

WORLD CONGRESS OF PHARMACY AND PHARMACEUTICAL SCIENCES

Anticounterfeiting measures

We conclude our coverage of the International Pharmaceutical Federation congress in Sydney with reports on counterfeiting, concordance, ethical decision-making, hospital pharmacy and issues surrounding oral drug delivery

On the 8 September, FIP's Laboratories and Medicines Control Services Section presented a comprehensive examination of the extent of the problem and some surveillance measures and newer analytical methodology that countries might adopt to combat the scourge of counterfeit medicines. The session was chaired by Frans van de Vaart (Scientific Institute of Dutch Pharmacists, and president of the LMCS section).

GLOBAL PROBLEMS

Dr Sabine Kopp, World Health Organization, provided a WHO consensus definition of a counterfeit medicine as one which is "deliberately and fraudulently mislabeled with respect to identity and/or source". Counterfeiting of medicines can apply to both branded and generic products. Generally, counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with incorrect quantities of active ingredients or with fake packaging.

She contrasted this definition with definitions adopted by individual countries, eg, a wider one from the Philippines, which also subsumed unregistered imported products or products containing less than 80 per cent of the labeled amount. Although WHO has received over 1,000 national reports of cases of counterfeit drugs since 1982, there may be a lack of homogeneity in assessing the extent, through confusion between those substandard preparations and those explicitly counterfeit. She emphasised that data derived from these reports must be viewed with caution because most cases cannot be validated or confirmed in the reports sent to WHO.

While recognising that the trade in counterfeit medicines is widespread, affecting both developed and developing countries, she noted that it is more prevalent in countries where there is weak drug regulatory control and enforcement, or scarcity or erratic supply of basic medicines, with unregulated markets and distribution chains, and where drug prices are high and significant price differentials exist.

Dr Kopp emphasised that trading in counterfeit medicines is a serious criminal activity that endangers human health: society and all stakeholders in the health care chain and in the pharmaceutical sector are victims when counterfeiting of medicines occurs. She noted the variety of medicines that had been counterfeited — many (45 per cent) were antibiotics but 15 other drug classes each represented 2 to 8 per cent. With respect to variable composition, 60



per cent of 325 counterfeit products in a new study contained no active substance at all.

For the years 2000–01, 42 cases were reported to WHO, of which 43 per cent had no active ingredient, while a further 21 per cent had low content, 7 per cent had the wrong ingredient, and 24 per cent were of generally poor quality. She illustrated some counterfeit preparations and their branded equivalents, such as sildenafil (Viagra) tablets and filgrastim (Neupogen) liquid. In some, but by no means all, cases, the suspect material was of observably poorer presentation. She cited two reasons for substandard quality: illegal, poor conditions of manufacture and poor storage and distribution. Many countries had reported counterfeit products: she instanced Italy in 2000 (240,000 packs and 2 tonnes of raw materials), South East Asia (30 deaths in Cambodia in 1999) and the Russian Federation (150 reports in 2000).

Dr Kopp commented that patients, industry and governments are all victims. Patients are victims primarily because it is their health, and even their lives, that are put at risk when they take counterfeit medicines; governments too are victims because funds are used to purchase medicines of unknown quality and safety and health care professionals suffer loss of patient confidence in their services. Governments may be lax if they believe that counterfeit supplies help populations by providing cheaper drugs, and in some states there may be corrupt officials or blatant disregard for international patents. Legitimate manufacturers are also victims, not simply because of direct loss of revenue but also because confidence in their products is undermined, leading to loss of sales and the reputation of the company and image of the products are both lost.

What then are the measures that can be taken to identify counterfeit drugs interna-

tionally and what can international organisations and national authorities do to combat the problem? Dr Kopp looked to participation of the public and of all the stakeholders. At national level, governments need to be encouraged to advocate awareness in their populations and to campaign for an international convention and regional control organisations. Law enforcement agencies need to train less experienced countries in investigation and successful prosecution, and health professionals, the pharmaceutical industry, importers, distributors and consumer organisations should all, she said, "adopt a shared responsibility in the fight against counterfeit drugs".

Dr Kopp drew attention to the importance of co-operation between countries, especially trading partners, for combating counterfeiting. Such co-operation should include the timely and appropriate exchange of information and the harmonisation of measures to prevent the spread of counterfeit medicines. "There needs," she claimed, "to be a basic will to react and prosecute."

DETECTION OF COUNTERFEIT MEDICINES

Detection procedures were discussed by Larry Kelly, chief chemist to the Australian Therapeutic Goods Administration. He noted that in Australian legislation, the meaning of "counterfeit medicines" was broader than in many other countries. In Australia, the term "medicine" falls under the umbrella of "therapeutic goods", which include, among other things, medical devices, herbal products and other complementary remedies, as well as the more mainstream over-the-counter and prescription products that most people are familiar with. The Australian offence of dealing in counterfeit therapeutic goods refers to intentional manufacture, supply, import or export, of therapeutic goods known to be counterfeit. The offence is punishable, on conviction, by up to five years imprisonment or a fine of A\$220,000 (or both), and a corporate body could be fined up to A\$1.1m.

Dr Kelly noted that the Indian parliament was debating setting a death penalty for "peddling fake drugs". The offence goes beyond that used by, for example, WHO, which extends to all aspects of the product including labels, ingredients, manufacturing and testing processes as well sources of materials used in the product.

For the detection of counterfeit medicines, Dr Kelly's approach was wherever possible to compare with a genuine product, carefully study their respective packaging and labeling, check all associated documen-

tation with the suspect goods, and then perform appropriate compendial or other regulatory tests in parallel. In particular, he looked for an unusual amount or nature of discovered impurities.

His choice of analytical methods to detect the various types of counterfeit medicines encountered in Australia favoured two techniques. Gas chromatography has been particularly useful for confirming essential oils, residual solvents, volatile constituents (especially from herbal medicines increasingly popular in Australia) and undeclared ingredients. High performance liquid chromatography was convenient for profile of a herbal substance, detecting adulterants and organic residues. Both techniques use different types of detection methods according to the specific issue under investigation. He demonstrated the use of "decision tree" software to identify substances by an HPLC response at a specific retention volume. Other separation methods that produced pharmaceutical fingerprints are:

- LC-MS-MS (liquid chromatography-coupled tandem mass spectrometry) to identify particular, or unexpected, impurities or marker phytochemicals in herbal preparations
- ICP/MS (inductively coupled plasma sourced mass spectrometry) to give clear elemental profiles, and ion chromatography for anion/cation profiles

Medicines investigated by his laboratory ranged from traditional Chinese medicines through to the active pharmaceutical ingredients in prescription medicines. Dr Kelly provided specific examples of testing for characteristic residues in active ingredients in prescription medicines using GC and HPLC, and testing for undeclared ingredients in herbal medicines using hyphenated LC-MS-MS.

Throughout his presentation, his consistent theme was the concept of "pharmaceutical fingerprints" to characterise an ingredient or product and thereby enable detection of a counterfeit medicine. He summarised:

- Know the product and manufacturing process where possible, considering which typical related impurities should be expected to be present
- Select the appropriate analytical method
- Check the product for characteristic byproducts and contaminants

NEAR-INFRARED SPECTROSCOPY

The methodology of near-infrared spectroscopy (NIRS) was described by Professor Tony Moffat (University of London School of Pharmacy, and chief scientist, Royal Pharmaceutical Society). He defined counterfeiting as the "deliberate and fraudulent mislabeling of medicinal products with respect to identity and/or source". This he carefully distinguished from "diversion", which he described as the supply of a prod-



Tony Moffat: fortunately, counterfeiting in the United Kingdom is a rare occurrence

uct to a third party for one particular market but eventually sold in a different market.

He referred to many global tragedies concerning the effects of counterfeiting medicines, including the deaths of 109 children in Nigeria after taking a fake preparation containing the poisonous solvent diethylene glycol, and in Uganda where 60 per cent of malarial deaths were attributed to fake quinine sulphate tablets that did not contain the active ingredient. He claimed that in monetary terms, if 8 per cent of the global supply of medicines were counterfeit, this trade could be worth as much as \$32bn per year, and in Britain alone, parallel trading is costing the pharmaceutical market £1bn a year. Fortunately for the UK, he said, the level of counterfeiting is nearly undetectable and is a rare occurrence.

Professor Moffat stressed the need to establish the nature of the whole tablet. He gave a number of reasons why he regarded NIRS as a good method for detecting counterfeit medicines: it is non-destructive, it can analyse active drugs and excipients, it is both qualitative and quantitative, it provides fingerprints of the whole matrix, and it gives "a huge amount of information".

He found NIRS particularly useful for analysing excipients, which often made up the bulk of a solid dosage form and there may be a complex mixture. For example, *Aremis* contains nine excipients as well as the active principle *sertraline*. Counterfeiters may put in the right active drug, and it might also be present in the right amount, but it is highly likely that the excipients used and their relative amounts will not all be the same as used by the genuine manufacturer. He said that a careful examination of the excipients could indicate whether a preparation was genuine or not.

He told the meeting that work his group at the School of Pharmacy had carried out on parallel imports had clearly indicated that the same preparation, when made at different sites, could easily be differentiated by NIRS. Some of the physical differences between tablets from different manufacturing sites can be removed by the usual mathe-

matical pre-processing techniques such as standard normal variate (SNV). The use of SNV can often uncover differences in moisture content between tablets, by measurement of the 1,940nm water band. However, he warned that tablets should be analysed as soon as they are taken from their blister packing, because hygroscopic tablets may change in the laboratory environment and accurate results may not be obtained.

Principal components analysis (PCA) can be used to differentiate between tablets taken from batches from different sites. The loadings may also be used to identify the features that are responsible for the differences, eg, water and some excipients. He explained that PCA may be extended to classify tablets as coming from a particular site of manufacture using single tablet data in three stages: first, select the appropriate sample; then determine the critical value with which to differentiate sites (if necessary refining by using second derivative spectra) and then externally validate that method.

Professor Moffat observed that the use of microscopy could yield even more information about the make-up of the tablet. Some older NIR-microscopes could scan a tablet in about 24 hours, whereas the newer NIR-imaging systems can accomplish the same thing in 20 minutes.

There is now the possibility of combining NIR-microscopy with Raman-microscopy to give complementary identification information about excipients. If one technique does not give good information the other might, he explained.

Professor Moffat summarised four advantages of NIR-microscopy and NIR-imaging: identification of the excipients, quantification of the excipients, assessment of the particle sizes, and measurement of the homogeneity of the mix. In addition, NIRS can give information about features such as hardness, compression, dissolution and moisture. When counterfeit *Viagra* tablets had been examined by these procedures, it had been easy to differentiate six counterfeit products from a genuine Pfizer product.

He concluded that NIRS could answer four key questions about a suspect product:

- Does it differ from a genuine sample?
- Are the differences significant?
- What are the differences due to?
- Is it therefore counterfeit?

Questions put to Professor Moffat focused on current choice of NIRS equipment, transferability of data between instruments, the time period to build a library of experience for testing in another laboratory, robustness of NIRS methods in field and on-line testing, and reluctance of regulatory authorities to accept it. Dr Kopp believed that NIRS was still not uniform enough for general acceptance and Dr Kelly dubbed it "the sleeping giant of pharmaceutical analysis". His laboratories had encountered a number of snags, including the need for authentic specimens for comparison. — *Contributed by Professor Geoffrey Phillips, a former Secretary of FIP Laboratories and Medicines Control Section.*

How to help pharmacists and the industry be allies in concordance

Introducing a workshop on concordance issues on 9 September, the chairman Astrid Kågedal (Sweden) explained that the aim was to discuss how to achieve better health care through improved concordance by educating patients with information provided by industry through the community pharmacy. She suggested the outcome of the workshop, which was jointly organised by FIP's Industrial Pharmacy and Community Pharmacy sections, should be the starting point for development of further action.

Setting the theme, Jane Nicholson (United Kingdom) defined "concordance" as an agreement between the health practitioner, whether pharmacist, doctor or nurse, on a therapeutic partnership. She looked at each of the players involved — patients, physicians, politicians, pharmacists and the pharmaceutical industry. In Europe, patients are playing an increasing role in the management of their own health and, as "informed" patients, are more likely to comply with their treatment. Physicians are dependent on a health team and general practitioners in primary care have had to become more business orientated. Governments are looking for efficiencies in health care resources and it is not difficult for politicians to see that one of the unnecessary costs is patient non-compliance. Several of the key roles identified by the Chief Pharmaceutical Officer for England that underpin the future direction of pharmacy provision include:

- Advise on the safe and effective use of medicines
- Promote patient safety by preventing, detecting and reporting adverse drug reactions and patient medication errors
- Prescribe medicines and monitor outcomes
- Provide medicines management services
- Act as a public health resource

From the above, it is not difficult to see the potential for co-operation between community pharmacy and the pharmaceutical industry. "Nobody knows more about a medicine than the company that developed it," said Mrs Nicholson.

The pharmaceutical industry is a source of information for pharmacists and other health professionals. This includes aspects of a product that may not be published as approved government documents. The industry is aware that its customers are no longer simply doctors, but a network of doctors, pharmacists, patients and payers. Industry wants to get closer to its customers and is providing educational programmes on subjects such as business skills, medicines management and medication review for pharmacy. Initial results of a national pro-

gramme on adherence to therapies organised by the American Pharmaceutical Association and sponsored by the industry have "shown it to be extremely successful", said Mrs Nicholson. A general training programme for counter assistants, sponsored by Reckitt Benckiser and devised with the National Pharmaceutical Association won a national training award and has trained nearly 50,000 pharmacy assistants in the UK. "Are there any objections to industry providing this type of training material," asked Mrs Nicholson.

An example of good co-operation has been the extensive list of products proposed as candidates for classification from prescription to pharmacy only sales. Co-operation between regulators, patient representatives, industry, pharmacists, nurses and doctors promises a wide range of up-to-date non-prescription products and, it is to be hoped, an easier mechanism for industry to deregulate products. This provides a great opportunity for community pharmacists to extend their counter prescribing.

Another example of existing co-operation is the joint effort between community and hospital pharmacists and regulatory agencies and industry in attempting to stamp out counterfeit medicines. Another example is the United States industry support for the Institute of Safe Medication Practices, an organisation working to reduce medication errors. Mrs Nicholson asked if there were any similar organisations, which industry is not currently, but should be, supporting?

CONSUMER INFORMATION

Despite repeated discussion and detailed assessment of patient-friendly leaflets, the European Agency for the Evaluation of Medicinal Products continues to provide guidelines that lack clarity and readability. Patients need to be informed and not overwhelmed with information and the European leaflets are too long, the information is in the wrong order and the leaflets do not meet the needs of the patient.

Mrs Nicholson showed several examples of direct-to-consumer advertising and compared them with "pull down" information from industry sites on the internet and their links to independent patient health-care sites. She mentioned pilot studies which will add "Medicines guides" to NHS Direct Online to contain generic product information that will complement patient leaflets. This co-operative exercise between industry, the Royal Pharmaceutical Society, the National Health Service, the regulatory



authority, patient groups and general practitioners will be initiated in October.

She wondered whether good medicines information is unacceptable because of pharmaceutical company involvement.

Bob Grant, a community pharmacist from Australia, stressed the need for the industry and health care providers to involve pharmacists at an early stage in the development of disease management programmes. There is concern that direct-to-consumer advertising has negative implications for patient outcomes. The Australian medication review programmes "are excellent tools for minimising side effects", noted Mr Grant.

QUALITY ASSURANCE

Deborah Mon, director, Medicines Australia, explained that consumer medicines information is regulated in Australia through a quality assurance reference group that represents industry, consumers, nurses, doctors and pharmacists. The group's tasks include the assessment of product-specific medicines information, maintenance of usability guidelines and vocabulary and promotion of consistency. Consumer medicines information is developed by the sponsoring company, distributed electronically and funded by the industry to reach the pharmacists' computers.

James Bronger, Pharmacy Guild of Australia, confirmed that it is providing a useful tool for pharmacists counselling. Empowered patients, improved communications and the promotion of effective use of medicines are the objectives of consumer medicines information, which, thus far, has provided a successful alliance between community pharmacy and industry.

Martine Chauve, a community pharmacist from France, described the community pharmacist as being a good channel of communication between the industry and the patient or the prescriber. She considered as dangerous the direct contact of patients with industry over the internet.

INTERACTIVE APPROACH

Parisa Aslani, University of Sydney, said that a change from the traditional one-way interaction to a more interactive approach to information and counselling is required. There are several factors which may influence concordance. These include the interaction between the patient and health professional, communication skills, the information provided to patients, patient's health beliefs and attitudes towards and

their perception of their illness and medications.

Using the Canadian product monograph as the example, Jeff Poston, Canadian Pharmacists Association, made a case for review of current approaches to the labelling of non-prescription medicines. He said that there was a need to develop a more balanced approach in the presentation of information to consumers, such as providing risk:benefit information, rather than warnings which have little relevance to the majority of patients. He emphasised the need to ensure that the primary goal of adherence is patient health outcomes and not the continuance of a product from a particular manufacturer.

The pharmaceutical industry plays an important role in providing accurate and consistent information about their prod-

ucts, said Kathy Mott, consumer representative, University of South Australia. She suggested there could be more effective communication between the pharmacist and the prescribing doctor. Her research on the role of the pharmacist in reviewing medicines in the home had highlighted the importance of the community pharmacist.

James McElnay, Queen's University of Belfast, UK, listed ways in which the pharmaceutical industry could assist community pharmacists develop pharmaceutical care:

- Lobby national health services and insurance companies to help ensure the concept of pharmaceutical care is adopted more widely
- Provide the "tools" for efficient education on both disease states and the medicines used in their treatment

- Produce user-friendly information sheets for specific products which give key product information such as side effects and the risk of their occurrence, whether side effects will be transient, tangible benefits achievable from taking the medicine
- Provide simple outcome monitoring tests that can be performed to help guide dosage adjustment such as diary cards

Closing the discussion, Mrs Nicholson noted that there is work to be done on the provision of appropriate product and general health care information to consumers and patients, on patient compliance and on the development of patient outcome monitoring programmes. — *Contributed by Jane Nicholson, Industrial Pharmacists Group.*

How to make ethical decisions

In the FIP document "Good pharmacy education practice" the seven-star pharmacist is required to be a care giver, a decision maker, a communicator, a leader, a manager, a teacher and a life-long learner. In this, the second of a series of forums addressing these skills, FIP's Young Pharmacists Group took a look at decision-making. (The first forum was held in Nice, France, last year; see *PJ*, 21 September, 2002, p402.)

The decision-making process is a reminder to slow down and deliberate, to consider the consequences, the constituencies and the options before making a responsible choice. This is how Betty Chaar, clinical pharmacist at the Royal Prince Alfred Hospital, Sydney, opened the FIP YPG forum on 8 September.

What is decision-making and what does it involve/require from the individual? How do we make the right decisions in pharmacy practice? We face decisions every single moment, said Ms Chaar. She expanded on the terms "decision-making" and "ethical choice" with the aim of assisting young pharmacists to identify the key elements of the process. She put everyone in the picture by drawing on examples from her own experience.

One hospital patient, she said, had complications. It transpired that he had taken Viagra but did not want his wife and close family to know. With this knowledge, the attending physicians would be able to manage his case more efficiently, but he was uncomfortable about sharing the information. What should the clinical pharmacists do, asked Ms Chaar. She said the pharmacist should take a decision, justify it and then revisit it and reflect upon it.

TAKING THE DECISION

To make the right decision ethically, a pharmacist must consider the facts, moral parameters, legal constraints and human values. In most ethical dilemmas, issues will pull us

in different, often opposing, directions. In the Viagra example above, should the pharmacist tell the attending physician, or keep to themselves the information the patient had shared? One option may be trying to convince the patient of the wisdom to share the information. Respect for the patient, his family, and the sensitive nature of the case demand attention as to who should be dealing with the patient, and the manner in which the case is dealt with.

Taking a closer look at the implications, the pharmacist is pulled in the direction of "do no harm" versus "maintaining patient confidentiality". At the end of the day, does the decision pass the "red face" test, asked Ms Chaar.

The "red face" test involves asking oneself the question: "Could I face the media tomorrow with the decision I have made?"

JUSTIFYING THE DECISION

Four ethical pillars of decision making underlie the duty of care. The pharmacist is ethically required to provide the patient the best care in his or her capacity. The four pillars are:

- Have respect for the patient's autonomy and provide full information
- Do no harm
- Act in the best interest of the patient
- Ensure a fair distribution of your services

REVISITING AND REFLECTING

Ms Chaar put some questions to the group. In thinking about the decision made, are we comfortable about it? Have we acted in the patient's best interest? A decision is not just an opinion, but based on a professional ethical principle. Have we stood up to our principles?

She told young pharmacists: "Stand up to a principle. Don't give in to domineering colleagues, assuming they know better."

WHICH MEDICINE?

In the final part of the forum the group was presented with seven options of a medicine that might be dispensed in response to a prescription. The options ranged from the most expensive brand from the originating company to the cheapest generic. Each option was associated with a different reason why a pharmacist would choose to dispense it rather than any of the others, eg, they were friends with the medical representative, or they had shares in the company, or they got better bonuses from the wholesaler.

Different participants justified their choices and a case was made for each choice available. The discussion became more exciting as people from different countries explained why some options would or would not be available in their respective countries. Some pharmacists would be stocking only one brand — the cheapest bioequivalent generic, while others were required by law (Portugal, for example) to have in stock every variety of a medicinal product available on the market.

It was pointed out that the principle of autonomy came into play to some degree in this case. In that, faced with such a choice, the fairest course of action may be to give the patient the choice, and assist with his or her questions in as honest and unbiased a manner as possible. — *Contributed by Daniella Zammit, chairman, FIP YPG steering committee.*

FIP YPG

Further information about the International Pharmaceutical Federation's Young Pharmacists Group is available from: FIP YPG, PO Box 84200, 2508 AE The Hague, The Netherlands (tel +31 70 302 1978, fax +31 70 302 1999, e-mail: ypg@fip.org) and from FIP's website (www.fip.org).

The importance of “quality use of medicines” in Australian hospitals

A half-day symposium, organised by FIP Hospital Pharmacy section on 9 September, explored in depth the “Quality use of medicines” (QUM) initiatives in Australian hospitals.

The subject of Australian national policies was developed by Professor Andrew Gilbert, University of South Australia. Professor Gilbert described the development of the Australian health care system, which, historically, was the responsibility of autonomous states, with little central involvement. Evolving centralised taxation and benefits schemes altered this balance and sought to ensure affordable high quality care was available to all Australians — free treatment in public (state-funded) hospitals and subsidised local medical and dental practice. However, the funding split between Commonwealth government and the states effectively resulted in poor continuity of care between hospital and community medicines priorities. Some relief to the latter was given by hospitals instituting a “home medication review”.

NATIONAL INITIATIVE

He described a national medicines policy initiative that flowed from a ministerial committee initiated in 1992, which had addressed concerns about the way medicines were selected, prescribed, dispensed, administered and used in society. Implemented in 2002, this enshrined the concept of QUM through judicious selection of treatment — or none at all — chosen within drug categories, and their safe and efficacious use.

The four-fold aim of the initiative was that QUM should meet the needs of the community, that there should be equality of access, that the safety, quality and efficacy of medicines should be assured, and that a viable domestic pharmaceutical industry should be maintained.

Implementation, which may take up to 10 years, has been through the Commonwealth Department of Health and Ageing.

Professor Gilbert reviewed Australian national resources available to support QUM. Key elements have been:

- Objective information, eg, through the Australian National Formulary, a national therapeutics bulletin, adverse drug reaction reporting and collation of patient insert leaflets
- An education and training strategy for all levels of health provision
- Intervention, through audit and review mechanisms, home medication reviews, and disposal of unwanted medicines
- Research and data collection



Guidelines to integrate best practice in medication management were introduced for residential care of the aged in 1997 and 2000, and for continuity of quality use of medicines between hospital and the community in 2003.

Professor Gilbert turned to a review of current outstanding QUM issues. He said that there are still too many (140,000/year) medication-related admissions to hospitals and general practitioner consultations for adverse drug reactions, perhaps half of which were potentially preventable. There was “good evidence of efficacious hospital methods but related problems needed follow-up post discharge”. He concluded that all health professionals must take full responsibility because too many patients were being readmitted to hospital.

STATE INITIATIVES AND ACTION

QUM action in individual Australian States was reviewed by Karen Kaye, New South Wales Therapeutic Advisory Group. She quoted the total Australian health expenditure of A\$61bn for 1999–2000, of which one third was earmarked for hospitals. State governments distribute and implement provision but state policies are not uniform.

She contrasted the centralised system in Queensland, with decentralised control in New South Wales, where funding is devolved through 17 autonomous regions according to a weighting formula. Further, states have no over-arching QUM policy: the state of Queensland operates through seven linked medication-related categories, whereas NSW relies on framework guidance on clinical governance factors and on widespread distribution of (official) information in circulars and bulletins to hospitals, as well as reporting and assessment of adverse incidents from hospitals. She said that NSW provides tool kits for change management and quality improvement.

QUM data collection, Ms Kaye explained, involves key clinical performance indicators, incident monitoring, and development of integrated IT systems. She noted some co-ordinated activity at state level, eg, Victoria takes a lead role in re-prescribing for hospitals.

Turning to the role of hospital boards, she described as “pivotal” the drugs and therapeutics committees which involve consumers as well as professionals. DTCs set a clear goal of “safe and effective drugs for all patients”. But, she said, “the reality is different”.

There are insufficient resources and capped budgets result in rationing of supplies. The stakeholders’ high expectations are to ensure best practice in use, equity of access, and adequately equipped and informed to make clinical and ethical decisions, through a truly consultative, sound and transparent process. Ms Kaye saw DTCs influencing medicines usage through opportunities to be involved in medicines acquisition, formulary management, hospital drug protocols and monitoring of drug use. Formulary management, she affirmed, “is a serious business”.

DTCs operate in a complex environment of pressure to cut costs, seeking better care despite inaccurate cost measurement. There is competition for capped funding, accountability for best practice, research activity and new drugs, especially in biotechnology, and last, but not least, a climate of comparing expected versus actual outcomes, clinical and economic.

Ms Kaye said that DTCs halve decision-making by bridging budgetary “walls” between operational areas and cost offsets from a sector different from that in which costs were expected, although this might result in undesirable incentives. She admitted that DTC decisions might sometimes be inconsistent, resulting in inequity of access and discontinuity of care.

STATE COLLABORATION

Ms Kaye contrasted the QUM networks in different Australian states. In Queensland, there is a standard “drugs list”. This controls new drugs until there is adequate experience, considers therapeutic efficacy and (from the state’s viewpoint) cost effectiveness, and operates central purchasing and wholesaling. West Australia set up a drug evaluation panel that provides independent advice on the effectiveness of higher cost hospital drugs. NSW has no central formulary management but instead relies upon collaboration of hospital DTCs with the state main Ethics Committee and state-wide pharmaceuticals contracts.

Between states, NSW maintains close liaison with therapeutic advisory groups (TAGs) and state-wide DTCs in Victoria, South Australia and Tasmania. These state networks share QUM information, develop strategies, and generally learn from each other's experience. She exemplified activity of the independent TAG for NSW — an incorporated non-governmental organisation funded by the state and sharing information via a state-wide intranet. Its key features are a grass roots approach, a sharing of expertise and its independence and credibility. As well as at its website, there are e-mail discussion groups and teleconferencing facilities.

Hospital support for DTCs is comprehensive, subsuming position statements, discussion groups (eg, on complementary medicines), opinion documents (eg, COX-2 inhibitors), contribution to TAG bulletins on the net and educational material. There may also be an input to state-wide policy, she suggested, such as a purchasing council, or pharmaceutical services, or safety of medication. She indicated that there was a somewhat similar action in Queensland.

Ms Kaye listed a variety of QUM collaborative projects in NSW, instancing a review of pharmacy service in (public) operating theatres (completed in 2000) and guidelines for GP prescribing for chronic pain (1998 and 2002). She gave examples of inter-state collaboration in awareness of drug use evaluation, eg, recommendations following a study of proton pump inhibitors in 39 hospitals (915 patients), and another of pethidine in emergency practice (in 2002), which led to a 47 per cent reduction in use of pethidine. Her key question was: "Does all such DTC activity make substantive differences?" In 1997, the NSW TAG developed performance indicators for DTCs and in 1998 a guidance manual of "indicators for drug use" in state hospitals, which was adopted by NSW Health, underwent trials in private hospitals and taken up in other Australian states. She was pleased to observe a current increase in collaboration between states, including sharing committee minutes, discussion groups, and joint position statements. This co-operation had "enormous potential" to share information and expertise.

She recognised several current issues — pharmaceutical funding reform, decision making on high cost drugs, and between-state differences in hospital systems. QUM groups are advisory and have no power of implementation, and need more support from hospital management. She concluded that in QUM there is "movement in the right direction" but success still relies on local action, which in turn "depends on engagement and commitment of individual practitioners".

QUM EXPERIENCE

Dr Rosemary Burke, director of pharmacy at Concorde, a 500-bed teaching hospital in Sydney, presented direct experience of QUM in pharmaceutical practice in NSW

hospitals. Clinicians prescribe directly by manual ward charts, and most pharmacists equally divide their time between ward rounds and the dispensary. However, because most pharmacy departments are usually open only eight to 10 hours for five working days, there has to be limited ward stocks of emergency drugs and some treatments for basic conditions. Following some critical incidents, quality standards for medication storage have been revisited and the hospital now favours a trolley system with closed drawers to ensure safer and timely access, and monitoring effectiveness and efficiency.

Dr Burke considered how the gap between public/private sectors affected QUM in hospitals in respect of formularies, drug committee protocols and decisions, outpatient policies, fragmentation of medication records, and the long-standing divide over use of generic, non-proprietary names versus the more patient-familiar brand names. She examined the continuum of care at the hospital/community interface, through a QUM map of activity at local level. There is particular emphasis on patient confusion, including change to use of generic names, hoarding of medicines, and adequacy of communication with a GP over changes in medication.

One three-year medication study focused on Vietnamese immigrants, where a multidisciplinary "ambulatory care team" found, relative to the whole community, a risk of 2.3 to 1 of readmission due to medication accidentally omitted on discharge. Two other projects studied patient confusion: one found differences in GP recognition of changed medication and another found significant potential (in 72 of 100 oncology patients) for misinterpretation errors.

She described programmes to assist community liaison pharmacy, one involving reconciliation of hospital discharge medication and one week later at home, and a pilot study "Mediconnect" of web-based recording of all treatment. In a Tasmanian study of preadmission clinics, pharmacist assessment of full patient history showed significant differences in number of interventions on admission, and indicated that the pharmacist often was "best placed to take admission history".

Dr Burke distinguished QUM systems at a macro level (such as drug committees, policy and protocol, audits and environmental systems), from a micro (local) level (clinical pharmacy, ward pharmacist reviews, counselling, dispensing, drug information). She listed a number of requirements for QUM:

- An ability to provide drug services and interventions
- A mechanism to facilitate and co-ordinate within or beyond the organisation
- Access to appropriate information
- Education and training to support best practice
- Routine evaluation of practice to ensure QUM

- Scope for pharmacy staff to work outside hospitals (although this could cause staffing difficulties)

She maintained that "appropriate information" is best when it is produced by manufacturers, is brand-specific and easily understood. This aids counselling and encourages QUM thereby enhancing therapeutic outcomes. Further information is obtained from journals, specialist texts (such as MIMS and Martindale), local hospital handbooks and shared QUM information.

QUM POLICIES, PROBLEMS AND STRATEGIES

QUM policies, Dr Burke suggested, include effective and judicious use of antibiotics, restricted use of certain (named) drugs, therapeutic choice and interchange, and restriction of formularies as to appropriateness and cost. She stressed that drug committee approval must be evidence-based, comparing the Public Benefit system and usage within the hospital.

Turning to QUM problems, Dr Burke quoted a 1995 national study that reviewed over 14,000 case notes from 28 hospitals and discerned around 2 per cent harm from adverse drug events, involving heart disease, hypertension, antibiotics, anticoagulants, non-steroidal anti-inflammatory drugs and chemotherapy; overall, two fifths of these were potentially avoidable. There were many medication safety groups operating at various levels:

- International — involving selected hospitals in Australia, New Zealand and Singapore
- Australian — through the National Safety and Quality Council, which gave grants, for instance, for safety innovation in treatment of the elderly
- State — such as NSW TAG administered grants
- Professional — including the Society of Hospital Pharmacists of Australia committee on specialty practice
- Local — including targeted investigations, eg, protocols for heparin and phenytoin

Discussing risk management strategies, she asked: "What is wrong? How do you deal with it?" Initially, one should consult literature and colleagues, and she instanced analysis of the risk of holding ward stocks of IV potassium. The "pharmacist's role in safety", Dr Burke summarised as detection, documentation, management, minimisation of drug-related problems, policy development, and "keeping an ear to the ground to find out what is needed to be done". QUM, she emphasised, demonstrated that hospital actions are "judicious, appropriate, efficacious and safe". In hospital pharmacy, it represents the "beginning of many initiatives which now find key places". — *Contributed by Professor Geoffrey Phillips, a former secretary of the FIP Laboratories and Medicines Control Section.*

Mechanisms and problem-solving in oral drug delivery and absorption

On 6 and 7 September, a two-day symposium organised by the FIP Board of Pharmaceutical Sciences reviewed oral drug delivery and absorption mechanisms and strategies.

DOES DRUG DELIVERY DELIVER?

Professor William Charman, Monash University, Melbourne, Australia, noted the remarkable growth in the literature addressing "drug delivery". In the 15-year period from 1966 to 1981 there had been just 167 papers (average 11 per year) mentioning drug delivery, whereas in the 1980s drug delivery began to be correlated with pharmacokinetics, and in the early 1990s was first reporting the role of bioequivalence in drug delivery. By the 1996–2002 period, drug delivery averaged 516 papers a year and pharmacokinetics and pharmacodynamics were recognised as drivers for the design of drug delivery systems.

Professor Charman said that the value of a drug delivery system could be determined through three questions:

- Does it meet a therapeutic need?
- Is there an optimal rate, time or site for its use?
- What is the most suitable design for that delivery?

However, he feared that these three questions were often asked in the wrong order, whereby the availability of an existing delivery system was then touted for a suitable drug to use it for.

He reviewed two existing therapies involving drug delivery systems. There are biodegradable polymers, linked to novel implant vehicles, which might be films, fibres, sponges, scaffolds or injectables. An example is carmustine in polymer base which is useful in prolonging life expectancy following brain cancer surgery in patients with glioblastoma.

Secondly, he mentioned liposomes. He said that cationic liposomes in DNA complex had been the most studied non-viral system. Current efforts were mostly targeted on "triggerable liposomes" and bypassing natural barriers.

Looking to the future, Professor Charman mentioned specific tissue plasminogen activator (tPA) systems, which are on the horizon in drug delivery. These are valuable in dispersing clots resulting from cardiovascular episodes, but currently dissolve the "good" thrombi along with the "bad" ones. Selective tPA systems are needed which invade the developing, potentially lethal, clots while not affecting established thrombi serving a useful purpose.

Dr Clive Wilson, University of Strathclyde, Glasgow, United Kingdom, said that

the issues surrounding drug delivery could be split into physiological and physico-chemical factors, although we cannot compartmentalise these factors and deal with them in an entirely independent manner. Inter-patient variability is a result of the interplay of these factors, which will vary as a function of gastrointestinal transit, diet, posture and previous history. We attempt to standardise as much as possible in pharmacokinetic trials. However, even the simplest deviation from a clinical trial protocol, such as substituting gaseous mineral water for plain water or giving a high fat meal 48 hours before the trial can cause huge effects which may alter drug permeability. Dr Wilson has adapted imaging techniques used in clinical medicine to follow the transit and deposition of formulations. These techniques allow the investigator to rationalise variability in terms of residence in different parts of the gut.

TAILORED MEDICINES

Medicines should be tailored to different patients for the maximum therapeutic benefit with the lowest adverse effects, explained Dr Paolo Colombo, University of Parma, Italy. He said that each individual has different requirements so the dosage form must be adaptable. Pharmacists of the future will be called upon to deliver one or several drugs to a specific site at an adequate rate for a specified duration.

A system capable of performing a multi-kinetics delivery in one dosage form has still to be invented, he said. However, a new release module consisting of a cylindrical tablet with one concave and one convex surface and capable of time and site control has been studied. The axial section of the module appears as a dome and the module is registered as Dome Matrix. The delivery module is flexible since several modules can be stacked to allow the division of drug doses or a combination of different drugs. The delivery module is a swellable matrix. Stacking results in a change of ratio between the area of delivery and the volume of the system.

An alternative configuration is to place two modules so that the concave bases face each other creating a void of air inside the system that allows it to float when immersed in water. The Dome Matrix assembly described allows the manufacture of a gastric system, a colon target, or simply a drug release modulation.

Dr Susan Charman (Monash University, Melbourne) discussed lead optimisation



strategies for improving oral bioavailability. She said that preclinical drug candidate optimisation has become an essential component of modern drug discovery and plays a critical role in compound selection and progression. Drug candidate optimisation integrates medicinal chemistry with the pharmaceutical sciences and provides a means of identifying drug candidates with the necessary chemical, biopharmaceutical and pharmacokinetic properties to enable rapid and successful development. Inherent in this process is the need to relate specific physicochemical properties of candidate compounds to their absorption, distribution, metabolism, excretion characteristics and to use this information predictively.

HEPATIC ISSUES

In his lecture on hepatic considerations and issues for drug delivery, Michael Roberts, University of Queensland, Brisbane, noted that hepatic clearance is a major determinant of oral bioavailability and can make the oral delivery route unsuitable. The extent to which the liver influences oral bioavailability during the first pass after oral absorption depends on a number of factors. These include the nature of the drug, the condition of the liver and physiological influences such as co-administration of food and drugs and the person's cardiovascular status and posture. Oral bioavailability may be modulated by enterohepatic recirculation and the nature of food ingested. Drug administration rate, metabolite accumulation and alterations in liver disposition caused by disease, ageing and drugs may also modulate oral bioavailability.

To reduce variation in hepatic metabolism, it is better to have drug candidates that are metabolised by several of the liver enzymes, explained Dr Roberts. Oncologists are now exploring how to improve oral therapy by temporary inhibition of drug transporters and the CYP450 liver enzymes.

LYMPHATIC DRUG DELIVERY

Dr Christopher Porter, Monash University, Melbourne, described lymphatic drug delivery as an "ignored pathway and opportunity". He explained the nature of the lymphatic system as an anatomical salvage circuit ultimately emptying into the blood circulation. In contrast to blood capillaries, in lymphatic vessels there is low pressure flow and walls permeable to colloidal molecules from the interstitial space. This specialised structure and function of lymphatics provides opportunities to enhance conven-

tional systematic delivery by targeting the capillary bed and specifically direct the delivery of drugs to, or through, lymphoid tissue.

Compared with conventional oral delivery, transport to intestinal lymphatics circumvents hepatic first pass metabolism. Using the sheep as an *in vivo* model, Dr Porter has shown that higher molecular weight proteins such as erythropoietin are exclusively absorbed through the lymphatic system.

Drug delivery strategies that enhance lymphatic transport may improve the utility of various immunomodulators, vaccines and anti-infectives. They may also provide a delivery benefit for cytotoxic agents designed to combat the spread of tumour metastases from solid tumours.

GENOTYPIC MEDICINES

Disease prevention, individualised medicine and genotypic medicine will soon become a reality, said Dr Vincent Lee, ALZA, California, in his presentation on the pharmacogenomic considerations in oral drug delivery. Dr Lee contrasted the roles of liver, kidney and intestine in absorption and elimination. For several therapeutic systems, he listed drug molecules and their corresponding substrates, and correlated peptides within the DNA chain involved in their transport. He said that there is increased awareness of potential involvement of many proteins in intestinal epithelial cells, notably drug transporters both influx and efflux and drug metabolising enzymes. These promote systemic drug bioavailability, including drug excretion into urine and this has precipitated systematic evaluation of conditions under which pharmacogenomics may play an important role.

THERAPEUTIC VERSUS ECONOMIC

Professor Hans Junginger, Leiden University, the Netherlands, divided his presentation on oral modified release formulations and pharmacoeconomic considerations between a therapeutic and an economic rationale.

Therapeutic considerations include the need for constant plasma concentrations, high elimination rates of active drug and less frequent dosing regimen to improve patient compliance. But there was also a need for the correct blood concentration within the therapeutic range.

Professor Junginger commented that the current market had many excipients, including polymers, that allowed the formulator to design an optimal release profile, such as diffusion membranes, a single or two-layer matrix, or even a coated matrix system. He instanced a sublingual preparation providing instant nitroglycerine treatment, then a peppermint layer, followed by a sorbitol ester. A drawback for some oral modified release preparations is that the release rate is not predictable and reproducible in the human gastrointestinal tract.

He referred to the effect of circadian rhythm and commented that a study in

1,209 subjects had shown 9am to 11am was the period of highest incidence of myocardial infarction and that this needed to be correlated with dosage regimens.

Turning to the economic rationale, he distinguished development of oral modified release preparations as aiming at higher patient compliance (with potential savings of \$100bn per year in the United States) reduced costs because of fewer side effects, better quality of life for patients with once-a-day administration and extended patent life for the product. He noted that one should always ask: "What is the added value?"

IS THE DELIVERED DRUG ABSORBED?

"How to teach an old drug new tricks" is one way of describing the strategic considerations for drug delivery, remarked Dr Rashmi Barbhaya (Ranbaxy Laboratories).

A variety of drug delivery technologies have been successfully employed to improve safety and tolerance or to allow rapid onset or longer duration of the desired pharmacological effects. Drug delivery systems have also helped to address issues related to poor and variable oral bioavailability.

In pursuit of identifying a suitable delivery system for a given drug, a number of factors, such as dose, physicochemical, pharmacokinetic and biopharmaceutical properties of the drug and clinical rationale need to be considered. The identification of an optimum pK profile for a drug delivery system is essential, said Dr Barbhaya. Clinical need for the desired dosage form, intrinsic pharmacokinetic and biopharmaceutical properties and knowledge of the influence of input rate on the pharmacodynamic effects of the drug as well as the strategy for development and registration of the product are all factors that need to be considered.

Metabolic enzymes (eg, CYP3A4) and efflux transporters (eg, P-glycoprotein) act synergistically to reduce the oral absorption of many drugs, noted Dr Yuichi Sugiyama, University of Tokyo, Japan, in his presentation on the role of transporters in oral drug absorption.

In new drug development, recombinant drug metabolising enzymes have been widely used to predict drug clearances and drug-drug interactions, and to conduct high throughput screening of potential new drug candidates. The recombinant transporters for drugs may be similarly used for drug screening. Dr Sugiyama summarised the recent progress made in his laboratory, focusing on the role of transporters in the intestinal absorption and hepatic uptake/ excretion and predictions from *in vitro* studies using isolated cells, plasma membrane vesicles and/or cDNA-transfected cells.

Due to their broad substrate specificity, enzyme transporters can cause drug-drug

interactions. This is exemplified by the deaths of patients on cerivastatin when prescribed in combination with gemfibrozil or cyclosporin A.

PHARMACOGENETICS

Dr Andrew Somogyi, University of Adelaide, Australia, discussed the impact of pharmacogenetics on drug absorption.

Drug metabolising enzymes, particularly CYP3A4, are located in enterocytes lining the mucosa of the intestine and limit the body's exposure to drugs. However, uptake and efflux transporters are localised on the apical membrane of enterocytes and modulate the movement of drugs into and out of the gut cells. Dr Somogyi uses multi-lumen intestinal perfusion catheters (which blow up like balloons and isolate gut segments) to infuse drugs and aspirate cells from sections of the gut *in vivo*. This system has been able to demonstrate significant genetic variation between individuals in the metabolism of drugs such as digoxin and fexofenadine. Although it may be possible to genotype an individual and calculate the dose of a medicine to be given, Dr Somogyi considers specifying an individual's therapy based on their genetic make-up is still a long way off.

NEW DELIVERY SYSTEMS

Dr Hans Junginger also discussed his work on modern delivery systems for peroral absorption of peptides.

With the advent of recombinant DNA techniques and other biotechnological processes, the mass production of therapeutic peptides becomes reality, he explained. However, the development of suitable oral dosage forms has not kept pace and peptides have still to be administered by injection.

The reasons for this failure include breakdown of peptides in the gastrointestinal tract and poor permeation of these hydrophilic macromolecules across the mucosa of the gut and the mucus barrier.

Using superporous hydrogels (made of 3-methyl chitosan), reproducible and predictable peroral peptide absorption becomes feasible.

These hydrogels swell to 200 times their initial volume in the physiological environment. This increase is sufficient for swollen hydrogels to stick mechanically to the intestinal gut wall and to deliver the incorporated drug directly, simultaneously inducing the opening of the tight junctions of the gut wall and inhibiting local enzyme activity.

After the peptides have been delivered and absorbed across the gut wall, the hydrogels become over-hydrated and their structure is broken down by the peristaltic forces of the gut and the remnants of the delivery systems are easily excreted together with the faeces. — *Contributed by Jane Nicholson, Industrial Pharmacists Group.*

