525), as well as genomics (p531) and stem cell technologies (p530). **Dawn Connelly** covers the address given by Sir Michael Rawlins (p529) and reports on point-of-care testing (p533). **Rachel Graham** considers automated dispensing (534) and tackling infection (p535). **Christine Clark** reports sessions on new medicines (p528 and p532). Photographs from the conference start on p526

Opinion is divided as to whether pharmaceutical science is relevant to practice, Sandy Florence, dean of the School of Pharmacy, University of London, told BPC delegates. "There is a dichotomy of opinion and we as pharmaceutical scientists need to work very hard in explaining what it is we do," he said.

Professor Florence was emphatic that many of the increasingly difficult problems encountered in pharmacy practice could be resolved by the application of pharmaceutical science, which he described as a unique subject.

Pharmaceutical sciences have an impact on all areas of drug delivery — from administration site to target. "It is a complex journey. From the gross delivery system to the minutiae of the receptor. This is at the very heart of patient care," he said.

Professor Florence urged pharmacists to take pride in the innovations developed by researchers working within schools of pharmacy.

"This pride in our sciences and scientists should drive our profession forward," he said, adding: "A profession that does not recognise

the worth of its scientists or science and does not use and expand its knowledge of science . . . will become a derivative profession always using someone else's knowledge."

He also stressed the importance of pharmacy's role in the development of new drug delivery technologies, warning that if pharmacists did not take an interest, others would. There was a need to take forward novel procedures, drugs and delivery systems, an area sometimes viewed as passé by pharmacy undergraduates. "Chemical engineers are rushing to fill this void," he warned.

Professor Florence was worried that if pharmacists were no longer concerned about medicinal products they would not have the knowledge to make medicines safe.

"Our unique role is that we understand both the product and the patient, especially that increasingly complex relationship between the two," he continued.

Looking to the future, Professor Florence said that new approaches were needed in science and practice because of the variability of human responses to medicines, the unpredictability of adverse drug reactions and the slow progress with gene therapy.

"Individualisation of medicines must happen. In the post genomic era we must tailor dosages of drugs more precisely to patient profiles," he said.

However, he pointed out that scientists often believed that taking theory into practice was easy. The problems associated with delivering gene therapy showed this was not the case and identified a role for pharmaceutical scientists. "If we do not understand it or do not tackle it within the pharmaceutical sciences we will never get gene therapy non-viral vectors," he said.

Another role for pharmacists was to come up with suitable dosage forms required for unusual situations. And an understanding of the pharmaceutical sciences gave them the confidence to tackle such situations.

"There is a generation of practising pharmacists who have become scared of this experimental approach," he said.

This worried Professor Florence, who urged delegates to embrace the pharmaceutical sciences. "We need to apply basic sciences to clinical problems. Not only to drugs but to formulations. Forgetting about formulation is a real drag on our ability to intervene."

## Non-adherence with drugs more likely if patients' beliefs are ignored

Pharmacists should encourage patients to share their views on medicines and illness, Rob Horne, director of the Centre for Health Care Research, University of Brighton, told delegates.

He explained that patients' non-adherence with medicines can be intentional and is related to their beliefs about medicines and illness. There are two factors that appear important when a patient makes decisions about whether or not to take their medicines: the extent to which they believe they need the medicine and how they balance this with their beliefs about the risks involved. "Typically, over 30 per cent of patients harbour strong concerns," he said. "What is more, patients tend to have an exaggerated perception of risk."

He explained that patients' ideas about medicines tend to be derived from their ideas

about illness. He cited the example of asthma, seen by clinicians as a chronic condition needing persistent treatment. Patients may doubt the need for daily inhaled corticosteroids because their view of the disease is centred around symptoms.

"Pharmacists may make the assumption that the patient in front of them shares the same value system," Professor Horne said. In reality there may be two sets of opposing beliefs. "Often it is difficult for patients to tell us [that they have a different view] so we get surreptitious non-adherence."

Patients might think that their scepticism about a medicine will be interpreted as lack of confidence in the practitioner. However, beliefs need to be shared and declared if concordance is to be achieved. "We need to invite patients to give us their views and tell us frankly, without judgement, what they do with the treatment and why," he commented.

Patients' ideas about treatment and disease have an internal logic but there is evidence that patients' beliefs are "not set in stone". They may be changed through education and negotiation. "The future of pharmacy, in



**Rob Horne: beliefs not set in stone**

common with the future of medicine, lies beyond the medical model. This is a key challenge for the next decade," Professor Horne concluded. "Taking account of psychological and social, as well as biomedical, factors will allow pharmacists to work in partnership with patients to get the best from medicines."

The 2004 **British Pharmaceutical Conference** and Exhibition "Medicines: from cell to society" took place at Manchester International Convention Centre from 27–29 September

# We need to develop new medicines more quickly and more economically

The need for innovative approaches to the accelerated development of new, safe medicines prompted the European Federation for Pharmaceutical Sciences (EUFEPS) to draw up its "New Safe Medicines Faster (NSMF)" initiative, Ole Bjerrum from the Danish University of Pharmaceutical Sciences, Copenhagen, told the audience. The thinking behind the initiative is that new medicines needed to be affordable and safe and that it is important to keep a significant amount of pharmaceutical development work in Europe (and not lose it to the US).

In general, EUFEPS believes that the conditions for research and training need to be improved and that the drug development process itself has to be optimised by removing the current bottlenecks. In addition, it would like Europe to have the best systems and state-of-the-art technology, and thinks that the bureaucracy currently associated with drug development will have to be rethought.

Turning to specifics, Professor Bjerrum said that the NSMF initiative calls for new techniques and tools for drug selection and screening and new approaches to drug delivery and targeting to be used. In addition, it recognises the need for advanced pharmaceutical materials and processes to be developed. In particular, it believes that the use of "prediction methodology", which enables the modelling and simulation of many processes, will be important. This will require libraries to be created, and will necessitate wider access to information through readily accessible databases, Professor Bjerrum pointed out. Moreover, double-blind, randomised controlled trials might not be the only types of study that should be used, he added.

Although EUFEPS clearly has a European outlook, the US Food and Drug Administration (FDA) shares some of its concerns. In its March 2004 document entitled

"Innovation or stagnation?", the FDA concludes: "Often researchers are forced to use the last century's tools to evaluate this century's development."

## Reduce costs to survive

The drug industry needs to change radically if it is to survive, was the stark message from Professor Colin Garner, chief executive officer, Xceleron, York. The costs of new drug development are now considerable and the time is right to evaluate new technologies, he added.

Up to 30 per cent of new drugs fail at the phase 1 testing stage. The main reasons for this are shortcomings in the clinical efficacy, safety and toxicology profiles. Some of these failures are caused by an inappropriate dose being used in phase 1 studies, resulting in too much or too little drug reaching the site of action. To prevent this, it is critical to understand how drugs are metabolised at an early stage in the research and development process (ie, "phase 0"), he said.

To this end, two "big physics" techniques are now available that can be used to obtain pharmacodynamic and pharmacokinetic data. These are accelerator mass spectrometry (AMS), which can be used to determine drug kinetics and positron emission tomography (PET), which can be used to characterise pharmacodynamics.

## Microdosing using AMS

Professor Garner went on to explain in more detail about AMS. The technique is based on that developed in the mid 1970s for carbon dating in archaeology. With carbon dating, however, 9,000 carbon atoms (ie, a sizeable sample) are needed in order to observe a single decay event. AMS, however, is much more sensitive — attogram ( $10^{-18}$ g) and zeptogram ( $10^{-21}$ g) quantities can be analysed.

This gives rise to the concept of microdosing, in which tiny, subtherapeutic, subtoxic

doses of drugs are given. A typical radioactive tracer dose would be 80–100 microCuries, but for AMS a nanoCurie amount could be given. For illustration, Professor Garner pointed out that a typical adult contains 400 nanoCuries of naturally occurring  $^{14}\text{C}$  and a banana contains about one nanoCurie of naturally occurring  $^{14}\text{C}$ .

Samples of blood, urine, faeces and plasma can be analysed, Professor Garner continued. In each case the sample is processed in the laboratory to convert biological carbon into inorganic carbon. The sample is then loaded into the instrument. AMS counts atoms rather than radioactivity, although the results are still expressed as "disintegrations per minute". Providing a  $^{14}\text{C}$  atom can be inserted into a molecule, then its progress in the body can be followed, Professor Garner pointed out.

Hitherto, drug discovery has involved the synthesis of large amounts of large numbers of compounds followed by *in vitro* studies or animal testing. Microdosing allows the rapid comparison of several molecules or several dose levels and means that a smaller amount of each compound needs to be produced for testing. The responses observed in microdosing are 70–80 per cent predictive of the response that will be elicited with pharmacological dosing, he said. The technique is also fast — it only takes a few seconds to "count" a sample.

Currently, preclinical studies can take up to 18 months at a cost of \$3–5m. Microdosing techniques could reduce the time to four to six months and the costs to \$0.35m per new molecule, Professor Garner explained.

The current disadvantages of AMS are that the equipment is expensive and large — it takes up space equivalent to two tennis courts. Smaller and cheaper instrumentation is likely to be developed in the future though, Professor Garner concluded.

## JPAG

The Joint Pharmaceutical Analysis Group is a focus for the presentation and discussion of matters of importance to those interested in pharmaceutical analysis. The group's remit is "to encourage, assist and extend the knowledge and study of pharmaceutical analysis and quality control by the holding of scientific meetings, by the promotion of lectures, practical demonstrations and discussion, or by any means consistent with the aims and objects of the sponsoring bodies and the with the rules of the group".

The group normally holds scientific meetings in January, March (with the group's annual general meeting), May, October and December. The meetings are generally held on Thursdays at the Royal Pharmaceutical Society's headquarters in London. The group also encourages joint meetings with other organisations. In some years, one or more sessions are organised within the British Pharmaceutical Conference.

The group's sponsoring bodies are the Royal Pharmaceutical Society and the Royal Society of Chemistry. Membership is open to members of either society and is free to members of the Royal Pharmaceutical Society. Pharmacists wishing to join the group should apply in writing, giving their registration number, to the Secretariat, Joint Pharmaceutical Analysis Group, Royal Pharmaceutical Society, 1 Lambeth High Street, London SE1 7JN. A programme of meetings is available from the secretariat.

## APS

The Academy of Pharmaceutical Sciences is an independent professional body which aims to provide scientific training through conference and seminar programmes, support focus groups for networking in specialised subject areas, collaborate with other organisations in Europe and the United States and represent views nationally and internationally.

The APS works in partnership with the Royal Pharmaceutical Society to develop programmes for scientific events, including the BPC science programmes. Further information can be found on the APS website, [apsqb.org](http://apsqb.org).

# Call for a different way of analysing clinical trials, funded by public money

**W**e should be looking at different approaches to designing and analysing clinical trials, Sir Michael Rawlins, chairman of the National Institute for Clinical Excellence, told participants during his keynote address at the British Pharmaceutical Conference.

"The classical approach to looking at clinical efficacy is the randomised controlled parallel group trial," said Professor Rawlins. The analysis of clinical trial data is conducted according to frequentist principles, ie, the probability of a random event occurring according to its relative frequency, using a null hypothesis and generating a *P*-value. Professor Rawlins explained that this approach is based on the work of Ronald Fisher and two of his enemies, Jerzy Neyman and E. Pearson, in the early part of this century. "Fisher was a genius but he was also a bully . . . and he had many vile disagreements with both Neyman and Pearson," he said. As a result of Fisher belittling other forms of statistical analysis, few statisticians over the next 50 or 60 years even considered arguing against the basis of the frequentist approach.

## Alternative statistical approaches

However there are alternative approaches to the design and analysis of clinical trials, said Professor Rawlins. He explained that historical controlled trials have almost fallen into disrepute. However many treatments that we use are based entirely on data from these trials. He cited insulin for diabetic ketoacidosis and thyroxine for myxoedema as examples. Historical trials can be analysed following Bayesian principles, ie, that probability applies to degrees of plausibility given incomplete knowledge. The Bayesian theory is named after Thomas Bayes, a non-conformist minister who lived in the 18th century, explained Professor Rawlins. "He produced a book describing his approach to probability and the calculation of probability densities." Probability densities are another way of looking at the effectiveness of a drug.

In 1992, Byar *et al* promoted criteria for accepting data from historical trials. These are:

- There is a biological basis for the trial
- The condition is life-threatening or permanently disabling
- The condition has a known and predictable natural history
- There is no effective treatment

Professor Rawlins said that he would add "effect size is large" to this list.

The Bayesian approach has many advantages over the frequentist approach, he explained. It does not require a null hypothesis, it does not



**Sir Michael Rawlins: I believe we need clinical trials analysed by Bayesian approaches alongside frequentist approaches**

require predetermined power calculations or type I and type II errors, you do not have to have prespecified subgroup analysis and there are no *P*-values. Bayes's hypothesis (the way of calculating the probability density) requires that you have a "prior", that is what you believe about the state of knowledge before the experiment. "In the case of a historical trial the prior is the data from the historical control," said Professor Rawlins. But in some circumstances it can be difficult and has led some Bayesian statisticians to resort to getting the opinions of experts about how good they think a treatment might be before it is given. "As you can imagine this has produced some degree of sneering among frequentist statisticians," said Professor Rawlins.

He explained that historical controlled trials could be more widely used than in the past, particularly if the natural history of diseases can be established in advance of their treatment. "It would be a great advantage if we could do this as it would cut down the rate and the duration of drug development substantially." He concluded: "I believe we need clinical trials analysed by Bayesian approaches alongside frequentist approaches".

A participant at the conference asked Professor Rawlins who will carry out these studies since it will not be a cheap investment. Professor Rawlins replied that he envisages that a company running a conventional trial via a frequentist approach could run a Bayesian statistical analysis in parallel. "That would be funded by public funds. I do not think it is reasonable to expect the company

to do that," he said. He added that the Government, through the Medical Research Council and the Department of Health, is interested in principle in joining forces with the pharmaceutical industry in this way.

## From market to NHS

Professor Rawlins then went on to talk about getting the drug from the marketplace to the NHS. "This is where NICE comes in."

He summarised the roles of NICE and set out his thoughts for the future. "We need to develop methodology better. There are some areas, particularly looking at cost-effectiveness and guidelines, where methodological developments need to be undertaken," said Professor Rawlins. He told participants that although implementation was not part of NICE's role when it was set up, it will now be taking on responsibility for encouraging it. "Somebody else was going to do it, but unless someone else does it, we are a waste of space," said Professor Rawlins.

Another important area for NICE is public health. "We have been asked to take over responsibility for giving advice on public health that formerly rested with the Health Development Agency," he said. He predicted that this will almost double the staff and the budget of NICE. "It offers a real opportunity for us to ensure that public health issues come into our guidance and that public health benefits from the experience that we have gained in the past few years, particularly in the area of cost-effectiveness."

# Pharmacy education is at a crossroads

**P**harmacy: a bridge between science, industry and practice, was the title of the Harrison Memorial Medal Lecture 2004 given by Bill Dawson, of Bionet Ltd. He spoke about the shift in education and training of pharmacists to fit the changing perceptions and needs of the profession over the past 50 or so years.

Professor Dawson also described the opportunities for pharmacists in many areas and how the teaching of them needs to reflect their needs and their future careers. "A pharmacy qualification gives you the opportunity to work in industry, research, academia, practice and education."

In Professor Dawson's view pharmacy education is at a crossroads and the profession needs to see the wider picture in education. In the future the need for integrated science and practice will be driven by patients' needs, the new sciences of genetics and genomics, and the impact of point-of-care diagnostics.

Ian Wong, who delivered the *Chemist & Druggist* Practice Research Award Lecture, spoke about improving the health of children and the research priorities related to children's medicines.

Dr Wong, who holds a joint post at the School of Pharmacy and Institute of Child Health, University of London, scotched the myth that the reason so little research was carried out on the use of medicines in children is on technical and ethical grounds. The main reason, in Dr Wong's opinion, is the lack of suitably trained investigators to carry out such research.

He then described a number of different studies that are now being undertaken with children. He highlighted the prescribing of psychotropic drugs as one area that is now having more attention. He also revealed the poor evidence base for the prescribing of antidepressants in children and also the high rates of dosing errors in children in hospital.

The Conference Science Award Lecture was given by Jean-Yves Maillard of the University of Brighton. The award is given to a researcher under the age of 35 years.

He spoke about the need to control and eradicate super-bugs and how understanding the mechanism of action of biocides may be a way to prevent microbial resistance developing.

Although high concentrations of biocides are effective, they are usually available in practice at much lower concentrations. Are these lower concentrations actually promoting the development of resistance, he asked.

Dr Maillard then described the different mechanisms of action of glutaraldehyde and ortho-phthalaldehyde and how an understanding of these can be exploited to make them effective biocides at low concentrations without leading to the development of resistance.

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# Tissue engineering set to bring benefits for patients

Details of the latest tissue engineering techniques to benefit patients were presented to conference delegates in a session devoted to stem cell technology.

Molly Stevens, of the Imperial College of Science and Technology, London, explained that conventional approaches to tissue engineering — adding stem cells to solid scaffolds in the presence of growth factors — are still commonly used but are associated with problems when engineering highly vascularised or complex tissues. The approach being developed in Dr Stevens's research group overcomes some of these problems.

The technique involves developing an *in vivo* bioreactor — using the patient's own body as a cell source and scaffold. There is no need to harvest cells or to culture them *in vitro*. "This means that immune rejection is not an issue," Dr Stevens explained.

The methodology has been tested in rabbits to grow new bone. "The results were dramatic," said Dr Stevens. "After six weeks there was a huge amount of new bone." Not only was it revascularised, the bone cells were also organised correctly. Adding growth factors did not affect bone growth significantly and an average patient would not need them, she said. After it had grown, bone could be easily harvested and transplanted into a non-healing defect where it fully integrated.

Sheila MacNeil, of CellTran Ltd and the University of Sheffield, described the surface technology and cell culture techniques being used to improve skin replacement materials. The conventional technique involves collecting cells from the intact skin of patients. These are then cultured and grown as sheets on a donor dermis layer.

## Stem cell culture: new technology looks set to improve skin replacement materials

One of the drawbacks is that the cultured cells take several days to form an integrated sheet. The functional shelf-life of the sheets is inflexible. It takes nine to 10 days for the sheets to grow and they have to be used within one to two days or the sheets blister and will not attach to the patient.

"Even when we have the same people managing the patient and growing the cells it is difficult to time the sheets to benefit the patients," said Professor MacNeil. The sheet of cells produced is also fragile and difficult to handle.

"This methodology has been around for a long time and has helped many patients survive," she said. However, it relies on mouse fibroblasts to provide a feeder layer, as well as a combination of growth factors and bovine fetal calf serum. "It is a combination of man, mouse and cow," she continued.

Because of these problems the technique has not been routinely adopted in clinical practice. "We needed a simpler way of getting the cells from the lab to the patient," she added.

Professor MacNeil's research group used plasma polymerisation to develop a surface that keratinocytes would attach to, grow on and then leave to go into the wound bed. Improvements to the technique have led to the development of a product called MySkin.

The first proof of concept study was in six patients with diabetic foot ulcers — healing was seen in six out of nine ulcers and one ulcer reduced in size. MySkin has also been tested in burns patients and in patients with post burns complications and those with long-standing ulcers resistant to standard therapy.

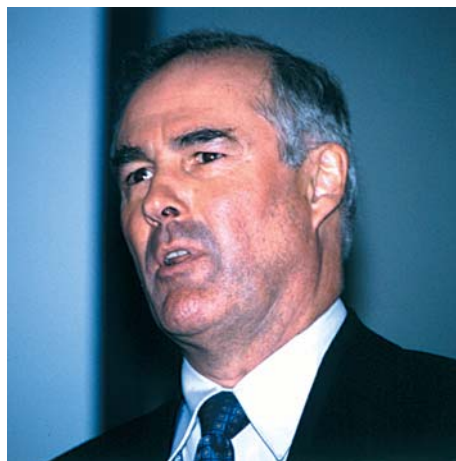
# Regulators likely to insist on genetic testing soon

Regulatory agencies are a whisker away from including genetic testing requirements in marketing authorisations for new drugs, according to Tony Moffat, chief scientist at the Royal Pharmaceutical Society.

Professor Moffat predicted that for certain drugs genetic tests would be made mandatory before the drug could be prescribed. He illustrated his point with the example of Strattera (atomoxetine), a new drug licensed for the treatment of attention deficit hyperactivity disorder.

The drug is primarily cleared by CYP2D6 cytochrome P450 enzymes and, in clinical trials, patients who were poor metabolisers suffered more adverse drug reactions than those who were extensive metabolisers. When considering the application for marketing approval of Strattera, the US Food and Drug Administration suggested that genetic tests should be conducted before use.

"That was ground-breaking," said Professor Moffat. The FDA could not go further than this because there were no FDA-approved tests. Had there been an approved



**Tony Moffat: genetic tests mandatory**

test, Professor Moffat believes that genetic testing would have formed an integral part of the drug's licence.

"We are now at the brink — the FDA has said you should test, but they are only a gnat's whisker away from saying you must test."

Professor Moffat went on to say that the FDA also wants to improve the risk benefit ratios of four other drugs — azathioprine, mercaptopurine, warfarin and irinotecan — by including pharmacogenetic information in their marketing authorisations. "The FDA is asking companies for information about pharmacogenetic testing of individuals and the adverse drug reactions that those patients experienced so it can consider whether to change the marketing authorisation of the drugs. That is going on now," he said.

In the case of mercaptopurine, Professor Moffat explained that the degree of bone marrow toxicity seen in a particular patient was dependent on their genetic profile. Those with a limited capability for metabolising mercaptopurine needed a lower dose than extensive metabolisers. One in 300 patients would need just 10 to 20 per cent of the normal dose if they were to avoid bone marrow toxicity. "The FDA is revising the [marketing authorisation] now. Tests are available and I think they will make it mandatory to test patients before these drugs are given," he said.

## Formulation can influence gene expression and response to drugs

Delivery systems, as well as drugs themselves, can influence gene expression, Saghir Akhtar, University of Cardiff, warned.

He reminded conference delegates that drugs do not work by themselves and need formulating. Much has been said about how genes influence the response of a given drug. "We have probably forgotten about the formulation. What does the formulation do and how critical will that be in altering our prescribing habits," he asked.

This is a question that Professor Akhtar has tried to answer. In laboratory experiments his research group has shown that drug delivery systems alter gene expression in cell culture and animal models. "They can actually switch on or switch off gene expression. That seems fascinating to us," he said. He warned that these changes, which are not well understood, would be important for gene medi-

cines where only a single specified gene change is sought by the clinician. "We need to take a step back and understand why [these genetic changes are happening] and what are the consequences to patients."

He gave the examples of dendrimers and branched polyethyleneimines (PEIs), formulations used to deliver gene medicines. When dendrimers are added to cells in culture, genes are both up- and down-regulated. "In some cases, this will lead to phenotypic changes that are quite obvious very quickly," he said.

One is programmed cell death, a chain of events triggered, not by a drug, but by the delivery system.

Likewise, when branched PEIs are introduced into tumour cells in an animal model, gene expression changes. Professor Akhtar reported that over 800 genes were upregulated

and over 700 were downregulated in an array of 20,000 genes.

Laboratory results also suggested that excipients, already commonly used in medicines prescribed today, can alter gene expression.

Professor Akhtar said that changes had been observed in a diverse range of genes — from changes in ligands that are responsible for interacting with cell-surface receptors and changes in the receptors themselves to changes in signalling molecules.

What are the consequences of these gene changes on drug action and will potential polymorphisms in the altered genes change clinical response to drugs and their formulations? Professor Akhtar did not have the answers to these questions but warned that pharmacists should be aware of the influence that delivery systems can have on gene expression and drug response.

## Delivery is key to developing gene therapy products for patient use

Delivering sufficient DNA to the nuclei of the appropriate cells and having it stay there long enough to achieve protein expression remains a big challenge when developing gene therapy products. This was one of the main messages from the presentations of Tony Phillips, of Phillips Consulting, and Len Seymour, of the University of Oxford, who gave their perspectives on the issues that need to be overcome when developing gene therapy products, from an industrial and academic stand point, respectively.

Various delivery methods are being looked at, including coating DNA onto gold particles and firing it into the skin. Once in the epidermis, the particles are taken up by antigen presenting cells, eliminating many barriers traditionally associated with delivery to the immune system, Dr Phillips said.

Challenges other than delivery include those relating to manufacturing and quality control and product safety. Products using non-viral vectors are generally manufactured using *Escherichia coli* fermentation techniques

and so there is a need to limit endotoxin content and the amount of bacterial DNA and RNA present. It is also important to make sure that a minimum amount of the therapeutic DNA is in the supercoiled form, since this is more prone to strand breakage. For viral vectors, yield is an issue, particularly when retroviruses are used, Dr Phillips said.

Another challenge is the expense of research and development. "The costs of getting products into clinics are prohibitive for academia," Dr Seymour added.

# Nanomedicines: now in clinical use

Products relying on nanotechnology — known as nanomedicines — are now in routine clinical use, delegates heard. These include medicines incorporating polyethylene glycol (ie, pegfilgrastim), stealth liposomes (ie, Doxil), polyglutamation (ie, polyglutamated paclitaxel, Xyotax) and antibodies (ie, gemtuzumab, Mylotarg).

## Pegfilgrastim

Attaching polyethylene glycol (PEG) to filgrastim avoids the need for the product to be injected daily, according to Graham Molineux, from the Department of Hematology at Amgen, California. Filgrastim is used to avoid febrile neutropenia in patients undergoing bone marrow transplantation.

The hypothesis behind the development of pegfilgrastim was that if renal clearance of filgrastim could be eliminated, the only remaining route of removal would be neutrophil-mediated clearance. Neutrophils are actually the product of filgrastim action, so the clearance of the drug could be linked to the drug's effectiveness — the faster the recovery, the quicker the drug is cleared, and the slower the patient's response, the longer the drug persists.

Dr Molineux explained that filgrastim has five potential sites for linkage of PEG (via free amine groups on lysine or methionine moieties). In the process of developing the final product more than 40 different pegylated filgrastim molecules were synthesised, using linear and branched chain PEGs, PEGs of different molecular weights and with PEGs of different sizes at different sites. The product that was finally selected has a linear PEG attached to the N-terminal methionine of granulocyte-colony stimulating factor, so that the bulky PEG component does not interfere with the rest of the molecule or its ability to interact with its cognate receptor.

Turning to the clinical use of pegfilgrastim, Dr Molineux described how a daily injection of filgrastim enhances the diurnal variation of neutrophil levels. However, pegfilgrastim produces a relentless increase in neutrophil levels. Normal filgrastim is associated with a 48-hour response as it steadily leaks out via the kidneys, but this is not the case with pegfilgrastim. Moreover, the half-life of pegfilgrastim increases with increasing dose, suggesting that there is a saturable element to its clearance. Had a form been developed that was not sensitive to neutrophil-mediated destruction it was possible the drug could have lasted an inordinate length of time in the body, raising concerns about the possibility of excessive exposure to the drug, Dr Molineux said.

Phase 3 studies have been conducted in breast cancer, one trial dosed by weight and the other using a fixed dose. A curious feature of pegfilgrastim is that as body mass increases the bioavailability of the drug increases, with



**Graham Molineux: nanomedicines such as pegfilgrastim are now in the clinic**

the result that heavy patients are effectively exposed to larger doses. "This is one instance where one size really does fit all," Dr Molineux noted. Further studies have shown that the dose effect holds over a wide range of body weights, although there is still uncertainty about the correct dose for children, he said.

## Stealth liposomal doxorubicin

Stealth liposomes differ from conventional liposomes in that they are coated with polyethylene glycol (PEG), explained Alberto Gabizon from Shaare Zedek Medical Centre, Jerusalem. This enhances their hydrophilicity, and enables them to "evade" the reticulo-endothelial system, thereby slowing their clearance from the body. They have been used to develop "stealth liposomal doxorubicin" (Doxil), Professor Glabizon explained.

There can be 10,000 to 15,000 drug molecules inside a single stealth liposome making the concentration so high that the substance is gelified. Once the liposomes reach permeable (eg, tumour) tissue, they leak into the interstitial fluid and release their drug cargo. The drug can then diffuse into the tumour cells. Higher concentrations of doxorubicin are therefore achieved in tumour tissue after administration of Doxil than after free doxorubicin and the inhibition of tumour growth is correspondingly greater. Doxil is four times more effective than the equivalent dose of free doxorubicin and a small increase in the dose results in a large increase in the dose delivered to tumour tissue. One critical parameter that affects drug delivery is the diameter of the liposome — particles greater than 400nm in diameter are hardly extravasated at all and therefore deliver little of the drug, explained Professor Gabizon.

Stealth liposomes that contain other drugs for cancer treatment are being developed, said Professor Gabizon. They include cisplatin, a mitomycin prodrug and a targeted form of Doxil.

## Polyglutamated paclitaxel

A polyglutamated form of paclitaxel (Xyotax) has made it possible to deliver large doses of the drug without the need for extensive premedication and without the risk of alopecia, Jack Singer from Cell Therapeutics Inc, Seattle, Washington, told delegates.

Conventional paclitaxel injection is formulated in "toxic solubilising agents" because of its poor aqueous solubility. It is given by injection over a three-hour period, preceded by a battery of premedication. Xyotax, however, is water-soluble and can be given over 10 minutes. It achieves plasma levels that are 12 times higher than the conventional form with little or no free drug in the plasma. The absence of free drug in the plasma is thought to account for the low systemic toxicity of Xyotax, Dr Singer explained.

Experiments suggest that Xyotax is taken into tumour cells by a process of active endocytosis and that the drug is released as a result of intracellular enzyme action. This might form the basis of its ability to overcome the effects of the multi-drug resistance pump, unlike conventional paclitaxel, Dr Singer postulated. In addition, Xyotax is synergistic with other cancer treatments. In particular, it increases radio-curability of animal model tumours. The results of trials of Xyotax in non-small cell lung cancer are expected early in 2005, Dr Singer told delegates.

## Gemtuzumab

Gemtuzumab (Mylotarg) is a humanised antibody linked with the anti-tumour antibiotic calicheamicin. It is licensed in the US (but not yet in Europe) for the treatment of certain patients with CD33-positive acute myeloid leukaemia, according to Michael Eaton, from Celltech R&D.

Calicheamicin is too toxic for human use on its own, Professor Eaton explained, but when linked to an antibody, its toxic effects can be targeted. The antibody portion of the molecule binds to the CD33 antigen, which is commonly expressed by myeloid leukaemic cells. The drug binds to the minor groove of the DNA molecule and causes irreparable double-stranded breaks to occur.

## More about nanomedicines

Further details about nanomedicines on the market or undergoing clinical trials and their development were set out in last week's coverage of the British Pharmaceutical Conference (PJ, 20 October, p485).

# Point-of-care diagnostic testing: new technologies move from lab to desktop

A session on point-of-care diagnostic testing began with an overview of the science behind the tests and a look at technologies in development. Gary Thorpe, of the Wolfson Research Laboratories, University of Birmingham, explained that point-of-care testing is applied in many different disciplines and that many different types of tests are available. "They are bringing down the cost of manufacture so that you can now throw away instruments," Dr Thorpe added.

A simplified look at the science behind point-of-care tests revealed that they work by three main mechanisms:

- Specific chemical reactions
- Specific enzymes
- Specific antibodies

Dr Thorpe explained that with all of these reactions, a colour change is monitored or a device is used to produce a current or voltage which is then measured. Generally, all the reactions are dry-phase reactions and some kind of strip or electrode is used.

Moving on to recent developments, Dr Thorpe described a non-invasive continuous glucose monitoring system that might be available in the future. It is in the form of a disposable biosensor on the back of a watch. The test works by reverse iontophoresis: a small current is applied to the surface of the skin through which ions are dragged. Electrochemical detection can then be used to measure glucose levels every 20 minutes. The biosensor needs to be replaced twice a day. Dr Thorpe pointed out that the system was not perfect; users have to wear the watch for three hours to equilibrate it with their skin and a finger prick sample is still necessary in order to calibrate the system.



**Gary Thorpe: we are entering an exciting stage of new technologies**

"We are entering an exciting stage of new technologies, assays and applications which will become commercially available and I think that it will have an important impact on health care, the biotechnology industry, pharmacies and the general public," Dr Thorpe concluded.

## Pharmacogenetic testing

Pharmacogenetic testing can be used to predict a patient's ability to metabolise a drug and this information can help to reduce the incidence of adverse drug reactions.

"The process of 'take a pill and come back if you have a problem' clearly is back to front. We should really be looking to a future where we, and the pharmaceutical industry, look to tailor the medication far better to the needs of the patient," said Paul Debenham, director of life sciences at LCG, an independent analytical laboratory.

He told participants that the US Food and Drug Administration has started to prompt pharmaceutical companies to introduce pharmacogenetic data into their clinical trial dossiers. The FDA is focusing on a small number of genes that it considers are valid, for example, CYP2D6. This gene has a mutation called \*4, which inactivates an enzyme in the liver and reduces a person's capability to metabolise a vast range of drugs. Dr Debenham explained that people with this mutation are at risk of suffering adverse reactions since the recommended dose is determined in clinical trials using subjects who metabolise the drug at a normal rate.

The challenge has been how can we take pharmacogenetics from the laboratory to the GP practice, said Dr Debenham. Traditionally, pharmacogenetic testing has been conducted in laboratories by extracting DNA from a sample of blood, saliva or urine and analysing it. He explained that several companies are currently developing a system of direct sample analysis. This means that the sample can be analysed in one step, without the need for DNA extraction. In a system that LCG is developing, target amplification and sample analysis can be carried out in 16 minutes, said Dr Debenham, but it should be possible to speed this up in the future. The instrument used is the size of a shoe box and it is capable of analysing 12 samples at one time; this could be 12 samples from different people or 12 different tests on one sample. The cost will be in the region of pounds (rather than hundreds of pounds) per test, and the instrument itself will be far cheaper than the necessary laboratory equipment. Dr Debenham told participants that LCG is currently in discussions with a manufacturer and hopes that it will be less than five years until this sort of technology reaches the marketplace.

## Pharmacists can help MHRA to regulate devices

The medical devices bill is set to overtake the drugs bill in the not too distant future, Susanne Ludgate, medical director of the Medicines and Healthcare products Regulatory Agency, told participants at the conference. There are currently 80,000 devices on the market. This represents about £10bn annually to the health service and £150m is spent annually on maintenance.

Point-of-care tests are increasing in number, said Dr Ludgate. They offer flexibility in terms of managing patients and allow patients to take control of their conditions. The MHRA has four separate roles (see *PJ*, 6 December 2003, p780):

- Evaluation
- Regulation
- Adverse incident investigation
- Provision of advice to the health service

Point-of-care tests that the MHRA has evaluated recently include blood glucose monitors, *Helicobacter pylori* tests, coagulation monitors and cholesterol tests, and the reports are available on the MHRA website. Dr Ludgate explained that since 2000 every point-of-care test that comes onto the market carries a CE mark that demonstrates compliance with the relevant essential requirements, which cover all aspects of safety and performance.

The MHRA also runs the largest user reporting system in the world. The vast majority of reports come from health care professionals. Last year 8,795 reports were received and 46 device alerts were issued to the health service. Dr Ludgate said that the MHRA will be issuing more advice to pharmacists and asking for their help. Point-of-care tests are going to become an increasingly important area for pharmacists, said Dr Ludgate. "You are going to need to know about the tests, and how to report adverse events."

She encouraged pharmacists to tell the MHRA if they need further guidance on any aspect of medical devices.

# Robots benefit patients and staff in hospital and community pharmacies

Introducing automated dispensing brings significant benefits to patient care and to staff in both hospital and community pharmacies, according to Pippa Roberts, chief pharmacist and acting director of governance and corporate affairs, Chelsea and Westminster Hospitals NHS Trust, and Andrew Gray, superintendent pharmacist at Grays Pharmacy, with branches at Berwick-upon-Tweed and Tweedmouth, Northumberland.

## Experiences from hospital pharmacy

As a busy department in a large London teaching hospital, it is easy to see why the pharmacy at Chelsea and Westminster is the sort of place where automation would be expected to make the dispensing process more efficient, Ms Roberts said.

What was more of a challenge, however, was convincing trust managers to release the necessary funds, she said. To do this, she built up a business case, identifying the main stakeholders and assessing what the key drivers were for them. For example, trust chief executives are concerned with meeting national targets, she said. At Chelsea and Westminster, there were issues with outpatient waiting time targets, not least because people were waiting two hours for their medicines to be dispensed. "But there was just not enough room to get any more pharmacy staff or stock into the small outpatient dispensary," she explained.

In addition, pharmacy staff were becoming increasingly involved in ward-based roles, she added, but finding the time to do these was difficult. This was particularly the case on a Friday afternoon, when even the most senior pharmacists were being called back to the dispensary to help with the workload.

Once the funds had been secured, the implementation process went fairly smoothly, she said. "The robot was put up in five days and we were able to preserve the service and work around it." More problematic were issues such as the costs of software interfaces, which are needed for the existing pharmacy computer system as well as the robot itself, she explained. Training and testing the system were key to successful implementation. "You can't do enough of either of these," she stressed. Also it is important to view the robot as just a part of a wider system change, she added.

Now it is up and running, the robot picks approximately 100,000 packs per month. A large portion of these are items for ward boxes, which are now selected overnight, Ms Roberts explained. "About 80 per cent of stock is now stored in the robot, including re-fragrated items," she added. Real time stock



**Dispensing robot in place at one branch of Grays Pharmacy**

control is another benefit, especially where there are satellite pharmacy departments housing expensive drugs such as those used for patients with HIV. The robot makes it easier to know where all the stock is located and enables overall stock levels to be reduced, she said.

For staff, one of the main benefits of having automated dispensing is that they now go home on time. There has also been a positive effect on recruitment. Even though there has been an overall increase in dispensary activity, 34 per cent fewer pharmacists and 52 per cent fewer technicians now work there, Ms Roberts continued. "This has refocused the way we can deliver services," she said. "These staff have been redeployed in pharmaceutical care." Outpatient waiting times for medicines are now down to 20 to 30 minutes, she added.

Using automation "as a platform for service improvement" brings significant benefits, Ms Roberts concluded.

## A community pharmacist's viewpoint

Relocating to a small, awkward-shaped site in a busy health centre was the main impetus for introducing automation into one of his company's two community pharmacies in Scotland, according to Andrew Gray, superintendent pharmacist for Grays Pharmacy. As well as the space issue, there was a need to free staff time, in order to introduce new patient services such as carrying out medication reviews.

Cost was clearly an issue, Mr Gray continued. A wholesaler would fund the software, but not the robot itself, and it was too difficult to share the equipment with other local pharmacies. Some limited funding was avail-

able from the local primary care trust, he added. In the end, a simple "hire purchase" deal was agreed with Mr Gray's bank. "The bank was used to setting up these for financing tractors and combine harvesters," he said, "but this was its first dispensing robot."

Installing the robot took about two weeks, he said, with filling it and training staff taking another week. His tips for installation include designing the pharmacy around the robot and giving it as much capacity as possible.

One of the main benefits of installing automation is that technicians now work individually at a computer terminal. It is no longer the case that one technician produces the label with another technician finding the stock. This will make it easier to introduce technician checking, he pointed out. The dispensing service now provided seems to be faster and more efficient, he added, although this is difficult to measure, given the move to a new site. Staff time has been freed too, particularly at the branch where the robot is not located, since some dispensing has been centralised to the automated branch.

On the downside, Mr Gray mentioned that the conveyors of the system are noisier than expected. Establishing a drug database for the robot was difficult, he said, but they did a lot of this work from scratch, which would not necessarily be the case for those installing automated dispensing systems now. Labelling interfaces are also an issue, with Grays Pharmacy being on its third labelling system and second wholesaler since the robot was installed five years ago. The full potential of centralising dispensing has also not yet been realised because of issues with patient medication records, he said.

Mr Gray pointed out that there was no simple formula along the lines of the number of prescriptions that need to be dispensed per month before the costs of automation can be justified. Issues such as the moves towards linking payment with service developments and the costs of, for example, building extensions to pharmacies need to be considered as well. "But if I were a medium sized-pharmacy with a few branches in a local area, I'd be thinking about automation," he said.

## But it is not suitable for all

Delegates at another BPC session were informed by Steve Churton, assistant pharmacy superintendent at Boots The Chemists, that a small scale trial of automation in two of its larger stores (in Oldham and Newcastle) "had not brought the benefits that we imagined it might".

# Holistic approach to MRSA is needed

Tackling methicillin-resistant *Staphylococcus aureus* in hospitals requires a multidimensional, holistic approach, according to Phil Wiffen, formerly a pharmaceutical adviser on antimicrobial resistance at the Department of Health and now part of the Cochrane review team. And pharmacists have a key role to play in several areas, not just in promoting the prudent use of antibiotics, he added.

To illustrate his point, Mr Wiffen went through the action areas for combating MRSA, as set out in the Department of Health's "Winning ways" document (see Panel). Four out of the seven action points could benefit enormously from pharmacists' involvement, he said.

## Pharmacists' roles

First, pharmacists can help make real inroads into reducing reservoirs of infection. A common source of MRSA infection is feeding lines in patients requiring TPN (total parenteral nutrition), Mr Wiffen explained. Pharmacists have expert knowledge about the components of TPN and how they support microbial growth. "We need pharmacists to be an integral part of TPN teams", he said.

As well as understanding the composition of TPN, pharmacists can also appreciate the science behind disinfecting equipment such as feeding lines. But this skill is often underused and pharmacists should become more involved in advising in this area, he added.

Second, hospital pharmacists need to protect themselves and their patients from infection by maintaining high standards of hygiene. "Clinical pharmacists often believe that they do not have physical contact with patients," he said, "but this can be a misperception." Pharmacists often shake a patient's hand, and could thereby transfer MRSA, he said. In addition, they touch drug charts and bottles of medicines, all of which can then become contaminated with MRSA.

Mr Wiffen suggested that protocols for pharmacy staff working on wards should be drawn up and that they should include hand washing directions. The protocols are relevant to both clinical pharmacists and ward-based technicians, he stressed. In particular, there needs to be awareness that pharmacy staff need access to alcohol hand gels and, if they are carrying out ward-based work, they need to use them, rather than just be part of the supply chain handing them over to doctors and nurses, he said.

Third, the type of management structure and organisation a trust needs to have in place to help it combat MRSA includes having senior pharmacists as members of its management team, a set up that helps to ensure pharmacists' contributions are properly realised.

Fourth, encouraging better prescribing of antimicrobials is a key area in which pharmacists should become involved, Mr Wiffen explained. He advocated the development of

## Coloured transmission electron micrograph of MRSA cells dividing

specific clinical roles for pharmacists and technicians to support prudent prescribing. Much has been achieved in this direction, especially as a result of the £12m funding for clinical pharmacy initiative announced by the Department of Health last year, he noted. But a lot also remains to be done. For example, when he made an internet search of hospitals' antibiotic prescribing policies and guidelines, he found several that did not even mention MRSA. Another area yet to be exploited to its full potential is joint initiatives between primary and secondary care, he added.

It is also important not just to concentrate on "chapter five" antimicrobials (ie, the antimicrobials for oral and intravenous use listed in chapter five of the British National Formulary), he said. Prescribing data for "chapter five" drugs show that their use has been steadily reducing, but the prescribing of "less obvious" antimicrobials, such as those combined with corticosteroids in preparations for the skin, is increasing. "This may well be contributing to part of the resistance problem," Mr Wiffen said.

## Action points from the "Winning ways" document

- Carrying out surveillance and investigation
- Reducing infection risks from the use of catheters
- Reducing reservoirs of infection
- Maintaining high standards of hygiene
- Promoting prudent use of antibiotics
- Carrying out appropriate research and development
- Having effective management and organisation in place

As with the other dimensions in the fight against MRSA, both "restrictive" (ie, telling prescribers that they can only use certain antibiotics) and "educational" (ie, providing suitable training) need to be adopted when promoting better antimicrobial use, he pointed out. That way, the number of MRSA bacteraemia cases, currently standing at an average of 65 per year for a 1,000-bed hospital, representing a 5 per cent increase since the financial year 2001-02, might start to reduce.

## Evidence base for interventions

Pharmacists and other hospital staff should look for evidence to back up the interventions they make and recommend to others when trying to combat MRSA, according to Jonathan Edgeworth, consultant microbiologist at Guy's and St Thomas' Hospital NHS Trust, London.

Mr Edgeworth conceded that this could be difficult. For example, a study reported in the *BMJ* looked at 4,382 abstracts, 254 papers and 46 reviews to find out whether isolation worked as a means of controlling MRSA. Out of all of these, there were no randomised studies and only four studies had been preplanned. "Best evidence" came from six studies, four of which found the measure to work, one of which found it to fail and one of which found it to work for a period of time before failing.

Reasons for the poor evidence base included that infection control measures could not be randomised, Mr Edgeworth said. Also, interventions are generally started at the height of an outbreak, which will progress back to endemic status anyway, he added. Moreover, multiple actions are usually taken, and so it is difficult to assess the influence of any particular single intervention.

Nevertheless, pharmacists need to look for evidence and if appropriate, carry out their own studies. For example, preliminary work carried out at the intensive care unit of his trust suggests that a variety of measures, including the use of nasal chlorhexidine, might help control MRSA. However, it is important to look at the wider implications of any interventions, he stressed. For example, he is aware that there is evidence to suggest that nasal vancomycin might reduce MRSA infection levels, but there are obvious reasons relating to antibiotic resistance why this is not a good strategy to adopt.

Although progress in establishing an evidence base for interventions has been slow, science has progressed rapidly in other aspects of the fight against MRSA, Mr Edgeworth said. Tools such as genetic sequencing and bacterial microarray can be used to explore the genetic make up of colonies involved in a particular incidence of infection and to determine whether they have, for example, incorporated additional virulence genes not routinely seen in that particular strain.