



Care must be sustainable

Sustainability of care, access to medicines, pandemic diseases, pharmacy ethics, pharmaceutical care, gene silencing technologies and counterfeit medicines were among the topics discussed at the CPA conference. **Harriet Adcock** reports

Drug discovery has been one of the most revolutionary contributors to improving the quality of health care, argued Dato' Dzulkipli Abdul Razak, a pharmacist and vice-chancellor of Universiti Sains Malaysia, in the conference keynote address. However, he questioned whether the processes of modern drug discovery can sustain continued improvements in quality.

Professor Dzulkipli highlighted three aspects of quality care. First, it should take account of intangible factors, such as values and needs. "These are difficult to deal with," he said. Secondly, quality care should encourage changes that are sustainable and, thirdly, it should be a continuous improvement rather than a static enforcement of standards.

Professor Dzulkipli presented figures that show medication errors are among the leading causes of death in the US and said such errors are likely to have a similar impact in developing countries. "There are alarming statistics associated with such errors," he said.

Problems are made worse because of the time it takes to translate knowledge from research into practice — one estimate is 17 years, said Professor Dzulkipli. "Many people suffer unnecessary problems because the sum of current knowledge is not used in practice." Variations in practice also lead to wastage and unnecessary spending that impact on quality care.

Professor Dzulkipli questioned whether some governments are more interested in profits and generating business than ensuring

quality care. He illustrated the point using World Health Organization rankings for health care systems. "The US does not rank very high compared with some European countries." This is despite the large amounts of money spent on health care in the US.

For developing countries the issues are more basic, said Professor Dzulkipli, with accessibility, equity and affordability being related to quality.

Professor Dzulkipli turned to the issue of research and development, explaining that expenditure has increased compared with a decade ago. "But the number of new drugs being produced is actually going down," he pointed out.

And for drugs relating to tropical diseases the situation is worse. Out of the 1,223 new drugs that came to market between 1985 and 1997, only 11 were treatments developed for tropical diseases. He argued that the situation is not sustainable given the size of the populations living in developing countries as well as the increasing costs associated with producing new medicines.

He also highlighted the fact that most breakthroughs in drug development are small. "This is not sustainable as far as innovation is concerned," he said.

Drug industry profits are illuminating, being far higher than those of other industries. Professor Dzulkipli argued that this is partly related to how the industry promotes itself as innovative. "But we know that is not necessarily the case," he added.

Turning to drug pricing, Professor Dzulkipli said that increases are far higher than inflation, which again raises the question of sustainability. Aggressive marketing of drugs, in particular the use of free samples, increases prices in the long term. For Malaysia, the issue of high drug prices has been deadly and the Malaysian ministry of health recognises that some form of control is needed.

"A lot of money is spent but resources are never sufficient in terms of meeting urgent challenges of quality care, particularly in lower income countries," he said.



Malaysia's Petronas Towers

Professor Dzulkipli also raised the issue of inequity as a barrier to quality care. He cited an estimate that for every person in the world to reach present US levels of consumption, including those for health care, would require four more planet earths.

The issue of inequity is starkly illustrated by the 1.5 billion people in the world who are overweight, some 200 million more than are suffering from malnutrition.

However, he argued that there are ways to meet the health care needs of developing countries. With HIV/AIDS, for example, development of technology meant that as early as 1995 there were drugs available to mitigate the problem and significant reductions in the number of people dying from HIV/AIDS had occurred in the US.

"This is possible in the US, but is not possible in Africa and is not possible in Asia — why," he asked. "Of course it is the prohibitive cost of drugs," he concluded, adding that there is merit in the observation that "the health care industry focuses on people with the greatest ability to pay rather than the greatest need for care".

He pointed out that for many households in the poorest parts of the world, medicines

Details

The 9th Commonwealth Pharmaceutical Association Conference, held in partnership with the Malaysian Pharmaceutical Society, took place in Kuala Lumpur, from 1 to 5 August. Over 500 participants from 37 countries attended the conference. The theme was "Quality care for better health". The next CPA conference will be held in association with the Pharmaceutical Society of Ghana in Accra, Ghana, from 5 to 9 August 2009.

are their largest health care expenditure. "In over 38 countries public drug expenditure is less than US\$2 per capita, which is certainly not a figure we can be proud of."

Professor Dzulkipli argued that the United Nations' millennium development goals will not be sustainable unless environmental factors are considered. Climate change is associated with a number of environmental stresses that impact on health.

"It has been predicted that death rates for the world's poor will rise by 2030 as a result

of global warming-related illnesses of malnutrition and diarrhoea." And the health impact of climate change will be exacerbated in developing countries because of their lower capacity to adapt because of a lack of financial, institutional and technological resources and access to knowledge.

There will also be changes in the risks of acquiring malaria through climate change. Regional population growth will lead to migration and increased demands for food. Malnutrition, forest clearing and associated

changes in mosquito habitat will raise the risk of acquiring the disease. And the problem will be exacerbated by increased demands for energy production.

Looking to the future, Professor Dzulkipli predicted that quality care will be difficult to achieve and maintain without addressing the issue of sustainability. "We as pharmacists can begin to look at our profession in the context of what's happening today and become relevant to the demands of the population," Professor Dzulkipli concluded.

Drug affordability major access factor

The affordability and availability of medicines are major determinants of access to treatment, according to Margaret Anne Ewen, principal, Global Projects for Health Action International.

Ms Ewen presented data from surveys being conducted by Health Action International and the World Health Organization in over 50 countries that show treatments are often unaffordable and their availability poor. "Put simply, many people are going without treatment because they cannot afford to pay the price," she said.

The surveys form part of a project to improve access to medicines in which a reliable methodology for collecting and analysing price and availability has been developed. The aim is to achieve price transparency and to present the data on a freely accessible website to allow international comparisons.

To date, over 40 surveys have been conducted in all regions of the world. Prices of 30 pre-selected, commonly used medicines were analysed and expressed as a ratio whereby the local price was compared with an international reference price. Availability was calculated as the percentage of facilities having that product on the day of data collection. Affordability was assessed for 10 pre-selected courses of treatment compared with the daily wage of the lowest paid unskilled government worker for that country.

Data from a selection of Commonwealth and other countries show that prices paid for medicines can be over 50 times an international reference price and that people may need to work for over a month to pay for just 30 days of treatment.

There are huge variations in the prices paid for medicines by individual countries. Ms Ewen cited the examples of metformin 500mg tablets, phenytoin 100mg tablets, ciprofloxacin 500mg tablets, captopril 25mg tablets and glibenclamide 5mg tablets.

Most Commonwealth countries purchase generic metformin at prices less than the reference price, she reported. But there are examples of other countries, such as Mongolia, the Philippines and China, that are buying either generic or branded metformin at prices that are up to 9.6 times higher than the international reference price.



Margaret Ewen: taxes on medicines can make them unaffordable

Ms Ewen also highlighted instances where countries charge patients far more than the procurement price for some medicines. Ghana, for example, buys generic metformin for less than the reference price and sells it on to the public at three times the procurement price. And Indonesia, although it buys phenytoin for around twice the reference price, it sells the medicine to the public at over 20 times the reference price.

"If governments are concerned about the price of medicines, is this a wise move," she asked. However, Ms Ewen pointed out that some health care systems are funded through the sale of medicines.

Looking at the price ratios for captopril sold from private retail pharmacies, Ms Ewen cited several examples where the branded medicine is sold at over 15 times the reference price and one example — Indonesia — where the branded medicine is sold at over 20 times the reference price.

"Does this matter," she asked. "It is certainly a cause for concern in countries where availability of the generic medicine is not good," she said.

For glibenclamide, there are huge price variations between countries and big differences between the generic and originator brand within countries. Availability is also a

problem. In Tanzania, for example, there was no branded glibenclamide available, and generic medicines were available in only 13 per cent of pharmacies at the time of data collection. This compares with a country such as Morocco where glibenclamide was available in 100 per cent of pharmacies and is also supplied free of charge to patients. Shandong province in China had just 5 per cent availability. "If people need glibenclamide, they are clearly going without," Ms Ewen said.

The affordability of medicines is also an important factor. A one month course of captopril 25mg twice daily requires over six days' work to pay for the originator brand in the Philippines, and over two days' work to pay for the generic.

One month's supply of the originator brand of fluoxetine in Kenya requires over 40 days' work. The generic requires over nine days' work. "This is not affordable," Ms Ewen declared. She suggested that treatment guidelines, for example recommending tricyclic antidepressants instead of selective serotonin reuptake inhibitors, can help where affordability is a problem.

Turning to taxes on medicines, Ms Ewen reported that some countries' taxing policies result in medicines becoming unaffordable for the public. In Tajikistan, value added tax of 20 per cent is levied on medicines, along with various other taxes and retail mark ups. Together, they increase the manufacturer's price by 123 per cent. Eliminating the government taxes reduces the price increase to 74 per cent.

"This is still high but taking away the taxes could make the difference between the medicines being affordable or not," she said.

It is important to understand what patients are paying for their medicines and then to act, said Ms Ewen. There are many policy options for tackling the issue of affordability.

"Stop taxing essential medicines. Where there is little competition, consider regulating prices — from manufacturers' selling price to margins in wholesale and retail.

"Educate doctors and consumers on the availability and acceptability of generics, and publicise the price of generics. And separate prescribing and dispensing," Ms Ewen concluded.

The next infectious disease pandemic: what will it be, and when will it come?

Patterns in the ways infectious diseases have emerged over the past 40 years are a serious cause for concern, Mark Collins, director of the Commonwealth Foundation, told conference participants.

"By the late 1960s many diseases were believed to be under control and on the verge of eradication. Sadly, that optimism was misplaced," he said.

New diseases, HIV, then SARS (severe acute respiratory syndrome), appeared, tuberculosis re-emerged and malaria increased its range. Resistance to antimicrobials also began to be a real problem. Animal diseases such as bovine spongiform encephalopathy led to fears that a new variant of Creutzfeldt-Jakob disease would strike. And, more recently, new outbreaks of avian influenza have threatened to cross to human populations.

Dr Collins highlighted the fact that infectious diseases are responsible for over 20 per cent of human deaths. "They hit the poorest countries hardest," he said.

He also pointed out that the social and economic impact of emerging pandemics on those who survive can be huge. In Africa, HIV/AIDS has created over three million orphans and left essential services without people in key professions.

Focusing on the United Nations' millennium development goals, adopted in 2000, Dr Collins said they include some important targets for health: to eradicate extreme poverty and hunger; to reduce child mortality; to improve maternal health; and to combat HIV/AIDS, malaria and other diseases.

The goals are scheduled to be reached by 2015 but, at the halfway point, the picture is mixed, said Dr Collins. "In some quarters there is a feeling that commitment is running out of steam." However, Dr Collins warned that addressing these goals remains vital if the impact of future pandemics is to be predicted, managed and controlled.

The lack of any significant increase in overseas development assistance since 2004 is disappointing, he added, and makes it hard even for well-governed countries to meet the development goals. "For Africa, with the worst health care facilities on the planet, it is a tragedy."

On the eradication of extreme poverty, Dr Collins said that there is some good news. "The proportion of people living in extreme poverty worldwide fell from nearly a third to less than a fifth between 1990 and 2004. If the trend continues the poverty reduction target will be met for the world as a whole, although pockets of poverty will remain where governance is poor or war continues," he said.

He added that the burden of disease, in crops and animals as well as in humans, con-



Mark Collins: challenge for pharmacists

tinues to be an impediment in sub-Saharan Africa. Failure to maintain veterinary and agricultural services, especially in East and West Africa, has allowed diseases like contagious bovine pleuropneumonia, controlled 25 years ago, to prosper and spread, Dr Collins explained.

Progress to reduce the maternal mortality ratio by three quarters has been extremely slow. "Over half a million women still die each year from treatable and preventable complications of pregnancy and childbirth, almost all of them in sub-Saharan Africa or Asia," he said. The odds of a woman dying from complications of pregnancy and childbirth in sub-Saharan Africa is one in 16 over her lifetime, he said, while in the developed world the odds are just one in 3,800.

Child mortality has declined globally, although only slight reductions have been achieved in sub-Saharan Africa and parts of Asia. "It is becoming clear that the right life-saving interventions, including drugs and vaccines, are proving to be effective in reducing the number of deaths due to the main killers, such as measles."

On combating HIV/AIDS, Dr Collins warned that prevention measures have failed to keep pace with the spread of the disease. For malaria, key interventions to control the disease have been expanded, but it remains the world's fifth biggest killer. For tuberculosis, on the other hand, the epidemic appears to be on the verge of decline.

The impact of infectious diseases differs greatly between developing and developed countries. In developing countries the underlying burden of infection is greater and children are severely impacted. Malnutrition makes matters worse. Developing countries are also more vulnerable to pandemics because of slow detection.

A UK study identified six potential sources of pandemics over the next 25 years: pathogens that are currently unknown; pathogens acquiring resistance to antimicrobials; zoonoses; HIV/AIDS, tuberculosis and malaria; acute respiratory infections; and sexually transmitted infections.

The problem of pathogens acquiring resistance is getting worse, said Dr Collins. "Currently controlled diseases could re-emerge as a result."

Transmission from animals is a continuing trend. "There is some likelihood that the risk of zoonoses could increase in future, both from domestic and wild reservoirs." Intensification of animal husbandry, poorly considered feeding systems and increased transportation of domestic animals all add to the risk. And in the developing world contact with wild animals is a major concern.

"Perhaps most frightening is the prospect that deadly viral haemorrhagic fevers like Marburg and Ebola could quite easily mutate into less lethal forms that would have a far better chance of spreading across Africa and worldwide. For this reason the bushmeat trade is much more than a conservation worry," Dr Collins argued.

A profound decline in veterinary services across Africa adds to the problem, since slaughterhouses are not checked, diseased animals are not identified, and transgressions of basic standards go unpunished.

Dr Collins argued that HIV, AIDS, TB and malaria will remain the dominant sources of epidemics in Africa for the foreseeable future. "They need to be considered together because they are found in the same areas and are associated with poverty and gender inequality," he said.

The most important threat from acute respiratory tract infections comes from the avian influenza virus H5N1, which took hold in 2003. "Sensitivities are high, partly from the relatively recent threat of SARS," said Dr Collins.

The disease has been confirmed in 60 countries, reaching 24 in the first seven months of 2007 giving an indication of the speed of the spread. "Within nine months from now it is expected to be in every country in the world," warned Dr Collins.

Dr Collins reported that the World Health Organization fears H5N1 could infect 40 per cent of the world's population and that the US Centres for Disease Control and Prevention predicts H5N1 could kill between two million and 7.4 million people.

On the issue of sexually transmitted diseases, Dr Collins called for cheap, rapid and reliable self-test kits in order to improve detection and promote treatment.

"Pregnant women, in particular, need to be routinely tested, in order to avoid transmission of STIs to their newborn children."

Dr Collins went on to discuss the impact on disease of environmental change. He explained that climate change can increase the risk of infectious disease in three ways: by directly assisting survival and spread of pathogens, hosts and vectors; by changing ecosystems and habitats in ways that favour spread of disease; and by indirectly affecting the way people behave in terms of transport and migration, or through conflict over shared water and food resources.

"Although a generally warming climate is considered to be an important driver of infectious disease, it is difficult to predict when and where such increases might occur," he said.

He added that, contrary to many reports, malaria is not likely to return to Europe because suitable habitats for the mosquitoes are

no longer there and people are much less exposed to the risk of insect bites.

Dr Collins also argued that the risk of pandemic disease in the developing world is multiplied by inadequacies in the health system. "Lack of trained personnel is an over-arching issue," he said. In addition, lack of motivation and poor skills means that misdiagnosis and mistreatment are commonplace.

Migration is a huge problem. In Ghana, of 944 pharmacists trained between 1995 and 2002, 410 had left the country by 2002.

The HIV/AIDS epidemic is also having a massive impact. "In several African countries one in four nurses is HIV positive," he said, adding that in Mozambique 20 per cent of student nurses died of AIDS in 2000.

Dr Collins pointed out that the risk of pandemics is increased because of problems with drugs, including national shortages, expense, counterfeiting and poor quality, inappropriate prescribing and use, and inefficient

logistics systems. He argued that developed countries should make overseas development assistance available in line with the Monterrey consensus of 0.7 per cent of gross national income, and that significant new investments in health care systems are needed.

Dr Collins also pointed out that medical training schools in the developing world are, in effect, providing a service to the developed world. "The way forward is to recognise this and assist those schools," he said.

Detection, identification and monitoring systems have to be improved if future pandemics are to be stopped. He also argued that access to and affordability of genuine vaccines and drugs needs to be extended, while the inappropriate use of drugs has to be stopped to reduce drug resistance.

"There is a huge challenge to pharmacists in playing their part in stopping counterfeit drugs, making drugs affordable and improving distribution and use systems," he concluded.

Pharmacists need to understand ethics

Pharmacists need a more fundamental understanding of ethics, contended David Badcott, of the centre for applied ethics, Cardiff University, Wales.

"Traditionally, ethics or moral philosophy has not rated too highly in pharmacy students' curriculum," he said. This is interesting since pharmacists are often placed in surveys among the most trusted of professions and do not have a reputation for being unethical.

"Most practising pharmacists probably associate ethics with 'pharmacy law and ethics' in which law is the dominant partner," Dr Badcott said.

For some, ethics is seen as more of a concern for doctors and nurses where contact with the patient is more intimate. In many countries, the perception of pharmacy is strongly associated with the pharmacist as dispenser and supplier of medicines. Nevertheless, Dr Badcott suggested that there is an ethical dimension to this work based on patient vulnerability and professional obligation.

He explained that patients are vulnerable in two respects: to the disease for which they are seeking treatment and to the treatments they receive. "It is because of this state of vulnerability and because the health care professional undertakes to help, that a professional obligation is incurred," Dr Badcott added.

Being a pharmacist automatically brings a state of professional obligation relating to the technical and legal aspects of pharmacy and to its ethical aspects. And while it is easy to overlook or even dismiss the relevance of ethics to many of the routine aspects of pharmacy services these are no less important than other aspects. "Indeed it can be argued that dispensing is the most important area of pharmacy," he said.

Dr Badcott pointed out that although there is a strong relationship between law and



David Badcott: relevance of ethics to dispensing easily overlooked

ethics there are many situations not covered by law. "Ethics helps you to decide what you ought to do when the law is silent," he explained.

Our understanding of ethics is based on concepts such as justice, fairness, respect, obligation and, importantly, human dignity.

Dr Badcott cited the four principles relating to health care ethics known as the "Georgetown mantra": beneficence, non-maleficence, autonomy and justice. However, he said that this approach does not appear to have found favour or have been applied within pharmacy, perhaps because ethical behaviour in pharmacy has largely been associated with legal compliance.

He pointed out that many professional codes of ethics, including the recently revised

code introduced in the UK, are mandatory. "There is perhaps a danger of observing the code simply because to do otherwise could result in sanction," Dr Badcott said. "This would be altogether to misunderstand the crucial difference that we should behave ethically because it is the right thing to do and not because we fear being punished."

Dr Badcott explained that the thrust of modern health care ethics, particularly virtue ethics or ethics of care, which are well known in nursing, is focused on the rightness of an action for its own sake. "There is a risk that this aspect may be largely eclipsed by the tone of professional codes of ethics."

Dr Badcott highlighted three aspects of the supply of prescription medicines with ethical dimensions that arise from patient vulnerability and professional obligation — supply of generics, counterfeits and issues concerning the beginning and end of life.

In terms of supply of generic medicines and the risk of counterfeits, pharmacists have a technical responsibility but there is also a need to think ethically. "Do we ever go to a supplier and ask for a paper chase — do we identify drugs with bioavailability problems," he asked.

As far as end-of-life decisions are concerned, pharmacists have little involvement at the moment. But this is likely to change. "Who will provide the treatments to assist terminally ill patients to die," Dr Badcott asked. "Pharmacists will be involved. These will be matters of conscience," he said.

Dr Badcott concluded that pharmacists should cultivate an ethical awareness of what is happening in health care around them. "It may not be of immediate interest, but it helps to develop your ethical skills," he advised.

David Kong, a lecturer in pharmacy practice at Victoria College of Pharmacy, Monash



David Kong: contact with industry linked to inappropriate prescribing

University, Australia, discussed the difficult relationship between practitioners and the pharmaceutical industry.

He told conference participants that patients are the primary concern of health care professionals. However, pharmacists cannot

pretend they have nothing to do with industry. It funds research, training and conferences. Pharmacists read brochures and talk to sales representatives. Some own businesses, buying from industry and selling to patients.

“The health care industry is a key ally in the battle against disease and suffering. But at the same time we must recognise that they have shareholders — they are there to make money.”

Although community pharmacists have been ranked as the second most honest profession (in Australia) behind nurses and ahead of doctors, they are exposed to promotional material and this is likely to influence their personal activities.

Dr Kong described several studies that suggest frequent contact with the pharmaceutical industry is linked with inappropriate prescribing. There is evidence to suggest that when sales representatives go on holiday, for example, prescribing of new products drops. And attendance at sponsored conferences is linked with increased prescribing of a sponsor's product. “Because of the close relationship, it is hard to have no contact. But there needs to be a balance,” he added.

Most codes of professional practice are self-regulated. However, a World Health Organization report suggested that self-

regulation is not effective. “Legislation works a little bit better,” Dr Kong said.

One problem is that health professionals tend to believe that they cannot be influenced. “The response is always ‘I am not vulnerable,’” said Dr Kong, adding that this is unlikely.

There needs to be strategies for ethical relationships, including codes of professional practice, guidelines and policies; non-industry-based funding for activities such as continuing education, conferences and journals; and accepting responsibility for one's own vulnerability. However, Dr Kong questioned whether non-industry-based funding is achievable for such activities given the costs involved.

Dr Kong argued that ethical attitudes need to be instilled in health care professionals early, at undergraduate level. A survey of medical and pharmacy schools revealed that while there is room for improvement, most (approximately 70 per cent) cover ethics within their curriculum. However, problems were identified including a lack of integration with other parts of the curriculum and a lack of continuation in clinical training.

“And of course, students like to receive free gifts from pharmaceutical companies,” Dr Kong added.

Pharmaceutical care research: study design may not always be appropriate

Pharmaceutical care in the UK has evolved rapidly and has changed the whole philosophy of how medicines are used and how pharmacy provides its services, Ian Wong, Department of Health public health career scientist, The School of Pharmacy, University of London, UK, told conference participants. As part of this evolution, new services have been introduced, including pharmacist-led medication reviews.

Professor Wong described the findings of four major randomised controlled studies that evaluated the effectiveness of medication reviews for elderly patients — Zermansky *et al*, published in 2001, Krska *et al* (2001), Holland *et al* (2005) and Wong *et al* (unpublished).

Although the basic structure of each study is different, together, they provide data on over 2,000 patients.

The trial conducted by Zermansky, involving 1,131 patients aged 65 years and over, used a single practice pharmacist to review the appropriateness and efficacy of patients' treatments, the progress of the patients' conditions, compliance and actual and potential adverse effects and drug interactions. The researchers concluded that a clinical pharmacist can conduct effective consultations with elderly patients in general practice and that such reviews result in significant changes in pa-

tients' drugs and save more than the cost of the intervention, without affecting the workload of GPs.

Professor Wong went on to describe the trial conducted by Krska, which involved 332 patients with at least two chronic illnesses and who were 65 years and over. Clinically trained pharmacists saw patients at home to identify pharmaceutical care issues. Information was obtained from the practice computer, medical records and interviews. For 168 patients, a pharmaceutical care plan was then drawn up and implemented. The remaining 164 patients continued to receive normal care.

After three months, a number of pharmaceutical care issues were identified with more having been resolved in the intervention group. These included adverse drug reactions, monitoring issues, potentially ineffective treatments or dosages, untreated conditions and drugs being used where there was no indication identified for them. There were no changes in medicines costs, health related quality of life, or hospital clinic attendance. There were slightly fewer hospital admissions but the number was too small to be tested statistically.

The researchers concluded that pharmacist-led medication review has the capacity to

identify and resolve pharmaceutical care issues. “This is a key message,” said Professor Wong.

Professor Wong moved on to describe the trial conducted by Holland, which involved 872 patients aged 80 years and over who had been discharged from hospital after an emergency admission. Pharmacists with postgraduate qualifications and training arranged to see the patients at home and received their discharge letters for review. Patients' ability to self-medicate and their adherence to treatment were assessed. The pharmacists provided information and advice to the patients and their carers, removed out-of-date drugs and reported possible adverse drug reactions or interactions to the patients' GPs. Need for a compliance aid was also reported to the local pharmacist. A follow up visit six to eight weeks later reinforced the original advice.

The results of this trial were surprising and caused a lot of debate, said Professor Wong. Emergency readmissions were higher in the intervention group than in the control group (234 compared with 178). Quality of life was reduced in both groups and scores on a visual analogue health scale fell, with the difference being in favour of the control group. There was no change in GP clinic attendance and no change in the number of medicines prescribed.

The researchers concluded that home-based medication review for older people recently discharged from hospital increases hospital admissions and worsens patients' quality of life.

Professor Wong pointed out that patients seen by the pharmacists may have adhered better to their drugs, with a resultant increase in adverse effects. "Alternatively, the intervention may have provoked better understanding and help-seeking behaviour," he added.

The last study described by Professor Wong, known as the RESPECT pharmaceutical care trial, is as yet unpublished and is the only study to have used patients' usual community pharmacists, nominated by the patient, to provide medication reviews. The study involved 760 patients aged 75 years and above who were being prescribed five repeat medicines and who were relatively well and mobile.

The study was a randomised multiple interrupted time series trial in which five primary care trusts implemented pharmaceutical care at quarterly intervals and in random order. "We followed patients, who also acted as their own controls, for 36 months between recruitment and final visit, including 12 months when they were receiving pharmaceutical care," he explained.

The design of the study meant that it had more power to detect changes and would also reveal whether any benefits obtained from the pharmaceutical care were retained or lost after the intervention was stopped.

Both pharmacists and GPs attended training before starting the intervention. Pharmacists then interviewed patients at the community pharmacy and developed a pharmaceutical care plan that was shared with the



Ian Wong: lack of positive results can be explained

patient's GP. Monthly medication reviews were conducted for one year.

The study used the UK Medication Appropriateness Index (UK-MAI) to assess changes in outcomes. Patients' medicines were scored between 0 and 20 depending on their appropriateness (0 = completely appropriate, 20 = completely inappropriate).

"Overall, we saw the mean UK-MAI score going down, so it was improving. But this was only a trend," reported Professor Wong, adding that the reduction was small and not statistically significant.

Pharmaceutical care had no significant effects on the number of hospital admissions, the number of GP clinic consultations, mortality rate and quality of life scores.

"We judge that this lack of evidence stems from our experience that pharmaceutical care

is difficult to implement in full in a community setting."

Professor Wong summarised the conclusions of all four studies: "Pharmacists are able to identify pharmaceutical care issues and initiate change. However, traditional research instruments are unable to detect positive change in clinical outcomes."

He suggested that a debate around pharmaceutical care and how its effects are measured is needed. He reminded participants that pharmaceutical care originated in the US where the health care system is different from that in the UK. The UK already has effective gatekeepers — GPs and pharmacists. "Pharmacists are already intervening," he said. "To change from good to very good is difficult."

He added that in other health care systems, such as in Malaysia where pharmacists do not have a traditional dispensing role, there is the potential for pharmacists to make a huge difference in improving patient care.

The lack of positive results from the UK studies can be explained. "As a researcher, I think it is more likely to be about a lack of sensitivity," said Professor Wong.

He questioned whether the right instruments are being used to measure changes in outcome and whether the design of the studies is appropriate. "Are we measuring the right things," he asked. "We are trying to generalise, taking every patient regardless of whether they need pharmaceutical care."

Professor Wong suggested that identifying a need for pharmaceutical care is a sensible first step in any study. There is also a need to ensure that instruments used to measure outcomes in pharmaceutical care are sensitive enough to detect changes.

Gene silencing: promising new therapy



Computer illustration of siRNA blocking HIV infection

Gene silencing nucleic acids can be used therapeutically to inhibit disease-causing genes, Saghir Akhtar, formerly professor of drug delivery at the Welsh School of Pharmacy, Cardiff, Wales, and now of SA Pharma, Sutton Coldfield, England, told conference participants.

However, their large molecular weight and charged nature pose great pharmaceutical challenges to their clinical development. "If we cannot deliver these molecules to the right sites in the body then they will never become medicines," he said.

Professor Akhtar explained how, unlike conventional drugs that target proteins, gene silencing drugs — such as anti-sense oligonucleotides and small interfering RNAs (siRNA) — are designed to target messenger RNA and stop genes producing the protein in the first place.

He pointed out that because the molecules are nucleic acids themselves they latch on to mRNA in a sequence-specific way. Once bound, they then cause destruction and even-

tually degrade the mRNA. "The drug remains and goes back and finds another mRNA molecule, working as a catalyst to reduce the level of the protein that leads to disease. This process is called gene silencing."

At a molecular level, anti-sense oligonucleotides and siRNA can stop the protein or peptide encoded by the message from being formed by one of two mechanisms — either by binding to the mRNA through hydrogen bonding, which blocks the message from being read by preventing movement of ribosomes across the message, or by initiating the degradation of mRNA.

Gene silencing can be initiated by introducing long, double-stranded RNA into cells, said Professor Akhtar. However, in mammals this results in an immune response whereby all protein expression is shut down. By using small interfering RNA molecules, about 21 nucleotides long and which can be made synthetically, this immune response can be avoided. Once the double-stranded siRNA is unwound, the anti-sense strand (the

one that encodes the targeted gene message) is incorporated into a multiprotein complex known as RISC (RNA induced silencing complex). This complex then guides the anti-sense strand to its complementary message and, once bound, components of the complex selectively degrade the mRNA to cause protein translation to end.

Professor Akhtar explained that this is a naturally occurring mechanism to some extent, its purpose being to regulate the expression of certain genes.

The first clinical trials of therapeutic siRNA started in 2004. Currently there are trials being conducted to treat age-related macular degeneration, diabetic macular oedema and respiratory syncytial virus lung infection.

Professor Akhtar's own research involves trying to understand signalling mechanisms that lead to heart attacks, cancers and the vascular complications in diabetes. "If we understand the key components that cause the diseases then we can interfere with the genes that produce those changes," he explained.

Professor Akhtar said that microarray technology has shown that the gene for epidermal growth factor receptor is either upregulated, or that the phosphorylation of the protein is upregulated, and that this is important in inducing abnormal vascular function. "So maybe we can treat abnormal vascular function in diabetes by silencing the epidermal growth factor receptor," he suggested.

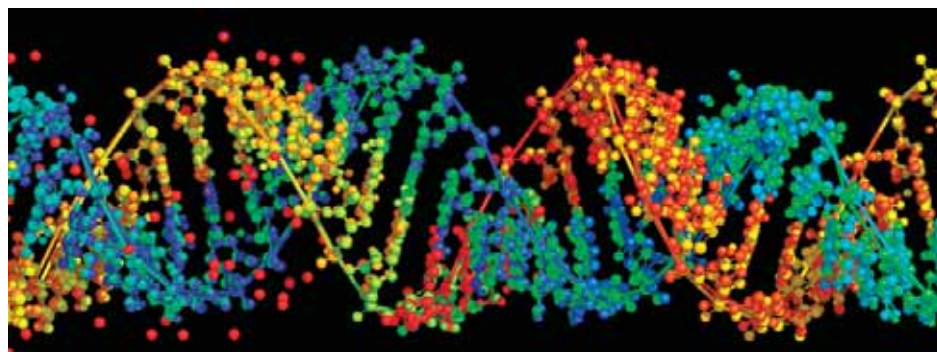
Professor Akhtar went on to describe the problems associated with delivery of gene silencing drugs. "We often call these gene medicines 'macromolecules with attitude'. They are big and have lots of charge. Both of these properties mean that they don't like to get into cells," he said.

Typically, gene silencing molecules are 4,000 to 13,000 daltons and in the case of anti-sense oligonucleotides tend to have 15 negative charges and siRNA typically has 40 charges.

"The biggest challenge for pharmaceutical scientists is to get these molecules formulated in such a way as to improve their delivery and pharmacokinetics."

He noted that viruses have been widely used to deliver nucleic acids into cells but are associated with significant problems. Non-viral vectors have therefore been designed to mimic how viruses enter the body.

Cationic polymers, dendrimers, cell-penetrating peptides and liposomes have all been tried as delivery systems for gene silencing drugs, said Professor Akhtar. Incorporating a drug into such systems can help stabilise the genetic material. It is also important that the system delivers the drug to the right cellular compartments. For anti-sense oligonucleotides and siRNA an effec-



Laguna Design/Science Photo Library

Double-stranded RNA

tive delivery system has to deliver the drugs into a cell's cytosol, their active site.

Delivery also needs to avoid off-target effects, which can occur in completely different pathways from the one being targeted.

Professor Akhtar described the factors that can affect the uptake of gene silencing drugs, including whether the nucleic acid is single or double stranded, its length and charge. The characteristics of the delivery system itself — its size, charge, architecture, shape and chemistry — are also critical in determining how much of the gene drug gets into the cell. Other contributing factors include the half-life of the gene target and its relative abundance.

"It's thought that if there is a rapidly turning over, low-abundant protein then that is going to be more amenable to gene targeting than the converse," he added.

Professor Akhtar described the development of a system for local administration of an siRNA to treat brain glioma. He noted that patients usually present with headaches and throbbing intracranial pressure that has to be relieved through surgery. "Local delivery into the brain seems a viable option considering the surgeon has to intervene — we envisage direct administration using sustained-release polymer implants," he said.

Entrapment of the gene drugs in slowly degrading polymer microspheres or nanoparticles would achieve sustained release and would protect the genetic material from being degraded by cellular enzymes.

Another approach to *in vivo* delivery is targeted, systemic delivery systems, said Professor Akhtar. Most success has been achieved using self-assembled modular systems — nanoparticles or nanocomplexes made by lipids or polymers. He explained that siRNA can be entrapped within the particle or associated through charges at the surface. Adding polyethylene glycan chains stabilises the particles and helps prolong circulation. In addition, tissues can be selected for by adding cell-specific targeting moieties.

Another important variable that needs to be considered in gene silencing applications,

especially *in vivo*, is the effect of the delivery system itself. "We need to ask what are the biological consequences of the delivery systems," said Professor Akhtar. He explained that the delivery system may alter gene expression and so contribute to off-target effects and to siRNA activity. RNA interference can be enhanced or subdued and any alteration can complicate the interpretation of the effect of the gene silencing drug. "[The delivery vector] needs to be not only biocompatible but also genocompatible — it should not adversely affect gene expression," he argued.

Professor Akhtar went on to describe several delivery systems that have been shown to affect gene expression. These include the cationic lipid systems lipofectin and oligofectamine, which altered about 20 per cent of the genes in the cells tested. This is significant since gene silencing is meant to alter just one gene.

Dendrimer delivery systems can also induce gene expression. However, the effects are not predictable. A diverse set of genes can be altered and delivery systems, with similar chemistry but different shapes, can produce opposing effects on the targeted gene. "This translates to give different apparent potencies of the same siRNA drug," said Professor Akhtar. Experiments have shown that such discrepancies do not result from different levels of uptake of the gene silencing drug or different internal cellular biodistribution.

"We showed for the first time that gene changes induced by delivery reagents, separate from their effects on cellular uptake, were important for determining the level of gene silencing achieved by siRNAs," Professor Akhtar reported.

And while it might be possible to enhance siRNA activity by selecting delivery systems that also inhibit the target gene, any beneficial effects on the apparent siRNA potency will have to be balanced by increased off-target effects. "Because of this problem it is probably wiser to advocate screening for genocompatible delivery systems that do not change gene expression of anything in the cell too much," Professor Akhtar concluded.

Ensure security of medicines' supply

Pharmacists can contribute to the fight against medicines counterfeiting by implementing good pharmacy practice and purchasing medicines only from reputable sources, Tony Moffat of The School of Pharmacy, University of London, UK, told conference participants.

"Be alert to differences in packaging, labelling or leaflets. In this way, you as individual pharmacists can impede the move towards use of counterfeit medicines," he said.

He advised pharmacists to check for evidence of tampering with medicines packaging. "Has it been opened up and restamped with a new batch number or expiry date?" He suggested comparing the packaging with an authentic specimen. "Also check the individual cartons inside the packaging and within these, the individual tablets and capsules." Professor Moffat acknowledged this is not possible all the time. "But it is worthwhile if you have a high volume of product."

He stressed that ensuring the security of distribution is the best way forward, using only approved suppliers. "Be wary of cheap deals, check with professional colleagues and report problems to your local pharmaceutical society and to local authorities," he added.

Professor Moffat reminded the conference of the Commonwealth Pharmaceutical Association's policy on anti-counterfeiting. "It urges national administrations to recognise counterfeiting as a serious risk to public health, to publicise the problem to the public, to recognise and promote safeguards provided by traditional supply channels, to put in place effective measures for detection and prevention, to adopt and implement World Health Organization guidelines and to impose punitive sanctions on manufacturers and distributors of counterfeits."

The CPA also urges national pharmacy associations to develop, implement and monitor good pharmacy practice. This includes reporting instances of counterfeiting to national authorities so information can be used as intelligence both locally and internationally.



Valerio Reggi: protect your reputations

The WHO, too, has several initiatives designed to combat counterfeiting. Professor Moffat explained that the idea behind the WHO's rapid alert system is to minimise the adverse impact of counterfeit medicines by rapidly distributing local notifications about incidents and promoting surveillance. This approach is supplemented by a far more important initiative: "The international medical product anti-counterfeiting taskforce — IMPACT — which aims to put a stop to the deadly trade in fake drugs."

Professor Moffat described an early counterfeit medicine case that he had been involved with — a preparation purporting to be an anabolic steroid that did not contain any anabolic steroids. "It was difficult to find an agency that would take [the prosecution] up," he said. The police suggested taking it to the regional drug squad which, because the product had been imported, passed it to customs which in turn suggested trading standards. "In the end it was the regulatory agency that picked up the bill and made the prosecution."

Professor Moffat argued that counterfeit medicines are a problem for all of these agencies, along with other interested parties, including pharmaceutical companies, professional bodies and individual pharmacists.

He encouraged conference participants to look to Nigeria's National Agency for Food and Drug Administration and Control. "This is an outstanding example of how a government agency and particular individuals have made a huge difference in the protection of their public." He explained that NAFDAC has created a blacklist of manufacturers that have supplied counterfeit medicines to Nigeria and asks other countries not to deal with these companies. "NAFDAC has taken outstanding steps to stem counterfeiting."

It is not just a problem for developing countries. "Counterfeit medicines have increased five times in Europe in the last year." Professor Moffat explained that the counterfeit medicine market within Europe largely consists of lifestyle drugs obtained via the internet. Some countries are taking steps to counter this. In the UK, for example, regulators advise the public not to buy medicines from the internet and have set up safeguards to protect those who continue to do so. The Royal Pharmaceutical Society of Great Britain regulates UK-based internet pharmacy sites and is currently testing the use of a logo to show customers whether the site they are using falls under its regulatory umbrella.

Professor Moffat described some of the ways in which manufacturers are tackling counterfeiting, such as tamper-proof outer packaging and through use of devices that cannot easily be copied by counterfeiters — microdots used as covert markers, radiofrequency identification, holograms, security inks, and two-dimensional barcoding. Another approach is the use of "medicines



Tony Moffat: use reputable suppliers

passports" where each package is uniquely labelled and has a guaranteed audit trail leading back from wherever the customer bought it to the manufacturer.

In the UK, Pfizer has introduced an additional precaution by making its supply chain shorter. "It decided to take full responsibility for the supply of its products, using a single wholesaler as distributor," explained Professor Moffat, adding that not everyone has welcomed the move, which has been referred to the monopolies commission.

Valerio Reggi, of the World Health Organization, argued that the problem of counterfeiting is made worse by current legal frameworks. In the US, for example, trafficking offences that fall under the Federal Criminal Code, such as the counterfeiting of T-shirts, attract a 10-year prison sentence and a fine of up to \$2m for a first offence. However, under the Federal Food Drug and Cosmetic Act, a first offence in counterfeiting medicines would be classed as a misdemeanour with up to one year in jail. "It is difficult to explain to people that it is a much more serious offence to counterfeit a T-shirt than it is to counterfeit a medicine."

Dr Reggi went on to describe IMPACT, the WHO taskforce already highlighted by Professor Moffat. "It is the first attempt at coordinating the international efforts of governments, intergovernmental organisations and global NGOs," he said. The underlying philosophy of the taskforce is that there is no one single centre that can combat counterfeit medicines. "We need them all to collaborate."

Dr Reggi urged pharmacists to protect their reputations. "Report and help investigate cases. And increase security and transparency of distribution systems." He suggested that in many countries pharmacists' monopoly of medicines supply was an illusion. "If you do not organise informal networks others will take care of it," he warned.

"Combating counterfeit medicines requires that we join forces and that we all play our specific roles in a concerted and coordinated way," he concluded.