

# Advances in the drug therapy management of the oncology patient

Our coverage of the World Congress of Pharmacy concludes with reports from **Geoffrey Phillips** on cancer therapy (this page) and international trials harmonisation (p493), from **Tony D'Emanuele** on new technologies (p491) and from **Lindsay McClure** on leadership by young pharmacists (p495)

A symposium on 5 September, organised by the Hospital Pharmacy Section, heard Jill Kolesar, an associate professor at the University of Wisconsin, Madison, US, discuss advances in treatment for cancers affecting the colon, lung, prostate and bone marrow, which together constitute the major proportion of cancers in the US.

Colorectal cancers affect about 100,000 Americans, of whom roughly half will die, although the outcome is enormously dependent on the stage at which treatment begins: if detected early (Duke stage A), 91 per cent recover, whereas only 5 per cent have a five-year expectancy following late stage (Duke stage D) treatment.

## New chemotherapy

Professor Kolesar reviewed new chemotherapy available as an adjuvant to surgery that would supplement classic 5-fluorouracil (5FU) and leucovorin (LV) therapy. This new approach involved restricting angiogenesis — the (re)growth of blood vessels — with suitable monoclonal antibodies that could interfere with vascular endothelial growth factors (VEGF). She reported clinical trials with bevacizumab, contrasting front-line therapy using 5FU/LV with or without this monoclonal agent. Survival rates increased by an average of five months, but cardiovascular adverse effects needed to be weighed: hypertension (requiring antihypertensive treatment), extra bleeding, proteinuria and some episodes of transient stroke.

She described the trials as “exciting” and ongoing as an indication of “first line” co-treatment, but emphasised the disadvantages of cardiotoxic effects and the need to wait for 28 days after surgery.

A different strategy, for “second line” treatment, involving endothelial growth factor receptors (EGFR), was still at the development stage. The monoclonal cetuximab, in combination with current use of irinotecan, is being assessed.



Professor Kolesar designated cancer of the lung as the worst disease in the US, with 172,000 new cases already in 2004, and 157,000 deaths in 2003. At stage 1 (affecting about 10 per cent of all cases), there was a two-thirds survival rate, whereas by stage 4 (40 per cent of cases) only 1 per cent survived. Clinical trials with altogether 5,700 patients post-surgery had focused on earlier stages, and most patients had shown some advance in survival for stages 1 and 2. Other “front line” chemotherapy adjuvants employed cisplatin (as first line treatment), then docetaxel (second line) and, controversially, as third line gefitinib. Some phase II trials had been small and unrandomised but gefitinib had gained Food and Drug Administration fast-track approval for phase III where, however, it revealed no marked improvement over placebo. She suggested that measurement of EGFR mutation should predict which patient should respond to gefitinib and could assign treatment accordingly.

Prostate cancer is also common in the US, with 200,000 patients per year, of whom 40,000 may die. Growth of the cancer is promoted by testosterone. In a major US trial, involving 18,800 men aged over 55, with no previous prostate history, the aza-steroid finasteride reduced the onset of cancer by 25 per cent but, unfortunately, those who did progress endured a higher rate of urinary retention and a more aggressive level of prostate cancer. It was her opinion that the “jury is still

out” on the value of finasteride, whereas alternative treatment with mitoxantrone alleviated symptoms but did not improve survival rate. She confirmed that the decline in PSA (prostate specific antigen) protein is still an effective measure.

Professor Kolesar referred to a new study — to be reported in full in May 2005 — that “alters everything” with the “first real improvement” in prostate chemotherapy. Docetaxel, in three-week spells, increased median survival from 16 to 19 months for hormone refractory prostate cancer, with a 24 per cent reduction in death outcome, lessened pain, enhanced quality of life, and PSA declined by 45 per cent compared with 32 per cent with classic chemotherapy.

Professor Kolesar went on to discuss myelo dysplastic syndrome, for which, she said, there is no treatment previously registered in the US. This is a bone marrow disease of the elderly, with an incidence in the US of 22 to 45 per 100,000 citizens aged 65 to 70 years. Present supportive treatment used epoetin and blood transfusions. Phase III trials had shown that azacytidine inhibited DNA methyl-transferase, improving 37 per cent of cases and increasing the median time to death to 21 months, compared with 12 months for standard supportive treatment. Azacytidine was well tolerated in seven daily doses paced over four weeks and she regarded it as a significant advance in front line therapy for myelodysplasia.

## Combating chemotherapy side effects

Phil Hall, an associate professor at the Medical University of South Carolina, discussed the role of “haematopoietic growth factors” in treatment of anaemia of various secondary causation. Moderate to serious anaemia is very common (50 per cent) in chemotherapy with cancer patients: maintaining haemoglobin concentration improves a patient's quality of life and survival. The malignant cancer can itself cause anaemia from bone marrow invasion and secretion of inflammatory cytokines, bleeding, nutritional deficiency and, of course, damage from myelo-suppressive therapy and radiation treatment.

The clinical consequences of haemoglobin loss include fatigue, reduced exercise capacity, apathy and mood swings, impaired concentration and cognition in work and domestic situations, and increased load on the local practitioner. Treatment options include blood

## Details

The World Congress of Pharmacy and Pharmaceutical Sciences was organised by the International Pharmaceutical Federation in association with the American Pharmacists Association, the American Society of Health-System Pharmacists and the American Association of Pharmaceutical Scientists. It took place in New Orleans, Louisiana, from 4 to 9 September

transfusion, or three doses per week of epoetin- $\alpha$  (EPA). Professor Hall referred to three trials with EPA, which all significantly increased haemoglobin and improved quality of life of the patient, following treatment in three or single weekly doses and concurrent monitoring of iron concentration,

Professor Hall asked why we need another erythropoietin (EPO) analogue. Darbepoetin  $\alpha$  is a new biochemically distinct protein, with a long half-life (which allows flexible patient scheduling over two or more weeks) and significant *in vivo* activity — binding to similar sites while remaining biochemically distinct from EPA. He reported several comparative trials with the two agents, which demonstrated comparable haematopoietic response and dose related improvement in quality of life. However, he voiced some concerns: one breast cancer trial had to be stopped because of higher morbidity; there had also been low EPA levels in people with head and neck cancers, and some ovarian and prostate tumours may express EPO receptors, resulting in more clots or red cell aplasia. He concluded that darbepoetin  $\alpha$ , because of its longer serum half-life, could be dosed less frequently and is equi-effective with EPA.

Professor Hall turned to discuss another common side effect of chemotherapy: febrile neutropenia. This can be caused by disease, age, prior radiotherapy, or dosage history, resulting in infection, delay of prevailing chemotherapy and reduced quality of life. He added that it also incurred additional health care expenditure. It can be treated by reducing chemotherapeutic dose, or by specific treatment with sargramostim, filgrastim or a modified release form, pegfilgrastim. A number of trials compared different amounts of filgrastim, or its pegylated derivative, with a placebo, during simultaneous chemotherapy and there had also been two retrospective studies. It had been concluded that the extended action of filgrastim might be clinically beneficial by reducing the frequency of injection, enhancing patient compliance and possibly increasing efficacy. He regarded the pegylated derivative as an attractive alternative to daily injections of filgrastim or sargramostim.

### Pharmacoeconomics

Lee Vermeulen, director of the centre for drug policy at the University of Wisconsin, examined the financially important question of pharmacoeconomics in oncology treatment. In the US, he said, there is an extensive record of the cost of supportive care, but much less on the economics of primary care. He assumed there would be general agreement on a “societal duty to control costs” below available commitment but choosing between two, say, non-toxic lipid-lowering agents “should be much easier”. “There is no political will to deny treatment in extending life by weeks,” he said, but the “morality of refusing deliberated choices remains questionable”.

Mr Vermeulen focused on the economics of oncology therapy and postulated a “value equation”. The estimated US health total annual expenditure is \$1.6 trillion, within which there is a drugs bill of \$160bn. The oncology (medicines and hospital costs) part is \$180bn — mostly for lung, breast, prostate and colorectal cancers, which together contribute 52 per cent of US cancer incidence and 55 per cent of national mortality. He expressed this as an annual cost of 4.2 M years potential life, and summed morbidity and mortality costs at \$33bn. “What then are the cost drivers,” he asked and named inflation (probably the largest), increased cost of older agents, patient expressed preferences (“I saw it on TV”), increased life expectancy, pharmaceutical innovation beyond proven classic drugs, and what he described as “marginal improvements at huge cost”. He constructed his equation axes of “Outcome” (O) vs “Cost” (\$); obviously, worse “O” vs high “\$” was rejected, and also poor “O” at low “\$” (although some other countries might tolerate slightly lower outcomes at dramatically lower cost). Whereas better “O” at lower “\$” is clearly ideal, the “difficult area”, unsurprisingly, is an enhanced “O” at higher “\$”.

He commented on five related economic questions:

- Whose perspective should you consider — local society or global priorities? He chose the perspective of the health provider, not the insurer, and said patient experience was less important in this debate.
- What costs and concerns are relevant? He said indirect “life lost” and direct cost centres are relevant. And whereas absence from work is not likely to be an issue in an older cancer patient, undoubtedly quality of life is.
- How much does current care and its consequences really cost? He compared the costs of “doing nothing” with doing something today.
- How much for new care? This represented the total cost of intervention — drugs, administration, side effects management, and the balancing of chronic and acute cases.
- What is the incremental return on investment? He described the “opportunity cost of those alternative options foregone that are critical for decision making”.

Mr Vermeulen emphasised that “cost effectiveness is a scale, not an absolute criterion”. He took two examples from the new drugs discussed in the symposium: trastuzumab (for treatment of metastatic breast carcinoma) and bevacizumab (for control of vascular endothelial growth factors). Their basic costs were compared with current conventional treatment and the large extra cost of months of life gained evaluated. He reminded the audience that in league tables of hospital expenditure, oncology was orders of magnitude greater than coronary heart disease.

Where there was only marginal advantage in life expectancy and poor disability for the patient during those subsequent months, one could not justify the extra cost. When is “capacity to benefit” exceeded? He contrasted patients, such as an octogenarian and his grandchildren, where he averred there is “a concept of futility”. But in other fields, such as vaccination or transplantation, such considerations were not weighed. “Because we can, does not mean we should!”

Mr Vermeulen challenged FIP’s Hospital Pharmacy Section to come up with a decision framework for optimising choice of opportunity lost.

### Dealing with nausea and vomiting

Laura Boehnke Michard, of the University of Texas, focused on “supportive care for the oncology patient”. She reviewed a group of 5-HT<sub>3</sub> receptor antagonists, the “setrons”, in the specific context of combating nausea and vomiting in cancer chemotherapy: specifically ondansetron, granisetron, dolasetron and the newer palonosetron. She commented that antiemetics available in US are used at dosing levels that maximise cost benefit. The newer palonosetron differs from the others in having a much longer half-life and slightly better, but not clinically significant, binding affinity. Interpatient variability may be due to differences in liver enzyme metabolism and enzyme inducers clinically relevant for most patients. Racial genotypes may differ in alleles with polymorphic forms of enzymes. She cited a German study with a number of racial divergencies from a Caucasian baseline. Dr Michard foresaw future research to correlate chemotherapy-induced nausea and vomiting (CINV) with allele identity in “abnormal” allele patients, which would merit special consideration.

Palonosetron gained FDA approval for acute CINV treatment but the ultimate decision would be based on pharmacoeconomics — the overall cost of treatment regimens. She illustrated mechanisms for different regimens said to improve patient tolerance of emetogenic chemotherapy. There were pharmacoeconomic issues with palonosetron: its greater cost was somewhat offset by less (even single) dose made possible by its longer half-life — but more data are needed. She confirmed that it is useful in situations, such as sarcoma treatment, where very high doses of interferons or other cytotoxic drugs are administered, with massive nausea and vomiting consequences that hitherto have required large amounts of steroids. However, some doubt arise about the consequences of omitting the steroid component: could this affect the overall chemotherapy, perhaps through some unexplored interaction?

She concluded that comparative efficacy of the “setron” drugs for anti-emesis depends on chosen level of dosage, whether any steroid is present, the trial conditions, the particular racial group involved, and what other medicines are used.

# How new technologies are working for the benefit of pharmacists and patients

A practice symposium on 7 September aimed to describe the benefits and challenges resulting from the electronic availability of drug information to both patients and pharmacists, explain how automation can improve medication safety, and discuss whether electronic prescribing and mail service pharmacy eliminate the need for the patient-pharmacist interaction.

Nicola Gray, of the department of pharmacy at the University of Manchester, UK, discussed the potential and shortcomings of integration of web-based information into pharmacy practice. She considered types of web-based information relevant to pharmacy, a comparison of these with traditional sources, challenges for users of web information, and how the internet may be brought into the pharmacy.

Dr Gray described the types of relevant web-based information that she was able to find on the internet. She noted that certain sites are primarily aimed at health professionals while others are aimed at consumers. Supplier information is also available for both patients and pharmacists, from manufacturers, wholesalers and online pharmacies, "and patients are able to access medicines previously unavailable to them".

Dr Gray then moved on to information relevant to pharmacists in the operation of their practice, such as professional guidelines and continuing education material. Online courses and virtual symposia that pharmacists can attend are made available by websites such as that of the American Society of Health-Systems Pharmacists. Group discussions are also described, which enable pharmacists around the world to communicate. The final type of information available is community information, with web sites described that could be useful for looking at the increasing public health roles of pharmacy, and looking at the relevance of local services that we provide. "These sites give ready access to information about local populations, in terms of age, gender, levels of deprivation and so on. Using wider information about the local and national community could help us to target pharmacy services better," she said.

Dr Gray said that some disadvantages of web information are that it is text-driven and that it has little to offer to those with low literacy. There are also issues of knowing whether a web site can be trusted and of dealing with large volumes of information.

Dr Gray said that the internet is not a major resource for drug information with lack of training and location of reliable links cited as reasons. However, a study by the National Consumer Council found that the internet is a significant source of health infor-



**Nicola Gray: drug information is equally available to pharmacists and patients**

mation for patients and that use was dependent on social class, with the internet being a more important source than pharmacists for the AB social grouping (professionals and senior management) but not for other groups. There has been a shift in the balance of information power, where once the pharmacist was a gatekeeper, we now have a situation where "drug information is equally available to pharmacists and patients — each brings their own knowledge with them to the consultation, and their sources of information might differ," she said.

The digital divide is also an issue with a large proportion of the world population unable to access the internet; even within developed countries with high levels of internet access there are significant differences related to ethnicity and location. Data from the World Bank show acute problems for people in developing countries wishing to access the internet with low availability of personal computers and high service provider costs. Where access is available, the prevalence of information in English may be a deterrent for many users. Even if the text can be read, health literacy may be an issue. "Health literacy problems are not confined to those with low general literacy. Health is a demanding field, with its own terminology and traditions that can challenge graduates as well," Dr Gray said.

She mentioned a recent report by the National Consumer Council that nearly half

of all US adults cannot understand basic health information; the figure is one in five for the UK. "Shame and stigma stop them asking for help. Health professionals need to make time to answer questions. Even if patients go on the internet, they may need support from pharmacists to make sense of what they find."

Finally Dr Gray focused on how we might bring the internet into the pharmacy. The main cited factors that may limit internet use include lack of time and competing activities such as printing labels and managing stock, "When are you actually going to get the time to do something on the internet? But have we thought enough about the business case that can be made for greater internet use? How about submitting invoices for payment? A service in some pharmacies in the UK for providing emergency contraception has online submission of data that can be used for audit and facilitates rapid reimbursement," she said.

Another important factor that may limit internet use in the pharmacy is priorities that are linked to payment systems and activities, "In the UK we are currently reimbursed mainly for dispensing prescriptions. We prioritise activities linked to products and dispensing, and these are not internet-based," she said. Pharmacists must also have the training to enable them to use the internet confidently. There is presently little added value in using some online versions of resources over current paper sources, and the online versions can sometimes be more onerous.

Several factors could promote the use of the internet in the pharmacy. "Risk management could be a big factor. Work moves on in areas such as reducing medication problems, increasing quality, audit and so on. Maybe the internet can promote audit and the use of integrated records and information sources. This could lead to better risk management, lower insurance premiums — that could be a driver." Patient expectations will also put pressures on the profession.

Dr Gray said that the potential is there to get rapid access to high quality information on a range of subjects, both drug-related and system- or locality-related. There is potential for more communication — and more meaningful and targeted — communication with patients. However, a concerted effort from national and international policy makers, pharmacy organisations and pharmacists is required in order bring the pharmacy into the internet, "It is all down to re-engineering pharmacy, to change our priorities, moving us away from process and product to patient and information," she concluded.

## Automated systems

Christopher Thomsen, of the Oklahoma College of Pharmacy industry advisory board, presented a US perspective on automation. US pharmacies are now filling more than 3.2 billion prescriptions a year as pharmacists prepare to meet the needs of an ageing population. Within the setting of a reasonably profitable business, the pharmacist must ensure the patient receives the correct medicines with appropriate counselling. However, a 2003 study estimated that 51.5 million errors occur each year during the filling of prescriptions. Dispensing errors were estimated to occur at a rate of four errors per day in a pharmacy filling 250 prescriptions daily. Mr Thomsen posed the question: "Can technology and automation sufficiently and positively address this concern?" He went on to state that pharmacies are continuing to automate their pharmacies with a variety of technologies and recent surveys indicate that there will be more automated counting devices, robotics, central filling facilities and automated workflow systems in the years ahead.

The volume of prescriptions is expected to increase by 46 per cent over the next five years, yet the projected increase in available pharmacists will be only 5.45 per cent over this period. Deploying additional personnel will not address the issues of increased prescription volume and patient safety, so can technology and automation help?

Mr Thomsen described a range of advanced dispensing technologies found in both community and hospital pharmacies that could provide increases in dispensing safety, efficiency, productivity and profitability. He pointed out that in the US most prescriptions (82.3 per cent) are filled from bulk whereas the rest of the world is in the process of converting to original packs. He described a pharmacy management system that could link to automatic counting and robotics technology and receive prescriptions via interactive voice recognition, the internet and e-prescribing systems. Automated counting systems range from simple to complex technologies and can cost up to \$40,000. Robotic dispensing systems are also available, with five different models on the market at a cost of approximately \$200,000. Systems that can handle patient packs are also available but can cost in the region of \$500,000.

Technology can be used to enhance general administrative tasks such as order entry and billing, provide access to patient information and drug data, and enhance information transmission and access. Automated counting and robotics can increase productivity and efficiency, eliminate manual tasks from the process and enhance dispensing accuracy. "Utilisation of simple prescription technologies, like bar codes and on screen drug images, can reduce medication dispensing errors by one full percentage point," Mr Thomsen

said. He compared the accuracy of robotics with that of a human: within two hours of continuous dispensing, accuracy can fall to 85 per cent with human dispensers whereas automated systems claim 99.9 per cent accuracy.

Dispensing errors can be costly. The average award per medication error-related insurance claim was around \$18,000 from 1982 to 1985 but, by 2000, the median compensation award rose to \$668,000. The causes of claims included dispensing the wrong drug (82.6 per cent), wrong strength (25.9 per cent) and wrong directions (7.4 per cent); 82.6 per cent of these claims could be resolved or eliminated by using the appropriate pharmacy automation tools," said Mr Thomsen.

He believed that automated workflow systems are required. "Product quality and safety can only be achieved when the entire process is standardised," he said. Workflow includes order entry, adjudication, labelling, filling, verification, quality assurance, storing and billing and delivery validation. Following automation, said Mr Thomsen, there is an increase in prescription volume, a decrease in time spent per prescription and considerable cost savings. Automation does not replace people but increases output. Drug distribution practice can be shifted to drug therapy and patient management using automation, leading to opportunities to redeploy pharmacists for clinical pharmacy practice, he concluded.

## e-Prescribing in practice — benefits demonstrated in a scheme in Sweden

Gunnell Bridell, of Apoteket AB, talked about the implementation of e-prescribing in Sweden. He said that four years ago the electronic transfer of prescriptions directly from the prescribers' computer to the pharmacy was introduced nationally. Approximately 65 million prescriptions a year are dispensed in Sweden. All pharmacies are computerised and have the same systems. In July 2004, 27 per cent of prescriptions in Sweden were sent as e-prescriptions and the goal is to increase this to 80 per cent by 2007.

E-prescriptions are clear and unambiguous and save time. If all prescriptions were sent electronically in Sweden, it is estimated that this would free about 0.5 million hours, time which could be used to improve patient contact. e-Prescriptions are complete so extra time can be devoted to pharmaceutical checks. Prescription fraud is also less likely with e-prescribing, he said.

e-Prescribing requires a new way of working with prescriptions because information such as dosage and patient sex and age are already entered into the computer system, thus there is a risk that this information may not be processed in the same manner as when the data are manually entered. Dispensing therefore becomes an important stage at which to check that the prescription is correct and appropriate.

Patients' response to e-prescribing has been positive, more noticeably so among younger people. Patients often experience shorter waiting times in the pharmacy, because prescription are often prepared before their arrival. Doctors have also in general been positive about e-prescribing, with interviewed doctors claiming a saving of about 15 to 25 minutes a day in reduced administration. "Work with the e-prescription has even produced some unexpected effects. One such effect — through our co-operative efforts with prescribers — has been to increase awareness of the pharmacists' expertise. We have created the prerequisites for an increased common view and better co-operation between the professions within health and medical care. The co-operation has led to a clearer view that the pharmacies and pharmacists constitute an important part of the care chain," said Mr Bridell.

There are certain risks associated with e-prescribing. One of these relates to failure of the technology, which can result in great inconvenience to the patient.

Software problems can result in serious problems such as erroneous prescriptions, a problem exacerbated by the fact that the prescriber does not see the finished prescription on paper.

A long-term goal is to create a complete prescription list for each patient. The prescription list will include all medicines prescribed for a certain patient, independent of whoever the prescriber may be. The pharmacies will provide information to the list regarding the medicines dispensed at the pharmacy and this list will be available to prescribers, other authorised care givers, pharmacists and, of course, patients themselves. The patient would be the owner of the information and the one to decide who will have access to the complete list.

"One of the greatest advantages of the e-prescription from a pharmacist's perspective is that it represents a first step towards receiving access to the patient's complete collection of prescriptions," said Mr Bridell. "Access to the patient's prescription list means that the pharmacist's advice to the patient can be improved. The pharmacists can more easily discover medicine-related problems in conversation with the patient. It is easier for us to carry on a conversation about compliance and to make the patient understand what happens if you don't follow the given prescriptions. In the long run this could lead to greater patient compliance to prescriptions." He added that the pharmacist has access to the same information as the prescriber, which is a strength in the patient dialogue and a security for the patient. "The pharmacist's role as pharmaceutical adviser becomes more clear to the patient when we can assume a unified responsibility for information about all the patient's medicines," he said.

At the beginning of the project it was not obvious to health care representatives why the pharmacist required access to a patient's prescription list. However, since its implementation, e-prescribing has made the advantages clear, and the pharmacist's role as a pharmaceutical expert has become evident. Patients have also become empowered to a certain extent, and more so once online access to their own records becomes available. Mr Bridell concluded by stating that technological developments are beneficial to pharmacists and the service they provide, and that technology is not a threat but presents new opportunities.

# Are the new EU clinical trials directive and GMP guideline fit for purpose?

Does the newly established EU system for clinical trials address the need for European harmonisation? That question was posed by Birka Lehmann, of the Enterprise Directorate-General of the European Commission, when she addressed a two-day symposium on international harmonisation of clinical trials on 6 and 7 September.

Dr Lehmann identified four key broad objectives of the new Directive 2001/20: protection of subjects participating in clinical trials, standardised information on the trial, single decisions by competent national authorities and ethics committees, and application of good manufacturing practice (GMP) and good clinical practice (GCP).

She said that progress towards achieving these objectives must address: the responsibilities of ethics committees, the national authority and the sponsor, investigator and legal representative; a framework for exchange of information; and a legally definitive interaction between study sponsor and ethics committee before trials can begin.

Detailed guidance set out in various annexes to the new directive includes format and documentation of applications to conduct trials, a Europe-wide database for trials and the collection, verification and presentation of reports of suspected unexpected serious adverse reactions.

The draft GCP directive largely follows International Conferences on Harmonisation (ICH) recommendations on manufacturing and import authorisation, said Dr Lehmann. It presents expectations for knowledge and training of inspectors and gives procedures for co-ordination of GCP inspection by member states.

The updated directive on GMP (2003/94) has replaced the long relied upon directive 91/356; in particular, its annex 13 deals with manufacture of investigational medicinal products (IMPs). It was intended that member states should implement the annexes within six months but so far none have these in place. She indicated that the Commission now "hoped for implementation by the end of 2004". There are still some questions to be answered, she said, instancing definition and responsibilities of the "sponsor", the definitions of IMPs and of "non-interventional" and "non-commercial" trials, and requirements of GMP in phase I trials.

People had asked her why the clinical trials directive was necessary. She listed some factors that had changed: increased but unified data and application requirements, selective pharmacovigilance reporting and, "last but not least", obligatory application of GMP to IMPs. She foresaw further measures for

improvement though: for example, the Commission needs to develop guidelines for implementation of the clinical trials and GCP directives, GCP inspectors need to offer advice and heads of agencies need to facilitate harmonisation of clinical trials.

Her "dream" is for a uniform mutual recognition system for clinical trials right across Europe, she concluded.

## Investigational medicinal products

Linda Broad, of Pfizer UK, in considering the impact of the clinical trials directive on supply of IMPs in a global manufacturing organisation, asked whether it is a useful path for companies. She believed that directive 2001/20 had great potential for reducing the diversity of current national application procedures, ethics arrangements, timelines and data expectation. It is "a step in the right direction", she said, but still a "real challenge" in that national differences in legislation might still remain.

She wondered whether there would be sufficient Qualified Person (QP) capacity at all relevant EU sites. Hitherto, it has merely been desirable that quality requirements from third country manufacture have been clearly defined in purchasing agreements, but now this is a formal requirement. She agreed it is "reasonable" that the EU-based QP should certify GMP for trial products from third country manufacturers, but she considered it "bureaucratic" to require QP declarations of [European] GMP equivalence within the clinical trials application. She recalled that comparator sources from within and outside the EU had for years been used safely but similar divergences were noted in some states; this, too, could impact on the flexibility and sourcing of trials.

Dr Broad had similar concerns with divergence over articles 14 (labelling) and 15 (inspections verifying compliance with GCP and GMP). All of these uncertainties about interpretations by individual member states might be large enough to persuade multinationals to take their clinical studies right out of Europe. She listed four factors for a "strategic response": (i) ensure IMP and placebo sources are already covered by an EU manufacturing authorisation or QP certification; (ii) anticipate regulatory expectations for comparators; (iii) be aware of EU guidance on relabelling and site-to-site transfers; and (iv) have a quality assurance strategy for GMP of external sources, with common standards and audit.

"Are we there yet," she asked. Not all member states had implemented the trials directive by 1 May 2004, extra country-specific requirements might continue through national guidance and there is continuing in-



**Linda Broad: need for uniform mutual recognition system across Europe**

dustry concern with the latest draft of the GCP directive. She agreed that there has been some progress towards harmonisation but there were operational challenges for multinational companies, and a need for active influence to achieve maximum flexibility to maintain Europe an attractive venue for conducting trials.

## Industry views of US and EU systems

Jeffery Sherman, of Neopharm, US, presented a US industry perspective of the current IND (investigational new drug) process and perceived hurdles to progress. He described "fast track development" (eg, for HIV treatment), "orphan drug status" (for rare diseases) and accelerated clinical trials approval (Phase II studies with surrogate data and a commitment to proceed to phases III and IV).

Dr Sherman described the effect of Food and Drug Administration reform legislation on the time frames available and the structure of the IND application. He illustrated the value of industry pre-discussion with the FDA to determine what is likely to be acceptable in the originating IND application and in revised proposals (eg, new toxicology or chemistry data) and annual reports. The FDA expects to see critical information in safety reports from sponsors and participating investigators, such as any significant subsequent laboratory animal results and adverse human experiences.

He confirmed that there is a single system throughout the whole of the US and FDA guidance is freely available on a website, with summary basis of approval for analogous marketed drugs and briefing packages from advisory committees released through the Freedom of Information Act. He saw the present time as pivotal, in considering divergences external to the US system and a target

opportunity for a single global process, perhaps through ICH?

Yves Juillet, of Les Entreprises du Médicament, France, wondered if the European approach is flexible enough to accommodate industry's needs. European promulgation of the clinical trials and GCP directives has been a long and complex process since September 1997, and former trials control varied greatly among member States. He was not convinced that conforming with ICH justified the legal enforcement of GCP and GMP to IMPs, but he welcomed reinforcement of the Helsinki declaration of ethical principles in research on humans and the establishment of an EU database for clinical trials. What he "found missing in the stated objectives" of directive 2001/20 is any enhancement and facilitation of trials performance. His expectations included the same dossier, standards, format and language across the EU; a single application to a national authority and ethics committee; short, predictable and competitive timelines; and a guaranteed high level of protection and safeguards for trial subjects.

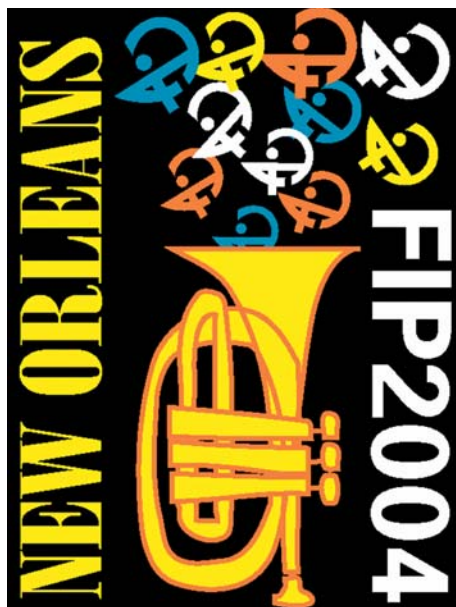
Dr Juillet specified three major challenges for industry: to fulfil all requirements; to conduct the "same" clinical trial in various member states despite different local opinions; and to optimise resources to prepare, organise and perform trials in the EU. While he accepted that GCP was "necessary" and that industry will certainly adapt and comply, he complained that:

- Regulations and guidelines are complex, leading to delay, and difficult implementation risks major disharmony
- There are major potential protocol problems for multinational industry
- There has been some confusion in respective responsibilities of ethics committees and certain national authorities
- It is too early to judge if there will be sufficient flexibility or linguistic difficulties
- Scarce resources will have to be optimised, with an uncertain effect on other potential sponsors and investigators

### Composition, manufacture and control

Mila Bozic, quality and business excellence adviser, Lek Pharma, Slovenia, discussed pharmaceutical quality assessment in drug development. The key parameters for her were understanding the quality context of the producer (where the issues are essentially the same for clinical trials and marketing) and competence of the assessors in relation to the quality system in place. Industry R&D is limited by the extent of validation performed, sub-optimal processes, quality management regulation not always in place, and the fact that QP roles are not standardised.

For standardisation of people, current national schemes include a clinical investigator's certificate (from the FDA), a QP standard examination (in the UK), medical laboratory accreditation (France), regular quality measurement surveillance (EU laboratories) and



the European regulatory affairs certification programme. For accreditation of systems, she compared national standardised underpinning of GMP with the ISO "systems approach" concept and reviewed the challenge for pharmaceutical industry development of building quality system compliance into an existing GMP mentality. She concluded that the global drug market must redefine its need for harmonised education and certification of QPs and regulatory professionals of the right personality — "self-confident, independent, ethical, diplomatic and brave" — with a scientific background and experience.

### The views of US and EU regulators

US requirements for CMC (chemistry manufacturing control) from a regulator's point of view were examined by David Lin, of the FDA Centre for Drug Evaluation and Research. He said the amount of information needed varies with the phase of the clinical trial, proposed trial duration and dosage form.

In phase I emphasis is generally placed upon sufficient evidence of identification, structure and control of the new drug substance, any difference between chemistry and manufacture of the trial material and the product used in animal and toxicology studies, and preliminary specifications with plausible limits. This should be backed with adequate information to sustain product stability for the duration of trial, although a detailed protocol is not needed at this stage. For the clinical trial dosage form, the FDA expects outline preparation, quality of ingredients, and proposed labelling of this product and placebo and comparator.

Dr Lin commended the practice of meeting usually the same FDA expert before proceeding to phase II trials, in order to agree what additional data are needed at this stage. By phase III, the FDA expects more sophisticated elucidation, control of critical steps and intermediates, new impurities identified and qualified, and complete analytical procedures, with suitable specification limits based on ex-

perience, and formalised stability protocol and stress studies.

Susanne Keitel, of the Federal Institute for Medicines and Medicinal Products, Germany, presented the corresponding EU regulator's view. She said that several member states, including Germany, had had directive 2001/20 implementation problems. She contrasted the limited previous regulatory provision for trial materials in Europe, with the new directive. There had been long-standing arrangements in some countries (for example, the UK), compared with basic, mainly clinical, requirements in, say, Germany where, she commented, 1,300 companies had rushed to register clinical trials before the new rules were implemented.

Dr Keitel said she was unsure whether legislative "backbone" and guidance in the trials directive provides sufficient detail to guarantee a uniform single market for the conduct of clinical trials.

On the status of future harmonisation, she referred to the tendency of member states to interpret requirements differently and the emphatic need for clear-cut harmonisation within the EU. Perhaps, she suggested, clinical trials is a potential topic for ICH discussion to achieve global harmonisation.

### What industry thinks

Rodney Horder, Abbott Global QA, US, considered whether EU and US requirements were compatible or "a hurdle impeding globally active companies". What then is the rationale for the basic CMC/GMP requirements? Essentially, it is to protect the patient, the product quality and the trial integrity. But he emphasised that "quality does not equate with bureaucracy". He then reviewed the growth of global practice, with multi-country trials all potentially remote from the site of CMC development and a single site for testing, multilingual labelling and electronic recognition.

His industry perspective identified some challenges, eg, varying guidelines and interpretation by EU member states and inspectors, some opportunities for developing harmonised applications based on ICH and the Common Technical Document, and a risk-based approach to GMP.

Dr Horder looked to the "good sense" of an EMEA (European Medicines Evaluation Agency) concept paper that recognised the need for genuinely harmonised documentation, sought to differentiate between clinical trials and marketing dossiers, and provided recommendations for IMPs. He suggested that an FDA initiative and the EMEA concept could collectively involve Japan through the ICH process, to achieve the global harmonisation that Dr Keitel had dreamt of. His personal "wish list" is for industry to harmonise data requirements, clarify labelling and inspection, develop risk-based approaches, develop mutual recognition of compendial excipients, reconcile expiry dating with phase of trial and staged distribution, and adopt a common technical format for IMPs.

# How to be a seven-star leader

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. On 7 September, the FIP Young Pharmacists' Group held the third in a series of special forums addressing these skills, looking this time at leadership.

Jerry Siegel, senior director for pharmaceutical services at the Ohio State University Medical Centre and College of Pharmacy, tried to take young pharmacists from crisis management to innovation in a presentation on creative leadership. He suggested that training on crisis management should be included in the undergraduate curriculum to support pharmacists in responding to critical situations in practice which may be time sensitive and resource limited. Mr Siegel believed that young pharmacists need to develop the skills necessary to plan for and direct such scenarios. The course of action and the attitude depicted lead to the innovation inherent in leadership.

"Young pharmacists need to start overcoming their fears now," commented Mr Siegel. In a crisis situation, fear itself may be the root of the problem. If young pharmacists do not take time to test their fears, they may not be able to cope later when problems do arise. After having tested their fears, young pharmacists who are faced with the same problem in the future will know with confidence that they are able to cope.

Mr Siegel used the analogy of a game of chess when describing how young pharmacists can plan to resolve a crisis. In chess, as in life, someone always has to make the first move. It is important to decide whether you want to play offensive, defensive or both. When making a move, it is important to think strategically. Some of the best chess players in the world are able to think up to 20 moves ahead. Often a decision will impact on other things.

Before agreeing to a change, you must first take time to consider the implications of each available option. In chess, there are also times when you may want to sacrifice a pawn to progress your game. In life, sacrifices can be measured. For example, if making a decision, consider the potential impact on your reputation and integrity. Sometimes the only way to progress an issue and to reach your goal is to have the courage to take a risk and make a personal sacrifice.

In responding to a crisis, young pharmacists need to be aware of potential traps such as misinformation, misconceptions and over-confidence. Mr Siegel encouraged young pharmacists also to be aware of the potential for "group failure". He referred to the *Columbia* space shuttle disaster, where group failure was quoted as one of the key causal factors. Ten astrophysicists had looked at the technical information about the suspected problem. They had received the same training and undertook the same analysis, convincing each other that there was not a problem. Mr Siegel encouraged young pharmacists always to seek an external viewpoint on a problem. In the clinical setting, other health professionals may be able to offer a different perspective.

## Ten Commandments of leadership

In a presentation on the qualities of a leader, Alison Roberts, a young pharmacist from Sydney, Australia, referred to 10 commandments of leadership.

- 1. Search out challenging opportunities** Search out challenging opportunities that allow you to change, grow, innovate and improve. Do not be afraid to question the status quo. One way to get involved as a young pharmacist could be to ask for observer status at the meetings of a local or national professional organisation. Organisations need people with diverse views and experiences and young pharmacists are often able to give a unique perspective on issues.
- 2. Be prepared to experiment and take risks** Young pharmacists should not be afraid of being vulnerable when taking on new roles; this is a good way to learn from mistakes and successes. A good place to start is speaking up on issues that are important to you.
- 3. Identify your vision** It is essential when taking on a leadership role to be clear about what you would like to change. What future do you see for the profession? Once you are in a leadership position, you will be asked for your opinion so it is essential that you have a clear view on relevant issues.
- 4. Enlist others in your common vision** A good place to start is identifying your constituents — those people who will have a stake in what happens today and tomorrow. When communicating with others appeal to their values, interests, hopes and dreams.
- 5. Foster collaboration** Once in a leadership role foster collaboration. Involve everyone, at all levels, when planning for change. It is essential that trust is built. If

only key decision makers are involved in agreeing changes there is a risk that your constituents and supporters will not follow your lead.

- 6. Strengthen people in your team** Share information and power and allow others to buy into your vision. Increase the visibility of others and delegate tasks to team members.
- 7. Set an example** Stay true to your stated values. All too often people get sucked into the power games and politics of an organisation and forget why they got involved in the first place. The desire to be a leader is not enough; you must also know what you want to lead on. Leaders must take time to audit their actions and reconfirm their original vision.
- 8. Promote consistent progress** Plan small wins to promote consistent progress and build commitment when working towards a large or complex goal.
- 9. Recognise individual contributions** Every successful project is a result of multiple individual contributions.
- 10. Celebrate accomplishments** Schedule regular activities to acknowledge achievements and continue enjoying what you do.

In conclusion, Ms Roberts said: "Young pharmacists are not only the leaders of tomorrow, but can also be the leaders of today and make a positive contribution now." She encouraged the young pharmacists present to take on leadership positions within the profession.

## Personal experience of leadership

Jack Chen, of the Taiwan Young Pharmacists' Group, was one of a number of young pharmacists from around the world who described their own personal experiences of local or national leadership. He described how getting involved in a young pharmacists group can give young pharmacists the opportunity to develop their leadership skills as well as share and learn from their peers, discover their interests within different professional fields and start making a difference early in their careers.

### Previous forums

The first FIP Young Pharmacists Group forum was held in Nice in 2002 (see *PJ*, 21 September 2002, p402) and the second in Sydney in 2003 (*PJ*, 4 October, 2003, p468).

### FIP Young Pharmacists Group

For more information about how to get involved in the FIP Young Pharmacists Group, visit the FIP website at [www.fip.org](http://www.fip.org), or by e-mail [ypg@fip.org](mailto:ypg@fip.org).

## Correction

Nicola Gray works at the School of Pharmacy at the University of Nottingham, not the department of pharmacy at the University of Manchester (p491).