WHO Drug Information

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Good Manufacturing Practices

Implementation of good manufacturing practices

Medicines are important tools in improving and maintaining health. Whilst standards for ensuring the quality of medicines at international level are becoming increasingly rigorous, quality assurance within many countries still remains a major public health concern. In recent years, there have been numerous reports highlighting problems surrounding poor quality drugs including contamination by toxic substances, increase in counterfeiting, and presence of substandard medicines on the market. Very often, these cases can be avoided by strict application of good manufacturing practices (GMP) which has an essential role to play in the quality assurance of medicines.

The need for inspection is intimately linked to the success of quality assurance systems. Without a competent inspectorate operating to high professional standards, neither GMP compliance nor licensing provisions can effectively be enforced. In addition, inspection of manufacturing facilities is pivotal to operation of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (1).

GMP Implementation Project

In 1998, the WHO Department of Essential Drugs and Medicines Policy received funding from the Government of Japan to operate a three-year project on Promotion of Implementation of GMP*. The aims of the project were:

- to improve the quality of locally manufactured pharmaceutical products by identifying obstacles to implementing GMP; and
- to develop tools and methods to assist countries improve implementation of GMP.

A WHO Working Group was established to plan, coordinate and evaluate project activities and oversee the development of training modules to be produced as a CD-ROM and aimed to build training courses on GMP and inspection (2). Material was focussed to the needs of government officials carrying out inspection of manufacturing facilities for either finished products, medicines or pharmaceutical starting materials.

Criteria for country participation in the project were to:

- sustain existing collaboration with WHO;
- be a developing country;
- have a functioning drug regulatory authority;
- be able to serve as regional centres for GMP training in the future; and
- have significant levels of local pharmaceutical production.

GMP training modules
GMP training material comprised 20 modules (see table on page 82), with slide presentations, tutorial notes, group session exercises, handouts, comprehension tests and answer sheets. Separate modules covered: Basic Principles of GMP, GMP Inspection Processes, and trainers' notes for the setting up and running of the course. These were completed in November 1999 for testing at the first WHO Pilot Training Workshop held in Beijing in December 1999.

WHO pilot workshops
The first workshop was organized in collaboration with the State Drug Administration (SDA), China. Participants comprised government inspectors and administrative officers with a good knowledge of GMP inspection from eight countries in the WHO Western Pacific and South-east Asia Regions.

The resulting material was tested at a second WHO Pilot Training Workshop held in Pretoria, South Africa, in July 2000, along with a first viewing of the GMP Implementation video.

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Two one-day courses were further held at the end of 2000 using finalized versions of two modules, and the GMP implementation video. Participants came from a broader range of backgrounds, such as government institutions, national and private pharmaceutical facilities and universities.

GMP implementation video
The 18-minute training video was developed during the first half of 2000 as part of the GMP modular package to serve as a stand-alone training tool. Film sequences and narrative illustrated examples show GMP-compliant and non-compliant situations in pharmaceutical manufacturing facilities and include scenes of manufacturing processes, premises and quality control procedures.

For the GMP-compliant footage, a facility was selected where a full range of pharmaceuticals was being produced. Illustrations of non-GMP compliance were taken from black and white film footage originally prepared by the US Food and Drug Administration during the 1970s. The persons and company featured in the scenes were fictional. However, the situations shown were based on true events and demonstrated the consequences of human error for product quality and end-user well being. The "compliant" example contained some "non-compliant" features for use as a case study exercise during training. The video was completed in June 2000.

GMP CD-ROM
Work on the production of a CD-ROM began in March 2000. The CD contains modular training texts, WHO published documents on good manufacturing practices and inspection (3), the GMP implementation video, and background project information. Copies have been distribued to drug regulatory authorities, WHO country and regional offices and participants of GMP workshops.

Project on Strengthening of Pharmaceutical Manufacturing Inspection

Upon conclusion of the GMP Implementation Project in December 2000, the Strengthening of Pharmaceutical Manufacturing Inspection (SPMI) Project was initiated to consolidate achievements of the former project and focus on strengthening pharmaceutical manufacturing inspectorates by promoting the global use of the completed training materials. The SPMI Project ended in March 2003.

WHO Basic Training Modules on GMP: a resource and study pack for trainers*

Basic principles of GMP

1	Introduction	8	Personnel
2	Quality management	9	Premises
3	Sanitation and hygiene	10	Equipment
4	Validation	11	Materials
5	Complaints and recalls	12	Documentation
6	Contract production and analysis	13	Sterile production
7	Self-inspection	14	Active pharmaceutical ingredients

GMP inspection process

15	Introduction	18	Types of GMP inspection
16	The role of the inspector	19	The inspection
17	Preparation for the inspection	20	Trainer's notes

WHO Supplementary Training Modules on GMP*

1 Validation
2 Water for pharmaceutical use
3 Air handling systems

**CD-ROM available from: Essential Drugs and Medicines Policy, World Health Organization, 1211 Geneva 27, Switzerland. e-mail GMP@who.int http://www.who.int/medicines*

Training workshops involving 134 participants from 31 countries were organized utilizing the GMP Implementation Project modules. Where possible, a visit to a pharmaceutical factory site or laboratory was included in the programme to enable participants to be exposed to practical aspects of GMP training.

Results of SPMI

Initial distribution of the CD-ROM in April 2001 was followed by a questionnaire to national drug regulatory authorities and participants of the workshops in June 2001. The questionnaire aimed to elicit feedback on the five components of the training package (slides, tutorial notes, group sessions, handouts and the GMP implementation video) in terms of technical content and user's opinion on the usefulness of the materials for developing skills in GMP inspection and compliance. A total of 702 questionnaires were distributed between June and November 2001.

Course evaluation and feedback from participants has indicated a strong desire for further training for inspectors and for longer courses to be set up encompassing all the modules. At the workshops in Chong Qing, China, and New Delhi, India, there was a particular focus on promoting GMP in the manufacture of antituberculosis drugs, and participants expressed a desire for further training to be specifically aimed at inspectors and manufacturers of these products.

It is hoped that wide distribution of the CD-ROM , together with availability of the materials through the WHO Internet (http://www.who.int/medicines), will greatly enhance accessibility to training possibilities supporting GMP. For some countries, however, the viability of future training will depend on the availability of computer equipment, software and translation of materials. The modules have also been translated into Spanish and produced as a CD-ROM by the Pan American Sanitary Bureau (PAHO). Feedback to date has indicated that further translations into other languages are planned, including Chinese, German, Japanese, Portuguese, Russian and Turkish.

An article describing the two projects in more detail has recently appeared in the journal *Quality Assurance* (4).

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3. World Health Organization. *Quality Assurance of Pharmaceuticals*. A compendium of guidelines and related materials. Volume II. Good manufacturing practices and inspection (1999).

4. Morimoto, K., Curry, J., Kopp, S. et al. Promoting GMP implementation: developing training materials for the international audience. *Quality Assurance*, **10**: 11–27 (2003).

Personal Perspectives

Pharmacogenetics and existing therapies

There is increasing evidence that pharmacogenetics will soon be playing a vital role in public health. Understanding genetic factors that determine the response to drugs, together with increased knowledge of drug action mechanisms and identification of drug targets is now leading to the design of drugs that are specifically targeted towards particular populations and that avoid genetic variability in therapeutic response. The ability to identify sensitive individuals before drug treatment using pharmacogenetic methods would be an improvement on the current time-consuming practice of attempting to match the most appropriate drug to each patient. It might also substantially reduce the need for hospitalization and avoid the costs associated with adverse drug reactions. Indeed, one day it may well be considered unethical not to carry out routine genetic testing to avoid exposing particular individuals to drugs that could be harmful and/or ineffective for them.

The development of pharmacogenetics provides at least one mechanism for taking prescription away from its current empiricism and progressing towards more patient-tailored, individualized drug treatment. The extent of genetic polymorphism in the human population indicates that pharmacogenetic variability is an issue for many existing therapies and may also be an issue for most new drugs. Thus, pharmacogenetics could pre-empt potential treatment failures, leading to better health outcomes for patients and reducing the waste associated with ineffective treatments. None the less, although pharmacogenetics promise to provide a mechanism whereby DNA testing can be applied to populations in general, we are still some way from having a pharmacogenetic DNA chip that general practitioners can use to identify those drugs which will individually benefit each patient.

Readers comments are invited on this article, which attempts to define the difficulties and opportunities facing manufacturers of both innovative and generic products, and the role of acadaemia and national drug regulatory authorities in the application of this challenging new area. Please address any comments to the author: Dr Lembit Rägo, Quality and Safety: Medicines, Essential Drugs and Medicines Policy, World health Organization, Geneva, Switzerland or e-mail: ragol@who.int

Despite the notable successes achieved in drug development during the past five decades, no therapy can yet be considered either fully effective or entirely safe. This contrasts starkly to the prevailing perception that taking drugs is invariably beneficial. In fact, it is probably true to say that a significant proportion of patients treated with existing therapies* obtain only minimal benefit. Depending on the therapy and endpoint used, efficacy can range from a rare 90% down to only a couple of percentage points. Historically, drugs have been produced in a "one-size-fits-all" model in the hope that all patients respond in the same way. More recently, however, scrutiny of the indications on new drug applications approved by regulatory authorities clearly shows a trend towards indicating those patients most likely to benefit.

Because existing therapies have been officially approved for marketing, they are generally assumed to be effective and safe. This has led to

** Within the frame of this article, the term "existing therapies" refers to those medicines currently available and approved by competent authorities (i.e. drug regulatory authorities) for the prevention or treatment of disease in humans, whether under or off patent. The term thus covers both multisource (generic) pharmaceutical products and innovative products which may or may not be covered by patent protection. In certain cases, it is also applicable to products that may have been withdrawn from one or all markets after initial approval.*

the assumption that the net outcome of treatment for populations in general is positive. However, this does not mean that all individuals benefit from treatment. Some individuals may not benefit at all from existing therapies and others may well suffer serious adverse reactions.

It was not until the 1950s that modern scientists discovered the presence of inherited enzymatic deficiencies that can lead to unexpected and even harmful effects from therapies. An important landmark was the publication of Motulsky's paper entitled "Drug reactions, enzymes, and biochemical genetics" (1) written upon invitation from the American Medical Association.

The paper described haemolysis caused by the antimalarial drug primaquine in about 10% of black American servicemen during World War II. This adverse reaction was very rare among white servicemen. Haemolysis and resulting anaemia were later shown to be due to an inborn fault of red blood cells or, more precisely, variation of the enzyme glucose-6-phosphate dehydrogenase (G6PD) gene leading to a deficiency of this enzyme (2) commonly found among people of African descent. Until now, however, this type of knowledge has resulted in only limited practical outcomes.

Individual variation in response to drugs is a substantial clinical problem. Variation in drug response ranges from response failure, adverse drug reactions, or drug-drug interactions when several drugs are taken concomitantly. The clinical consequences range from treatment failure and patient discomfort through to serious clinical illness and the occasional fatality. A recent US study estimated that 106 000 patients die and 2.2 million are injured each year by adverse reactions to prescribed drugs (3).

The role of pharmacogenetics*

Pharmacogenetics could lead to the improvement of existing therapies and seriously reduce the guesswork in prescribing by ensuring that the right drug is given to the right person from the very beginning. This will considerably reduce the time and resources taken in finding the correct treatment regimen. By avoiding prescribing to 'non-responders' and by reducing the occurrence of adverse drug reactions, better targeted or even individualized pharmacotherapy can be achieved.

Existing therapies: room for improvement

Typically, the physician prescribes the recommended medicines in the recommended dosage to his or her patient. If the medicine does not work, the doctor will usually try the best alternative. Time and money is lost through unnecessary visits to the doctor and the cost of ineffective medicine(s) either used or remaining unused, and which usually cannot be resold. It is now clear that much individuality in response to drugs is inherited and that not all patients can benefit equally, as demonstrated by the examples below.

Acetylsalicylic acid

The usefulness of low-dose acetylsalicylic acid (75–325 mg) in secondary prevention of thrombotic cardiovascular or cerebrovascular disease is well known. In many countries it is also approved for primary prevention of vascular events related to coronary heart disease. However, it is premature to suggest that all patients with the appropriate indications will benefit equally from the use of low-dose aspirin where there may be increased risk of haemorrhage, including fatal haemorrhagic stroke. Neither do we have the scientific means to determine whether acetylsalicylic acid is being given to patients who can really benefit or who may be at risk for serious side effects.

Angiotensin-converting-enzyme inhibitors

It is estimated that currently 35–40 million people are treated worldwide (4) with angiotensin-converting-enzyme (ACE) inhibitors for cardiovascular conditions. Pharmacogenetics may help to reduce the risks associated with increasing use. Some ACE inhibitors are already out of patent in a number of countries and others follow. There is no doubt that this group of drugs has the potential to

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* The European Union (EMEA/CMPM) definition for pharmacogenetics and pharmacogenomics [see: *WHO Drug Information*, **17**(1):17 (2003)] is:

"*Pharmacogenetics* is the study of interindividual variations in DNA sequence related to drug response.

Pharmacogenomics is the study of the variability of the expression of individual genes relevant to disease susceptibility as well as drug response at cellular, tissue, individual or population level. The term is broadly applicable to drug design, discovery and clinical development."

save millions of lives worldwide if access to them can be guaranteed. However, even in developed countries only 21–36% of patients with chronic heart failure are treated with ACE inhibitors (4–6), and over 40% of them discontinue the drug within 6 months of starting therapy (5). We need to know more precisely which individuals can benefit from ACE inhibitors with minimal or no risk of serious side effects.

Angio-oedema is a well-known side-effect of ACE inhibitors, with a reported incidence of 0.1–0.2%. This is probably an underestimate (6). Black people using ACE inhibitors are at a threefold risk of side effects and also for occurrence of fatal cases (7, 8). Learning more of the true incidence of angio-oedema may require monitoring of all patients, especially black patients, for this potentially serious side effect. If pharmacogenetics can offer tests with high predictability, patients at increased risk for angio-oedema could be switched to an alternative class of medicines and thus avoid extra costs of monitoring and risk of death. The benefits may well outweigh the costs of tests.

In the case of adverse drug reactions, we have at least some estimates of the magnitude of the problem, but in the case of treatment failure we have no studies to demonstrate how effective or ineffective many of the well established existing therapies really are. For example, how many years and how many patients does one need to treat with statins to avoid one death from cardiovascular disease? If it could be predicted with high probability in which individuals statins do or do not work, we could save enormous amounts of time and effort and avoid giving unjustified hope to patients — while focusing resources on finding alternative solutions.

Polymorphism and drug response

With recent advances in molecular genetics and genome sequencing, pharmacogenetic research has gained attention from scientific communities and the public. The introduction of new technologies has permitted rapid screening for specific polymorphisms (differences in DNA sequence among individuals), as well as recently gained knowledge of the genetic sequences (sequence of nucleotides in a particular section of DNA) of target genes such as those coding for enzymes, ion channels, and other types of receptors involved in drug response. As a result of the completion of the Human Genome Project and other public initiatives such as The SNP Consortium (SNP=single nucleotide polymorphisms, see http://snp.cshl.org) comprehensive maps of the human genome have been established including information identifying genetic variations associated with disease susceptibility as well as pharmacokinetics.

What do pharmacogenetics have to offer?

Research in pharmacogenetics is developing in two main directions:

- identifying specific genes and gene products associated with various diseases which may act as targets for new drugs and/or diagnostic tools; and

- identifying genes and allelic variants of genes that affect the response to existing therapies.

Pharmacogenetics may offer feasible solutions for better targeting of patients and provide a cost-effective method with a consequential benefit for public health. Increasing numbers of research programmes have sprung from the human genome project, including genome-wide screening to identify differences between individuals of a single base pair in DNA or single nucleotide polymorphisms. Single nucleotide polymorphisms can be used to map and identify specific genes associated with various diseases such as cancer, diabetes, and arthritis.

Many of the proteins encoded by these genes are expected to be new targets for drug therapy but may also improve our diagnostic capacities by helping to stratify diagnostic groups into more precise subgroups with different responses to existing therapies. The fact that these genes were identified by polymorphism analysis indicates that drugs directed at such targets may have different effects in different patients. This leads to the concept of drug stratification or individualized drug treatment, in which the choice of drug is influenced by a patient's genetic status.

Genomic analysis has generated an enormous amount of information on human polymorphisms. There are over 4 million single nucleotide polymorphisms in public databases and more will probably be identified in the next few years. However, a greater challenge will be in determining the function of each polymorphic gene or, to be more exact, of the gene product and its variant forms. In particular, it will be necessary to deter-

mine whether a gene product is of pharmacological or toxicological importance and whether individual allelic variants are of therapeutic importance. Such expression profiling enables testing of genotype-phenotype correlates and is extremely important for further advancement in pharmacogenomics.

The determination of the genetic variations that affect the efficacy of current drugs is much closer to clinical application. Polymorphism in any one of many genes including those encoding drug receptors, drug transporters, and cell signalling pathways can be important factors determining clinical response. The most immediate utility is likely to be polymorphisms of the genes involved in drug metabolism and disposition.

Functional polymorphisms in any one of the genes involved in drug metabolism can lead to either a lack of therapeutic effect or unexpected clinical responses including:

- lack of pro-drug activation
- metabolism by alternative deleterious pathways
- extended pharmacological effect
- adverse drug reactions
- drug toxicity
- modified drug-drug interactions.

Polymorphisms have now been identified in more than 20 human drug metabolising enzymes — several with substantial ethnic differences in their frequencies — which promote drug effects through affecting their metabolism.

In general, pharmacogenetics can be related to:

pharmacokinetics, which includes absorption, metabolism, generation of pharmacologically active metabolites, activation of pro-drugs, distribution and elimination i.e. the fate of the drug as a chemical compound in the organism; and

pharmacodynamics, affecting receptors and receptor-coupled mechanisms, modulation of drug effects via targeting physiologically-relevant systems without affecting the primary cause of the disease or symptom, i.e. anything that is related to the mechanism of action of the drug in the organism.

Important examples of how pharmacogenetics affect pharmacokinetics are polymorphisms in the cytochrome P450 enzymes and in thiopurine *S*-methyltransferase. Clinical problems can arise from the co-administration of drugs that inhibit or compete for CYP2D6 (one of the more studied cytochrome P450 iso-enzymes).

A drug may interact with and inhibit CYP2D6 to the extent that it is no longer functionally active, resulting in a patient responding as a poor metaboliser even though he or she has an 'extensive metaboliser' genotype. Thus, quinidine, a powerful CYP2D6 inhibitor, may exaggerate the effects of other drugs that are prescribed concomitantly or may prevent the metabolic activation of drugs such as codeine by CYP2D6.

Pharmacogenetics and changes in pharmacokinetics

Cytochrome P450 iso-enzymes

The cytochrome P450s are a multigene family of enzymes found predominantly in the liver (but also present in other tissues such as the brain) and are responsible for the metabolic elimination of most of the drugs currently used in medicine. Thus, genetically determined variability in the level of expression or function of these enzymes has a profound effect on drug efficacy. In 'poor metabolisers' the genes encoding specific cytochrome P450s often contain inactivating mutations, which result in a complete lack of active enzyme and a severely compromised ability to metabolise drugs.

Mutations in the gene encoding cytochrome P450 iso-enzyme CYP2C9, which metabolises warfarin, affect patients' response to the drug and their dose requirements (9). Polymorphism not only affects drug disposition but can also be important in the conversion of prodrugs to their active form. For example, codeine is metabolised to the more potent analgesic, morphine, by CYP2D6 and the desired analgesic effect is not achieved in CYP2D6 poor metabolisers. CYP2D6 (also known as debrisoquine hydroxylase) is highly polymorphic and is inactive in about 6% of white people. Thus, worldwide, millions of people are at risk of compromised metabolism or adverse drug reactions when prescribed drugs that are CYP2D6 substrates. Many such drugs are used for treating diseases such as psychiatric, neurological, and cardiovascular diseases having a narrow therapeutic window and common side effects (see table on page 88).

Another variant results from amplification of the entire CYP2D6 gene, with some individuals inheriting up to 13 copies of the gene, arranged in tandem (10). This amplification polymorphism

Examples of drugs that are substrates of cytochrome P450 CYP2D6

Drugs for treating cardiovascular disease
Alprenolol, amiodarane, flecainide, indoramin, mexiletine, nimodipine, oxprenolol, propranolol, timolol

Drugs for treating psychiatric and neurological disease
Amitriptyline, clomipramine, clozapine, desipraminc, desmethylcitalopram, fluvoxamine, fluoxetine, haloperidol, imipramine, levomepromazine, maprotiline, mianserin, nortriptyline, olanzapine, paroxetine, perphenazine, risperidone, thioridazine, tranylcypromine, venlafaxine, zuclopenthixol

results in affected people metabolising drugs that are CYP2D6 substrates so quickly that a therapeutic effect cannot be obtained at conventional doses. For example, it has been estimated that, while a daily dose of 10–20 mg nortriptyline would be sufficient for a patient who is a CYP2D6 poor metaboliser, an 'ultra-rapid metaboliser' inheriting multiple copies of the gene could require as much as 500 mg a day (11).

Thiopurine methyltransferase

Another clinically important polymorphism occurs in the enzyme thiopurine *S*-methyltransferase (TPMT), (12) which is responsible for the metabolism of the antitumour agents 6-mercaptopurine and 6-thioguanine. Genetic polymorphism at this gene locus is associated with difficulty in achieving an effective dose of these drugs in children with childhood acute lymphoblastic leukaemia (13). Children with inherited TPMT deficiency exhibit severe haematopoietic toxicity when exposed to drugs such as 6-mercaptopurine, whereas those with a high activity form of the enzyme require high doses of the drug to achieve any clinical benefit. The TPMT polymorphism is relatively rare, with only about 1% of the white population being homozygous for it, but, since these individuals show exaggerated toxic responses to normal doses of thiopurine, TPMT phenotype may be an important factor in the successful treatment of childhood leukaemia. Some centres already provide a diagnostic phenotyping service to guide the clinical use of 6-mercaptopurine. Other major polymorphic metabolizing enzymes, including members of the cytochrome P450 family and II phase enzymes (including G6PD, glutathione *S*-transferase, etc.) have recently been reviewed (14).

Pharmacogenetics and changes in pharmacodynamics

Pharmacodynamic changes that are caused by pharmacogenetic reasons have been less explored than pharmacokinetic changes. This probably reflects the relative complexity of mechanisms of action (receptor, ion channels, biology) and environmental influences that affect them.

Ethnic variations in the response to psychotropic drugs which are not connected to pharmacokinetics are well known (15). Genetic variation of adrenergic, dopamine and serotonin receptors as well as serotonin transporters and histamine have been examined and linked to therapeutic response in both schizophrenia and depression. Polymorphisms involved in the regulation of the serotonin transporter protein for instance have been described as influencing the therapeutic efficacy in depressive patients of selective serotonin reuptake inhibitors such as fluvoxamine (16) and paroxetine (17). Unfortunately, conflicting results have been reported in another ethnic group (18) without any explanation for the discrepancies at present.

Clozapine, an atypical antipsychotic drug used for the therapy of schizophrenia has potentially severe side effects and is efficacious in only 30 to 60 percent of otherwise treatment-resistant patients.

Predicting response would help clinicians tremendously and has been attempted with a number of gene markers by different researchers. One of the most comprehensive studies to date of a pharmacogenetic screening strategy combining 6 out of 19 candidate gene markers defined response to clozapine with a level of prediction of 76.9% (19). Unfortunately, another group applying the same approach could not replicate the findings later. Clearly more work has to be done in this area.

Other examples of polymorphisms of drug targets which could influence the therapeutic response, include beta-adrenergic receptors and response

to beta-agonists in asthmatics (20). Current research in asthma pharmacogenetics has highlighted associations between single nucleotide polymorphisms in the betadrenergic receptors and modified response to regular inhaled beta-agonist treatments (e.g. albuterol). Variants within the 5-lipoxygenase gene have been suggested to predict the response to antileukotrienes in subjects with asthma (21). Confirmation of these findings, together with the current rapid creation of new knowledge, may mark the beginning of the clinical use of genotyping at an individual level as an adjunct to pharmacotherapy for asthma and many other disorders.

There seems to be one substantial difference when comparing known pharmacodynamic and pharmacokinetic examples. In the case of mutations that result in pharmacodynamic effects these often seem to be family-specific. Genotyping may be useful in identifying carrier status (heterozygote) for instance, and as a research instrument to shed light on receptor control and structure. However, genotyping may not currently be useful outside such defined family groups. Compared with pharmacokinetic changes, at the current state of knowledge, pharmacodynamic changes have not been reported to be as important on a population basis, owing to low incidence and prevalence. It may well reflect current lack of understanding and could rapidly change in the future.

Gene expression and existing therapies

Increasing knowledge of gene expression represents a new aspect of genetics, including pharmacogenetics. Initiated by development of microarray analysis new methodologies allow determination of the amount of RNA or of protein produced by the gene to measure gene 'efficiency'. For decades it has been known that some drugs can increase their own rate of metabolism or that of other drugs, mostly through enzyme induction. The inducing drug may stimulate expression of the gene responsible for the production of the enzyme.

The use of microassays to measure rifampicin effect on the pattern of mRNA expression of drug-metabolizing enzymes in hepatocytes demonstrated that it had no effect on CYP2C18, CYP2E1 or CYP2D6. However, it caused almost a 3.7-fold increase of CYP2C9, 6.5-fold increase of CYP2C8 and 55.1-fold increase of CYP3A4 (22). Naturally, gene expression can be altered by many other factors including gene-gene interactions, diseases, hormones, foods and chemicals in the environment.

However, drugs already currently in use can potentially affect gene expression and we may not know whether a pharmacological effect results from the drug acting on the gene itself or on its protein product. Recent studies suggest that drug addiction may represent an alteration of genes by the drug (23). More knowledge on the variation of drug response due to altered gene expression may lead to better targeted therapy. In the past, pharmacogenetics studied the effect of genes on drug action but attention to the reverse, i.e. drugs affecting gene function should also be considered.

The current situation

Pharmacogenetic testing is currently used in a relatively limited number of teaching hospitals and specialist academic centres and is probably most advanced in Scandinavian countries. The most widely accepted application of pharmacogenetic testing is the use of CYP2D6 genotyping to aid individual dose selection for drugs used to treat psychiatric illness.

Several independent testing laboratories have started to provide the pharmaceutical industry and medical practice with high throughput DNA-based testing service for a range of pharmacogenetic polymorphisms. It is, however, difficult to predict to what extent the pharmaceutical industry will routinely incorporate pharmacogenetic testing into prescribing schedules for drugs that are subject to polymorphic metabolism. This will depend to some extent on the attitude taken by drug regulatory authorities.

The clinical applicability of pharmacogenetic testing depends on the relative importance of each polymorphism in determining therapeutic outcome. Doctors need to be aware of whether a drug they are prescribing is subject to pharmacogenetic variability and know how to use this knowledge. In addition, a reliable DNA-based testing service with affordable prices needs to be made available. For certain pharmacogenetic polymorphisms (such as CYP2D6) there is already sufficient knowledge about the implications of genetically-determined variation to instigate population based pharmacogenetic testing. Details of more than 20 drugs that are known to be CYP2D6 substrates are now pro-

vided in both the ABPI Compendium of Data Sheets in Britain and the Physicians Desk Reference in the United States (24, 25).

This may allow the choice and doses of specific drugs, particularly those for treating psychiatric disorders, to be used more appropriately. At present, adverse drug reactions occur in a substantial proportion of patients. A recent US study showed that, in patients prescribed psychiatric drugs that are CYP2D6 substrates, adverse drug reactions were observed in every patient with inherited mutations inactivating the CYP2D6 gene (21). Approximately 7% of people of Caucasian origin have genetically impaired activity of CYP2D6.

The future

The following developments may be predicted with some confidence:

- Changes in labelling and prescribing advice will start to relate dose to genotype and will highlight the possibility of drug interactions when multiple drugs are prescribed concomitantly.

- The step-by-step creation and implementation of prescribing guidelines based on clinical studies for drugs that are subject to substantial polymorphic metabolism will increase.

- The establishment and recording of individual patient genotypes and phenotypes i.e. 'personal pharmacogenetic expression profiles' will become part of medical records.

- Implemention of pharmacogenetics testing will substantially reduce the need for hospitalization caused by adverse drug reactions.

- Chanelling of public funds for improved use of existing therapies which will unfreeze finances for new therapies and lead to better overall health outcomes for the population.

The anticipated benefits of pharmacogenetics and pharmacogenomics could be considered as:

1. Improving rational drug use by identifying people who respond and avoiding use in those who are at risk of serious adverse reactions.

2. A review of failed drugs and drug candidates and expansion of the indications for drugs on the markets.

3. A stepwise elimination of "trial-and-error" and "one-size-fits-all" prescribing.

4. Saving resources by avoiding treatment of populations who cannot benefit from the drug in question.

Limitations

1. Funding motivation for research related to existing therapies may be low and have to compete with investment in new and innovative therapies.

2. Public acceptance of genetic profiling may need time.

3. Access to a personalized approach may be too costly to attract funds.

4. Distinguishing environmental factors from genetic factors may be more difficult than expected and cause failure to achieve better treatment outcomes with pharmacogenetic approaches.

5. Complexities of interactions with drugs and other types of health products may complicate a pharmacogenetic targeting approach.

6. Pharmacogenetic targeting may raise ethical considerations which need to be identified and debated openly.

With a view to promoting more effective and safe personalized medicine, existing therapies need to be reviewed in the light of new scientific technologies and data. It may be that some existing therapies can offer improved outcomes with relatively little investment and cost. However, more open discussion on how pharmacogenetics could improve existing therapies is vital if this is to become a reality in everyday clinical practice.

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Safety Issues

Fluticasone and adrenal crisis

There have recently been several reports worldwide of adrenal insufficiency developing in children using inhaled corticosteroids. The Australian Adverse Reactions Advisory Committee (ADRAC) has received 10 such reports from Australia. Eight involved the use of fluticasone, either alone (Flixotide®) or in combination with salmeterol (Seretide®) (1).

In 8 cases, the ages ranged from 3 to 10 years, and the doses of fluticasone from 250 to 1500 μg daily; the daily dose was over 500 μg in 6 of the reports. Six of the children had adrenal crisis, which was associated with hypoglycaemia in all cases, convulsions in two, and coma in one. In three of the reports the adrenal crisis had been precipitated by an episode of gastroenteritis.

Adrenal crisis associated with inhaled corticosteroid use occurs because of the systemic absorption of the corticosteroid and consequent suppression of endogenous glucocorticoids, leaving insufficient adrenal reserve to respond to stress (for example, infection). It may also result from abrupt discontinuation or non-compliance with treatment, leading to acute steroid deficiency. It may present as hypoglycaemia, abdominal pain, tiredness or vomiting, with or without convulsions or coma.

Although adrenal insufficiency can occur with any inhaled corticosteroid, it may be more common with fluticasone because of its greater potency and hence lower equivalent dose (half the dose of budesonide or beclomethasone) (2, 3).

The Australian approved dose of inhaled fluticasone for children is 100–200 μg daily. At this dose, adrenal suppression is unlikely (4). The use of higher doses, however, is common. The Thoracic Society of Australia and New Zealand recommends a maximum dose of 250 μg daily in children up to 5 years, and 500 μg daily in children over 5 years, before referral to a respiratory physician (5). The National Asthma Council recommends a maximum dose of 500 μg daily for all children, before referral to a respiratory physician. Higher doses may not confer greater efficacy; a meta-analysis of trials of fluticasone in adolescents (>12 years) and adults indicated that in patients using regular, long-term inhaled corticosteroids, maximal efficacy was achieved at doses around 500 μg/day, but 90% of the benefit was achieved at doses of 100–250 μg/day (2).

Prescribers are reminded that inhaled corticosteroids should be given at the lowest effective dose and reviewed regularly, and should not be discontinued suddenly. Screening for adrenal insufficiency in children receiving high dose inhaled corticosteroids is generally not useful. Instead, parents of these children should be warned of the potential for adrenal suppression, and advised to seek medical attention if the child experiences any of the symptoms described above, particularly in the setting of an intercurrent illness (6).

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Thiazolidinediones experience

Pioglitazone (Actos®) and rosiglitazone (Avandia®) are thiazolidinediones, a new class of oral antidiabetic drugs, which act on the peroxisome proliferator activated gamma (PPARg)

nuclear receptor to reduce tissue insulin resistance. These glitazones may be used alone or in combination with sulfonylureas or metformin. Pioglitazone is also approved for use with insulin.

The Australian Drug Reactions Advisory Committee (ADRAC) has received 44 reports associated with rosiglitazone, and 28 reports with pioglitazone. Twelve reports with rosiglitazone and 4 with pioglitazone were of hepatic reactions, including elevated liver enzyme levels (13 reports; 1 with jaundice), abnormal liver function (1), hepatocellular damage (1) and hepatitis (1). However, liver enzyme levels may be elevated with diabetes or obesity.

Twelve possible cardiac reactions were reported with rosiglitazone and 6 with pioglitazone. The events were myocardial infarction (4 reports), cardiac failure (4), prolonged QT-interval (2), ventricular fibrillation with cardiac arrest (1) and dependent oedema (7: all with rosiglitazone). In 3 of the 4 cases of myocardial infarction or cardiac failure with rosiglitazone the patient had a history of ischaemic heart disease. The cardiac events in these patients may be related to co-morbidities, including age, diabetes, hypertension and ischaemic heart disease. However, the glitazones have been associated with cardiac failure (1).

The first glitazone, troglitazone (Rezulin®) was briefly marketed, but was withdrawn due to hepatotoxicity. The glitazones should not be used in patients with liver disease (including increased transaminase levels > 2.5 times the upper limit of normal), or in patients whose cardiac failure limits their physical activity. Careful monitoring of hepatic and cardiac function is required, including liver function tests every two months for at least one year, even in patients with normal baseline liver enzyme levels.

The glitazones can increase subcutaneous fat, and cause fluid retention, with oedema and haemodilution. Clinical studies suggest that weight gain may be associated with improved glycaemic control, but treatment should be re-evaluated in patients with excessive weight gain. The effect of glitazones on mortality and their role in long-term treatment of type 2 diabetes are not yet established (2).

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Cefepime, ceftazidime and neurotoxicity

A recent study appearing in *Pharmacotherapy* has reviewed 42 cases of cefepime-induced neurotoxicity and 12 cases of ceftazidime-induced neurotoxicity. Both the frequency of drug resistance and the prescription of broad-spectrum antibiotics such as cefepime and ceftazidime have increased over the last decade. However, antibiotic-induced neurotoxicity seems to have been overlooked or misinterpreted despite extensive administration of these agents. Early recognition of neurologic toxicity and withdrawal of the offending antibiotics can avoid serious consequences.

Clinical characteristics and timing of diagnosis were examined. Common findings were confusion with temporospatial disorientation (96% of patients), myoclonus (33%), and seizures (13%). These neurologic disorders frequently are encountered in uraemic and elderly patients, who are often in a confused state when they visit their physician. The risk of delayed diagnosis was greater with cefepime than ceftazidime neurotoxicity.

Cefepime has had a good safety profile in terms of neurological complications. The occurrence of seizures attributed to cefepime and ceftazidime has been 1/10 000 and 3/1000 patients, respectively. Possible reactions were confused state, dysarthria, somnolence, psychosis, myoclonus, seizures, and sometimes, coma. Resolution of these manifestations after withdrawal of the implicated antibiotic was considered appropriate supportive evidence.

Mean age of 54 patients in the review was 61 years in the cefepime group and 65 years in the ceftazidime group. Confusion was the chief symptom in 93% and 91% of patients with cefepime and ceftazidime neurotoxicity, respectively. Myoclonus was subsequently detected in 29% of the cefepime group and 50% of the ceftazidime group.

Electro-encephalographic results were available for most patients (41/42 cefepime- and 8/12 ceftazidime-treated patients); three distinctive electroclinical patterns of antibiotic neurotoxicity were described. Patients in the cefepime group were in an encephalopathic state; their EEGs

showed loss of background activity, increased slow rhythms in the theta and delta range, and triphasic waves. Symptoms of neurotoxicity abated in these patients with discontinuation of the drug rather than because of any change in degree of uraemia.

In the ceftazidime group, EEGs demonstrated epileptic activity; that is, epileptiform discharges such as polyspike discharges, rhythmic slow waves, or irregular spikes or sharps, which initially might be confined to one region and become more widespread, subsequently spreading to both cerebral hemispheres. Spike and wave discharges were suppressed after intravenous administration of benzodiazepines. Electroencephalographic abnormalities in ceftazidime-treated patients were accompanied by either overt convulsions or continuous subclinical seizures. The latter condition, nonconvulsive status epilepticus, occurred in 35% of the cefepime group and 75% of the ceftazidime group. The condition is characterized by prolonged clouding of consciousness and confusion associated with persistent epileptiform discharges seen on EEG in the absence of motor convulsive activity. Generalized convulsive seizure was observed in six patients with cefepime neurotoxicity.

The median interval between symptom onset and diagnosis of cefepime versus ceftazidime neurotoxicity was 5 and 3 days, respectively (p=0.005). Delayed diagnosis of cefepime neurotoxicity may be due to lack of awareness of the adverse effect. Data gathered since these two broad-spectrum antibiotics were first marketed underscore the potential for neurologic adverse events secondary to their administration. Thus, clinicians' awareness must be increased so that the time between symptom onset and diagnosis can be reduced.

Reference: Kai Ming Chow, Cheuk Chun Szeto, Andrew Che Fai Hui, et al. Retrospective Review of Neurotoxicity Induced by cefepime and ceftazidime. *Pharmacotherapy*, **23**(3): 369–373 (203).

Interstitial nephritis and proton pump inhibitors

Interstitial nephritis is a well-recognized but rare hypersensitivity reaction to omeprazole (1). Patients present with non-specific symptoms of illness. The classic triad for interstitial nephritis of fever, rash and eosinophilia is uncommon (2). Laboratory investigation confirms the presence of renal dysfunction and urine examination, including microscopy, may show haematuria and proteinuria but may be unremarkable (3). The diagnosis can only be confirmed by renal biopsy. Management involves withdrawal of omeprazole and supportive treatment. Cases are commonly treated with glucocorticoids, but the efficacy of this therapy has not been demonstrated in controlled trials (2).

The Australian Drug Reactions Advisory Committee (ADRAC) has received 18 biopsy-confirmed reports of interstitial nephritis with omeprazole. The median age was 68 (range 47–86) years, with 5 males and 13 females affected. The median time to onset was 3 months (range 12 days to 12 months). In 7 cases the association was not made immediately, and withdrawal of omeprazole occurred 3 weeks to 6 months after the first symptoms of interstitial nephritis. Nine of the 18 patients had recovered at the time of the reporting, including two who showed rapid recovery over 2 or 3 weeks (4).

Presenting symptoms included weight loss, malaise, fever and nausea. Polyuria and polydipsia were present in one case. Elevation of plasma urea and/or creatinine was documented in most cases. Urine microscopy, in 3 cases, showed red cells, white cells and casts. In the 8 cases for which details of the results of renal biopsy were provided, mononuclear infiltrates of lymphocytes, plasma cells and eosinophils were usually present and some also had histiocytes.

ADRAC has also received two reports of biopsy-proven interstitial nephritis with rabeprazole (Pariet®). No reports have been received in Australia for the other proton pump inhibitors, but interstitial nephritis is listed as an adverse effect in the product information for esomeprazole (Nexium®), lansoprazole (Zoton®) and pantoprazole (Somac®).

Interstitial nephritis has also been associated with the ß-lactam and sulphonamide antibiotics, diuretics, NSAIDs, cimetidine, allopurinol and rifampicin. Patients taking a proton pump inhibitor, or any of the medicines listed above who become unwell without identified cause should have renal function assessed.

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Interactions with grapefruit juice

Following comments received after publication of its recent article (1), the Australian Adverse Drug Reactions Advisory Committee (ADRAC) has re-evaluated the literature, and wishes to revise its advice. Although there are no case reports of significant clinical problems occurring when grapefruit juice and medication ingestion have been separated by more than a few hours, studies suggest there is a potential for grapefruit juice to have an interacting effect for up to 3 days after ingestion, particularly with daily consumption. ADRAC now considers that the safest course is to avoid grapefruit and its juice altogether when taking medicines that interact (2).

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2. Interactions with grapefruit juice — amendment *Australian Adverse Drug Reactions Bulletin*, **22**: 2 (2003).

Spontaneous monitoring systems are useful in detecting signals of relatively rare, serious and unexpected adverse drug reactions. A signal is defined as "reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually, more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information". All signals must be validated before any regulatory decision can be made.

Current Topics

New network for guideline development

The World Health Organization has become a founding member of the new Guidelines International Network (GIN). This is a major new international collaboration involving organizations from around the world. GIN seeks to improve the quality of health care by promoting systematic development of clinical practice guidelines and their application into practice. GIN's aims are:

- To facilitate information sharing, education and knowledge transfer, and collaborative working between guideline programmes to promote best practice and avoid duplication of effort.
- To improve and harmonize methodologies for systematic guideline development in existing and new guideline programmes.
- To improve methodologies for dissemination and implementation of clinical practice guidelines and evaluation of their effects.
- To identify priorities for and support research relating to guideline development, dissemination, implementation, and evaluation; and to facilitate the application of research findings into practice.
- To build links between organizations to improve coordination with other health care quality initiatives.

So far, about forty organizations dealing with guideline development and quality of care from Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Ireland, Italy, Netherlands, New Zealand, Norway, Portugal, Slovenia, Spain, Sweden, Switzerland, United Kingdom and USA have become founding members, at EUR 2500 per year.

WHO has become a founding member with the aim of representing the global perspective, and especially the developing country perspective. WHO has also negotiated a limited number of subsidized GIN memberships for organizations from developing countries.

Reference: Guidelines International Network, PO Box 13163, Duns, TD11 3YT, UK. Tel: +44.1361.884012, Fax: +44.1361.884013 e-mail: info@guidelines-international.net. http:/www. guidelines-international.net

Fake artesunate tablets circulating again

In the late 1990s, counterfeits of artesunate, a vital life-saving antimalarial drug, were discovered circulating in South-east Asia (1). Up to 38% of 'artesunate' labelled as manufactured by Guilin Pharma, People's Republic of China, bought in pharmacies and shops in mainland South-east Asia contained no detectable artesunate. This has led to an unquantified but inevitably high mortality and morbidity amongst falciparum malaria patients in the region. Fakes described in 2001 were relatively easy to distinguish from the genuine product by the appearance of the packaging and holograms (2). A simple, inexpensive dye test allows one to reliably check the authenticity of artesunate tablets (3).

A team of researchers has now warned of two further sophisticated 'generations' of counterfeit 'artesunate', again labelled as produced by Guilin Pharma — bought in Laos and Cambodia — with new, convincing and very well crafted but fake holograms attached to the blister pack.

The first-generation fake hologram described in 2000 is not a true hologram but a sticker and easy to distinguish from the genuine hologram. This is still in circulation.

The second-generation hologram is a true hologram and only appears to differ from the genuine hologram in the shape of the mountain outline and the lack of the microscopic legend 'Guilin Pharma' printed below the 'waves'. The printing on the blister pack is not clear. Three blisterpacks were recently bought in southern Laos and one in North-east Cambodia with this second-generation hologram. All have the same

code, manufacture and expiry dates. It is likely however that artesunate with this second - generation fake hologram has or will be made with different dates and codes.

The third-generation hologram has a mountain outline similar to the genuine Guilin product but lacks the microscopic legend 'Guilin Pharma' printed below the 'waves'. The printing on the blister pack is crisp and similar to that on the genuine product. Two blister packs bearing this new hologram were recently bought in southern Laos.

All six artesunate blister packs with the second- and third-generation fake holograms were negative for artesunate by the Fast Red dye test and contained no artesunate on HPLC analysis. Fake artesunate with the new sophisticated second- and third-generation fake holograms are widely distributed but because of their similarity to the genuine product they are probably unrecognized by pharmacists, health staff and patients.

It is also possible that Guilin Pharma artesunate is now being sold in some West African countries, such as Togo, and fakes may also be circulating there.

PDF files of documents warning of the recent discovery of sophisticated counterfeit artesunate, with photographs of the different holograms, and a description of the Fast-Red dye test, are available from newtonpaul100@yahoo.co.uk or newtonpaul100@hotmail.com. Pictures of the genuine and fake holograms are also posted on the Shoklo Malaria Research Unit website (http://www.shoklo-unit.com/fakes2.pdf).

Communication to WHO from Paul Newton, Arjen Dondorp, Michael Green, Shunmay Yeung, Nicholas J. White on 19 June 2003.

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European Union enlargement: observers to EMEA

The ten accession candidate countries expected to join the European Union in May 2004 — Cyprus, Czeck Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, The Slovak Republic and Slovenia — began work with the European Agency for the Evaluation of Medicinal Products (EMEA) on 1 April 2003 in a new phase of cooperation and will join scientific committees and working parties as observers. This builds on successful PERF (Pan-European Regulatory Forum) (1) preparatory training and exchange programmes.

As part of the ongoing preparations for accession, the EMEA has put in place a programme of benchmarking visits to national authorities of the accession countries, including Bulgaria and Romania. The visits are intended to enhance the implementation of an integrated quality management system to ensure good regulatory practices in the EU and provide targeted audit training for participating quality professionals (2).

References

1. http://perf.eudra.org

2. Document EMEA/D/8004/03, 31 March 2003, http://europa.eu.int

Clinical cancer research review

The American Society of Clinical Oncology (ASCO) has released new recommendations to improve the cancer clinical trial review system. The new policy is unique in its recommendation that oversight and review of cancer clinical trials be centralized, reducing some of the burden on local institutional review boards (IRBs) caused by duplication in the system, improving patient safety, and streamlining clinical cancer research review.

ASCO has also released a revised conflict of interest policy requiring clinical cancer researchers seeking to publish or present trial outcomes to disclose virtually all financial ties to trial sponsors, and restricting the financial interests of principal investigators and other clinical trial leaders. The additional requirements apply to all those engaged in ASCO activities including presenters at the Society's Annual Meeting, authors who submit manuscripts for publication in the Journal of

Clinical Oncology, and anyone serving on ASCO's Board of Directors, committees, or task forces. The policies were developed by a special Task Force on Oversight of Clinical Research, and will appear in the June 15 issue of ASCO's Journal of Clinical Oncology. They are published online at http://www.jco.org.

Oversight of Clinical Trials
The Task Force examined the current structure, expertise and function of IRB's, including their initial and ongoing review and oversight of trials. The ASCO Task Force calls for centralized trial review, beginning with cancer trials conducted through the National Institutes of Health (NIH) cooperative group system. Under this system, a centralized review board (CRB) would be responsible for the initial ethical review of a trial, coordinate data gathering, monitor adverse events, and give local IRBs an analysis and summation of adverse events across the trial sites. The policy statement does not recommend changing the local IRB's critical role in monitoring patient safety onsite during a trial or ensuring proper staffing and adherence to protocol.

Recommendations:

- Education and Training: All IRB members, investigators, and members of the research staff should receive comprehensive, ongoing education and training on the ethical conduct of research to ensure the safety of research participants and the scientific integrity of research.

- Informed Consent: The IRB should focus attention on oversight of the informed consent process, not chiefly the informed consent document. Where possible, consent forms should be simplified to ensure understanding by potential trial participants.

- Oversight: The Department of Health and Human Services' Office of Human Research Protections (OHRP) and the Food and Drug Administration (FDA) should provide clear regulatory support and uniform guidance to local IRBs and modify regulations to allow greater use of centralized review.

- Resources Supporting Clinical Research Infrastructure: Institutions should devote adequate funding and institutional support to their research review system to ensure effective research oversight.

Conflict-of-Interest
The Task Force also updated ASCO's conflict-of-interest policy, outlining new financial disclosure levels, restricted activities for researchers in leadership roles, and general prohibitions for all clinical investigators.

The new guidelines also restrict individuals in a trial leadership role – including principal investigators, members of the data safety monitoring board, and members of the trial's executive committee – from receiving or holding stock or equity interest in the trial sponsor royalties or licensing fees, patents, position as officer, board of directors' member, or employee of the trial sponsor. Travel or trips paid by the trial sponsor Research-related payments, honoraria or gifts from the trial sponsor. The new conflict-of-interest policy will take effect April 29, 2004.

Reference: http://www.jco.org/early_release/.

New foundation will develop tests for infectious diseases

In response to a critical need for new tools to detect infectious diseases, the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) and the Bill & Melinda Gates Foundation have announced a new initiative focused on developing new diagnostic tests for the world's most deadly diseases. The Foundation for Innovative New Diagnostics (FIND) will work in collaboration with WHO/TDR, the diagnostics industry and other organizations to apply the latest biotechnology innovations to develop and validate affordable diagnostic tests for diseases of the developing world. The Gates Foundation has committed up to $30 million over the next five years to the initiative.

There is an urgent need for more accurate and cost-effective diagnostic technologies, particularly for diseases of the developing world. While the biotech revolution has yielded important progress in the diagnosis and treatment of diseases that affect affluent societies, these advances have not been applied to diseases that kill millions each year in developing countries. As a result, many diseases go undetected and untreated in the developing world, accelerating their spread.

Building on the accomplishments of TDR's Tuberculosis Diagnostics Initiative, FIND will

focus initially on TB, speeding up the development and evaluation of new tests to detect the disease, including drug resistant forms. TB was chosen as the first target for FIND because of the magnitude of the problem — one-third of the world's population carries the TB pathogen— and the ability of existing health systems to treat cases once they are detected.

Today's standard TB detection method, examining sputum under a microscope, was developed over a century ago. It is time-consuming and frequently inaccurate. While the success of the Global Drug Facility and other treatment programmes have improved the access of TB patients to effective therapy, diagnostics are now recognized as a primary stumbling block in TB control and patient care.

Research carried out over the past two years by the TB Diagnostics Initiative show that although TB and other diseases of the poor have been largely neglected by the bigger diagnostics companies, there is considerable work going on in smaller biotechnology companies and academic research groups. However, even when diagnostics are developed for infectious diseases, they do not always reach the public sector. FIND will also work with private industry, WHO, and other technical agencies to ensure that the tools in development match public health needs.

TB kills one person every 15 seconds. The case fatality rate of TB is high, in large part because of lack of diagnosis and treatment. More sensitive diagnostics will open the possibility of treating the less contagious cases before they infect others. Faster, simpler diagnostics will make TB control efforts more effective, especially in places where patients have difficulty reaching health care.

TB is responsible for 5% of all deaths worldwide and 9.6% of adult deaths in the 15–59 age group. TB kills more women worldwide than all causes of maternal mortality. The disease is concentrated in low income countries. Some 80% of all TB cases are found in 22 countries, with more than half the cases occurring in five South East Asian countries. Nine out of 10 countries with the highest incidence rates are in Africa, where prevalent HIV infection has fuelled the epidemic and further complicated diagnosis.

In addition to developing and evaluating tests, FIND will fund demonstration projects to determine the potential impact of newly developed products and improve their use in developing countries. WHO/TDR will be a key player in the interaction with researchers, in setting up clinical trials and carrying on the implementation research required during the introduction of the new diagnostic tools by the health services of disease-endemic countries. FIND represents an expansion of TDR's ongoing efforts to discover and develop diagnostics for neglected infectious diseases. In coordination with public health officials, the collaboration between WHO/TDR and FIND will ensure that appropriate technologies reach appropriate settings. Findings will provide input to the WHO on standard setting for diagnostics and regulatory harmonization.

References: http://www.who.int/tdr
http://www.gatesfoundation.org
http://www.finddiagnostics.org

TDR research training in 2004

The UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) invites applications for the award of research training grants from individuals who are nationals of and employed in developing disease-endemic countries with lesser developed research capacities. Grants are awarded on a competitive basis for studies leading to a postgraduate degree or for acquiring specialized skills.

Studies must be on one or more of the TDR target diseases — malaria, leishmaniasis, schistosomiasis, lymphatic filariasis and onchocerciasis, African trypanosomiasis and Chagas disease, leprosy, dengue and tuberculosis, in laboratory, clinical or applied field research disciplines relevant to TDR and/or national priorities. Training may take place in the home country, in another developing country, or in a developed country. TDR reserves the right to select the academic institution, research programme or TDR-funded project where it is felt the most suitable training can be obtained.

Research capability strengthening is a cross-cutting area of TDR established to promote and fund research training and institution development to increase the participation of developing countries in the development and use of new or improved tools for the prevention and control of communicable diseases. The long-term mission is to increase research self-reliance in endemic countries for identifying needs and developing solutions to public health problems caused by

neglected infectious diseases. TDR contributes to the attainment of these goals by strengthening research institutions, generating new scientific knowledge in biomedical and social sciences and building a critical mass of human resources to respond to research and public health needs. Partnerships, networking and promoting equal opportunities constitute the core of the strategy and the basis for promoting a gender and geographically balanced generation of scientists.

The TDR web site is available on http://www.who.int/tdr/grants/workplans and contains Research Capability Strengthening (RCS), Multilateral Initiative on Malaria /TDR (MIM)Task Force and other specific calls for research training applications and Career Development Fellowships. All applications must be received by 1 November 2003 at the following address: Research Training, UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR), 1211 Geneva 27 Switzerland Fax (41 22) 791-4854 e-mail: RCStraining @who.int

Reference: http://www.who.int/tdr/grants/workplans

Managing drug supply for primary health care

WHO, in association with the International Dispensary Association (IDA), Management Sciences for Health (MSH), and Réseau Médicaments et Développement (ReMeD), has organized a training course for pharmacists, physicians, senior health system managers and technical assistance professionals from non-governmental and governmental organizations.

The course, Managing drug supply for primary health care, has the following objectives:

- Expose participants to modern management techniques of drug supply systems and to teach them how to apply these in their own specific situation;
- Provide practical tools for decision-makers to improve performance of essential drugs programmes;
- Exchange views and experiences between senior decision-makers.

The course will be held in Amsterdam, Netherlands, from 15–26 September 2003 (in English) and from 20–31 October 2003 (in French).

This year will be the eighth year of organization of the course. Past experience has shown that it is particularly effective in helping to close the gap between what is known about public health problems and what is done to solve them.

For additional information and registration form, contact: Julie Pasquier, IDA Solutions, Tel: +31 20 40 33 051 Fax : +31 20 40 31 854 or e-mail: jpasquier@ida.nl

Reference. http://www.ida.nl

Latin American pharmacotherapy course

The Fifth Latin American Course on Pharmacotherapy will be held from 31 August –12 September 2003, in La Plata, Argentina. It is being organized by the Universidad Nacional de La Plata (Argentina) in collaboration with the World Health Organization and the PanAmerican Health Organization, Argentina.

The course, conducted in Spanish, will be operated for the benefit of two audiences: (i) trainers of trainers, who can replicate this course, and (ii) teachers of pharmacotherapy, clinical medicine, paediatrics, and gerontology working in undergraduate or postgraduate settings, medical schools, or teaching hospitals.

The general objective of the course is to provide knowledge and practical experience on a problem-based approach for pharmacotherapy teaching. At the end of the course, it is expected that the participants will have:

- Developed and identified methodologies to facilitate criteria selection in the choice and application of drug therapy and/or appropriate treatment to solve health problems.
- Obtained appropriate knowledge on problem-based methods of learning/teaching medicine and pharmacotherapy.
- Obtained the experience, knowledge and necessary skills to train teachers to develop abilities and be facilitators.

- Obtained the knowledge and necessary skills to plan, develop, implement and assess a problem-based pharmacotherapy course, in their own medical school or educational institution.

- Acquired critical appraisal in the use of sources of information about drugs and treatments.

The course is based on methodology developed by the University of Groningen, Faculty of Medical Sciences, Department of Clinical Pharmacology, Netherlands. The principles of the model underly those set out in the WHO Guide to Good Prescribing (1, 2). This course has been successfully introduced in Europe, Africa and Asia. Since 1999, it has been developed in America.

The Course will be run by academic staff of the Pharmacology Department, Faculty of Medical Sciences, Universidad Nacional de La Plata, with contributions from national and international guests. Representatives of the World Health Organization will also be present.

More information is available from: Centro Universitario de Farmacologia (CUFAR), Facultad de Ciencias Medicas, Universidad Nacional de La Plata, Calle 60 y 120- 3er piso, La Plata 1900, Argentina. Tel: 54 (221) 421-6932 Fax : 54 (221) 423-6710 e-mail: pmordujo@netverk.com.ar OR pmordujo@atlas.med.unlp.edu.ar

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1. World Health organization. Guide to Good Prescribing, WHO/DAP/94.11 (1994).

2. World Health organization.Teachers Guide to Good Prescribing. WHO/EDM/PAR/2001.2 (2001).

Regulatory and Safety Action

Gefitinib approved for lung cancer

United States of America — The Food and Drug Administration (FDA) has announced the approval of gefitinib (Iressa®) tablets as a single agent treatment for patients with advanced non small-cell lung cancer (NSCLC), the most common form of lung cancer in USA. Gefitinib is being approved as a treatment for patients whose cancer has continued to progress despite treatment with platinum-based and docetaxel chemotherapy, two drugs that are currently the standard of care in this disease.

Gefitinib was reviewed and approved under FDA's accelerated approval programme, which is intended to allow patients suffering from serious or life-threatening diseases earlier access to promising new drugs. As required by the accelerated approval regulations, additional studies will be performed to verify the drug's clinical benefit.

The mechanism by which gefitinib exerts its clinical benefit is not fully understood. However, gefitinib was developed to block growth stimulatory signals in cancer cells. These signals are mediated in part by enzymes called tyrosine kinases. Gefitinib blocks several of these tyrosine kinases, including the one associated with epidermal growth factor receptor (EGFR).

FDA based the approval on the results of a study of 216 patients with NSCLC, including 142 patients with refractory disease, i.e., tumours resistant or unresponsive to two prior treatments. The response rate (defined as at least 50% tumour shrinkage lasting at least one month) was about 10%. There were more dramatic responses in some patients and the median duration of response was 7 months. On September 24, 2002, the Oncologic Drugs Advisory Committee (ODAC) recommended that in third-line treatment of NSCLC, where there are no viable treatment options, a 10% response rate was reasonably likely to predict clinical benefit and recommended that gefitinib be approved.

Results from two large, controlled, randomized trials in initial treatment of NSCLC showed no benefit from adding gefitinib to standard, platinum-based chemotherapy. Therefore, gefitinib is not indicated for use in this setting.

There appeared to be substantial differences in response rates in subsets of patients, with higher response rates for women (about 17%) and patients with adenocarcinoma, and with lower response rates seen in men (about 5%) and smokers.

The sponsor has agreed to conduct further studies after approval to measure its clinical benefit. One study will evaluate treatment in patients with lung cancer resistant to two previous chemotherapy regimens and will determine whether gefitinib prolongs survival compared to best supportive care. A second study will compare treatment with an approved chemotherapy drug (docetaxel) in patients with lung cancer resistant to one previous chemotherapy regimen. The third trial will evaluate whether gefitinib will decrease cancer symptoms in patients with lung cancer resistant to all available chemotherapy.

Common side effects reported with gefitinib in clinical trials were nausea, vomiting, diarrhoea, rash, acne, and dry skin. Gefitinib may cause fetal harm when administered to pregnant women. A significant safety concern associated with gefitinib emerged just after the ODAC meeting. Reports from Japan described the occurrence of serious and sometimes fatal interstitial lung disease (ILD) in patients treated with gefitinib. The FDA extended its review by three months to review these reports.

After careful review of information from all sources, including a comprehensive analysis of updated toxicity information from clinical trials and the Iressa® Expanded Access Program, involving approximately 23 000 patients, FDA determined that the incidence of ILD was approximately 2% in the Japanese experience and approximately 0.3% in the United States, with about one-third of affected patients dying from this toxicity. FDA believes that this rare but serious toxicity of

gefitinib does not outweigh the benefits demonstrated in patients with advanced NCSLC.

Reference: *FDA News*, P03-36, May 5, 2003

New breath test for monitoring asthma

United States of America — The Food and Drug Administration (FDA) has cleared for marketing a first-of-a-kind, non-invasive test system to measure the concentration of nitric oxide in exhaled human breath. The test system should make it easier to monitor asthma.

Doctors can use the device in their office to evaluate their patient's response to anti-inflammatory treatment. A decrease in exhaled nitric oxide concentration suggests that the anti-inflammatory treatment may be decreasing the lung inflammation associated with asthma. Recent evidence has shown that nitric oxide levels are increased in the breath of people with asthma and that changes in nitric oxide levels may indicate whether or not treatment for asthma is working.

The test system, called the NIOX Nitric Oxide Test System®, combines equipment that detects nitric oxide and equipment that analyses exhaled breath with a special computer system. To use this new device, the patient places a mouthpiece, connected by a breathing tube to the computer, over his mouth. The nitric oxide concentration is displayed immediately on the computer screen.

FDA cleared the NIOX system based on clinical studies conducted by the manufacturer of 65 patients, both adults and children aged four years and older, with confirmed diagnoses of asthma. The patients were tested with the NIOX system before they began drug treatment and again two weeks later. The studies were conducted at nine medical centres in the United States. The results showed that most patients had a 30%–70% decrease of nitric oxide levels after two weeks of treatment with inhaled steroids. In this study, elevated nitric oxide levels above 30 parts per billion correlated with moderate to severe asthma.

Asthma is a highly variable disease affecting millions of people worldwide. With asthma, the lungs become inflamed and constrict, limiting airflow and making breathing difficult. The incidence of asthma in the United States has increased in recent years and it now affects about 15 million Americans, including almost five million children. Every year, asthma causes roughly 2 million emergency room visits, approximately 500 000 hospitalizations, and 4500 deaths.

Reference: FDA Talk Paper, T03-33, 1 May 2003

Risperidone: prescribing information update

United States of America — The manufacturer of the antipsychotic, risperidone (Risperdal®), has updated the prescribing information to include a warning of cerebrovascular adverse events, including stroke, in elderly patients with dementia. Action is based on data from four placebo-controlled trials conducted in elderly patients with dementia.

Cerebrovascular adverse events (e.g., stroke, transient ischaemic attack), including fatalities, were reported in patients (mean age 85 years; range 73–97) in trials of risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone compared to patients treated with placebo. risperidone has not been shown to be safe or effective in the treatment of patients with dementia-related psychosis.

Like all other antipsychotics, risperidone is not indicated for the treatment of dementia.

Reference: Communication from Janssen Pharmaceutica, 16 April 2003 accessed on http://www.fda.gov/medwatch.

Pan Pharmaceuticals product recalls

Australia — The Therapeutic Goods Administration (TGA), has suspended the licence held by Pan Pharmaceuticals Limited, Sydney, to manufacture medicines following a series of serious safety and quality breaches by the company. These included substitution of ingredients, manipulation of test results and substandard manufacturing processes. In addition, the TGA has ordered an urgent recall of 219 products which Pan Pharmaceuticals manufactures and supplies in Australia. Pan Pharmaceuticals is Australia's largest contract manufacturer of complementary medicines such as herbal,

vitamin, mineral and nutritional supplements. They also manufacture some over-the-counter (OTC) medicines including pain relievers (paracetamol & codeine) and cold and flu preparations (antihistamine & pseudoephedrine).

Other companies also use Pan Pharmaceuticals to manufacture their own brand products and the TGA will be working with these companies to identify which other products should be subject to recall. The action by the TGA follows advice received from an expert advisory group that the quality and safety concerns posed by the manufacturing breaches at Pan Pharmaceuticals needed to be urgently addressed. Acting on that advice the TGA has suspended the company's licence with immediate effect.

This is not the first action taken against Pan Pharmaceuticals. In January 2003 an anti-travel sickness tablet, Travacalm® manufactured by Pan Pharmaceuticals for another company, was the subject of a consumer recall. Faulty batches of the tablets were responsible for 19 people being hospitalized and 68 others experiencing potentially life-threatening adverse reactions to this over-the-counter medicine. Subsequent laboratory testing by the TGA of some of the tablets revealed that one of the active ingredients — hyoscine hydrobromide — varied in content from 0–700% of the listed dose.

The TGA undertook further audits of the company which also revealed serious deficiencies in the company's manufacturing and quality control procedures, including systematic and deliberate manipulation of quality control test data.

Some examples identified by the audit included:

- On 13 March 2003 the status of 270 raw materials was changed in the company's computer from Quarantine to Pass. In a random sample of these, none had been tested. It has been clearly identified that some were used in manufacture but not tested by the time of the audit on 14 April 2003. For example, 7 of these raw materials were used in the manufacture of 34 batches of products.
- Four recent examples of manipulation of the assay results of finished products in order to comply with specifications. These occurred between October 2002 and 22 January 2003 and involved an "energy" product, a vitamin product and a cough and cold formula.
- Four recent examples of the fabrication of finished product assay results of a vitamin product for export in order to comply with specifications. In two instances the product was over-strength (March 2003); in the other two, under-strength.
- In the past two and a half years, several instances of the use of beef cartilage in place of shark cartilage and one instance of use of shark cartilage in place of beef cartilage.
- Five instances where products were released and dispatched in the period 24 March 2003 to 31 March 2003 without completion of the testing of the raw materials used.

Reference : Therapeutic Goods Administration, on http://www.tga.health.gov.au

Telithromycine and myasthenia gravis

Spain — The Spanish Medicines Agency, in line with other Agencies of the European Union, has announced the urgent modification to the data sheet information concerning administration of telithromycine (Ketek®) in myasthenia gravis patients. Telithromycine is a semi-synthetic substance derived from erythromycin marketed in the European Union since July 2001. Its use is limited to adults for treatment of community acquired pneumonia, severe bronchitis or sinusitis. For patients over 12 years of age, it is also indicated in group A streptococcal pharyngitis and tonsillitis when beta lactam antibiotics are not considered appropriate.

Eight cases (one fatal) of exacerbation of myasthenia gravis have been reported in association with use of telithromycine. Symptoms reported were exacerbation of muscular weakness, dyspnoea, and acute pulmonary failure within a few hours of administration.

The mechanism of action causing worsening of myasthenia gravis is unknown, but cases have been reported in association with aminoglycoside, macrolide antibiotics, and certain fluoroquinolones.

The following points are brought to the attention of prescribers:

1. Given the severity of risk, telithromycine is not indicated in myasthenia gravis patients unless alternative treatment is not available.

2. Myasthenia gravis patients using telithromycine should be closely monitored and should report immediately to their physician any worsening of symptoms. Treatment should be discontinued in such cases.

Reference: No. 2003/05, 23 April 2003. http:/ www.msc.es/agemed

Astemizole: marketing suspension

Spain — The Spanish Medicines Agency has decided to suspend the marketing authorization for the non-sedating antihistamine, astemizole. Use has been associated with a risk of cardiac arrhythmia which has been demonstrated in a review of data. Consumption of astemizole in Spain and other European countries has decreased considerably.

Given this situation, the Committee on Safety of Human medicines has concluded that the benefit/ risk ratio is unfavourable since safer alternatives are available on the market.

Reference: No. 2003/04, 8 April 2003. http://www.msc.es/agemed

Somatropin: negative opinion

European Union — The Committee for Proprietary Medicinal Products of the European Agency for the Evaluation of Medicinal Products (EMEA) has adopted a negative opinion on the request for marketing authorization for somatropin (Serostim®) for the following reasons:

- A target population could not be identified for treatment.
- Doubts remain about the clinical relevance of the primary endpoints.
- Long-term efficacy data under controlled conditions are lacking.
- There is concern about the long-term safety profile.

Serostim® was designated an orphan medicinal product on 8 August 2000. The active substance is somatropin, a recombinant human growth hormone with anabolic effects.

Reference: CPMP/5330/02,. 25 April 2003.

Repaglinide and gemfibrozil: hazardous interaction

European Union — The European Agency for the Evaluation of Medicinal Products (EMEA) has issued a public statement concerning an interaction between repaglinide (NovoNorm® and Prandin®), a medicine used to lower blood sugar in diabetic patients, and gemfibrozil, a lipid-lowering agent.

A recent study indicates that the blood glucose-lowering effect of repuglinide may be markedly enhanced and prolonged when administered together with gemfibrozil, with an increased risk of hypoglycaemia. In addition, five reports of serious hypoglycaemic episodes in patients using repaglinide and gemfibrozil at the same time have been received.

Repaglinide is indicated in patients with Type 2 diabetes (non insulin-dependent diabetes mellitus) whose hyperglycaemia can no longer be controlled satisfactorily by diet, weight reduction and exercise. Repaglinide is also indicated in combination with metformin in Type 2 diabetes patients who are no satisfactorily controlled on metformin alone.

In view of the documented interaction and risk of hypoglycaemia, the concomitant use of repaglinide and gemfibrozil is contraindicated. Patients already receiving repaglinide with gemfibrozil should be reviewed and alternative combination treatment considered under close monitoring of diabetic status.

Reference: EMEA Public Statement. EMEA/11700/03 (2003).

Adhesion prevention solution global withdrawal

United States of America — The Food and Drug Administration (FDA) has received notification of a voluntary withdrawal of Gynecare Intergel Adhesion Prevention Solution® from the market. The manufacturer is urging customers to immediately stop using this device. This product has been distributed in Austria, Canada, Egypt, England, France, Germany, Greece, Ireland, Israel, Italy, Japan, Kuwait, Netherlands, Portugal, Republic of Singapore, Saudi Arabia, Scotland, South Africa, Spain, Sweden, Switzerland, United Arab Emirates and the United States.

This product is intended to be used in open, conservative gynecological surgery as an adjunct to good surgical technique to reduce post-surgical adhesions. The manufacturer is conducting this voluntary withdrawal to complete an assessment of information obtained during post-marketing experience with the device, including adverse events associated with off-label use in laparoscopy and non-conservative surgical procedures such as hysterectomy. However, from the launch of this device in 1998 to February 2003, the overall complaint rate worldwide is low.

Post-marketing reports include late-onset post-operative pain and repeat surgeries following the onset of pain, non-infectious foreign body reactions, and tissue adherence. In some patients a residual material was observed during the repeat surgery. Post-operative pain could be suggestive of other serious complications and physicians should be aware of this in managing patients in the post-operative period.

Reference: Communication to the FDA, 16 April 2003 on http://www.fda.gov

Counterfeit Lipitor®

United States of America — The Food and Drug Administration (FDA) has announced that three lots of 90-count bottles of the cholesterol-lowering drug Lipitor® have been voluntarily recalled and is warning of a potentially significant risk to consumers.

- The product was repackaged by Med-Pro, Inc., of Lexington, Neb., and the labels say "Repackaged by: MED-PRO, Inc. Lexington, Neb." in the lower left-hand corner.

- The following lots are involved in this recall:
  20722V - 90-tablet bottles, Expiration 09-2004
  04132V - 90-tablet bottles, Expiration 01-2004
  16942V - 90-tablet bottles, Expiration 09-2004

FDA is urging healthcare providers and patients alike to check the packaging very carefully before using this product. Any of the product (labelled as "Repackaged by MED-PRO, Inc.") with these three lot numbers should not be taken, but returned to the pharmacy.

FDA's investigation into this matter is continuing.

Reference: *FDA Talk Paper,* T03-38, 23 May 2003.

Paroxetine: avoid in children and adolescents

United Kingdom —The Chairman of the Committee on Safety of Medicines (CSM) has informed prescribers of new evidence relating to the efficacy and safety of the selective serotonin re-uptake inhibitors (SSRI), paroxetine (Seroxat®) in children and adolescents under the age of 18 years when used to treat depressive illness. Paroxetine is not licensed for paediatric use.

New data from clinical trials in children and adolescents were received by the Medicines and Healthcare products Regulatory Agency (MHRA) at the end of May 2003. These new data have been reviewed by an Expert Working Group on SSRIs and the Committee on Safety of Medicines. These data do not demonstrate efficacy in depressive illness in this age group and show an increase in the risk of harmful outcomes including episodes of self-harm and potentially suicidal behaviour in the paroxetine group compared to placebo. Various analyses suggest that the risk of these outcomes is between 1.5 and 3.2 times greater with paroxetine compared to placebo.

On the basis of these data, the CSM has advised that the balance of risks and benefits of paroxetine is unfavourable when used to treat depressive illness in this age group. The CSM has advised that paroxetine should not be used in children and adolescents under the age of 18 years to treat depressive illness. The efficacy and safety of paroxetine for children in other indications have not been established.

Prescribing advice for children and adolescents with depressive illness:

1. Paroxetine should not be prescribed as new therapy for patients under 18 years of age with depressive illness.

2. If a patient is being successfully treated with paroxetine, then the completion of the planned treatment course should be considered as an option in the management of the illness.

3. If a patient is not doing well on paroxetine, change of treatment should be considered.

When stopping treatment:

- Paroxetine should not be stopped suddenly because of the risk of withdrawal reactions.

- The dose should be reduced very gradually, using half tablets, and then alternating days, if necessary.
- If the dose is not tapered, there is a greater chance of experiencing side effects.
- For the majority of people, symptoms go away on their own within 2 weeks.
- If side effects are intolerable on dose reduction or stopping, the dose should be increased and subsequently reduced more gradually.

Adults: Paroxetine has been demonstrated to be effective in adults with depressive illness and the CSM advises that the balance of risks and benefits of paroxetine remains positive. However the implications of the new paediatric data on the safety of paroxetine in the adult population remains under close review by the CSM and its Expert Working Group.

Reference: Medicines and Health Care Products Regulatory Agency, 10 June 2003 (MHRA). http://www.mca.gov.uik

Aprepitant for nausea and vomiting during chemotherapy

United States of America — The Food and Drug Administration (FDA) has announced the approval of a new drug called aprepitant (Emend®), to be used in combination with other anti-nausea and anti-vomiting drugs for prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of chemotherapy known to cause these problems, including high-dose cisplatin.

Aprepitant is the first FDA approved treatment that prevents the delayed nausea and vomiting symptoms that many patients experience greater than 24 hours after receiving chemotherapy. Chemotherapy is often very distressing for cancer patients due to severe nausea and vomiting. These symptoms can be severely debilitating, often resulting in patients' refusing further courses of chemotherapy or in serious limitations on their lifestyle.

In 2002, the American Cancer Society found that over 1 284 900 new cases of cancer were diagnosed in the United States. Aprepitant can reduce nausea associated with chemotherapy treatments used to treat cancers such as lung cancer, head and neck cancer, and some female cancers. It is part of a three-drug therapy that works with other drugs to treat nausea and vomiting in a new way by blocking NK1 receptors in the brain. Approval was based on the results of two well-controlled studies that included over 1000 cancer patients receiving chemotherapy.

Aprepitant may interact with other drugs, including some chemotherapies, birth control pills, and blood thinners. It may reduce the effectiveness of oral contraceptives and women should use an alternative form of birth control. Patients being treated with blood thinners such as warfarin and Coumadin® will need to have their blood tested after the completion of their 3-day regimen with each chemotherapy cycle to see if dosage needs to be changed.

Reference; *FDA News* , P02–23 (2003).

Agalsidase beta approved

United States of America — The Food and Drug Administration (FDA) has approved the first treatment for patients with Fabry Disease, a serious metabolic genetic disorder affecting approximately one in 40 000 males. While it is believed that fewer females suffer the most serious consequences of the disease, they can be similarly and seriously affected as well. Because of a deficiency in an enzyme, alpha-galactosidase A, Fabry Disease causes certain fats to accumulate in the blood vessels over many years, leading to the involvement of various tissues and organs of the body, including the kidneys and the heart, which can then cause organ failure. As a result, patients with Fabry Disease often have to cope with significant pain and disability and typically have a shortened life span.

The new product, agalsidase beta (Fabrazyme®), is a version of the human form of the natural enzyme produced by recombinant DNA technology. It is given intravenously. This replacement of the missing enzyme reduces a particular type of lipid (fat) accumulation in many types of cells, including blood vessels in the kidney and other organs. It is believed likely that this reduction of fat deposition will prevent the development of life-threatening organ damage and have a positive health effect on patients.

Agalsidase beta was approved under an accelerated or early approval mechanism. Biopsies of the cells lining the blood vessels within the kidney

and other organs in patients with Fabry Disease have shown significant clearance of lipid deposits after agalsidase beta treatment.

The manufacturer will continue to conduct an ongoing randomized placebo-controlled trial to verify agalsidase beta 's benefit to patients and assess the drug's effects on the progression of kidney and heart disease and the incidence of strokes. In addition, the availability of information to determine long-term effects of treatment with agalsidase beta will be assured. A patient registry has been established to follow the long-term progress of patients who have been treated and to better understand Fabry disease and evaluate the long-term effects of treatment. Enrolment in this registry is voluntary.

FDA and the manufacturer are also discussing a variety of novel statistical approaches to analyse data and better assess the effectiveness of the treatment and include measures such as within-patient analyses of trends in creatinine levels (a measure of kidney function) on placebo and on Fabrazyme, and modelling utilizing historical information from matched patients.

In clinical studies, the main safety concern was infusion reactions, some of which were severe. These include fever, chest tightness, blood pressure changes, abdominal pain and headache. Most patients also develop antibodies to the product and some patients who experience allergic reactions may need to be further evaluated. Because of the potential for these severe reactions, appropriate medical observation and support should be available when agalsidase beta is administered.

Reference: *FDA News*, P03–32 (2003).

Imatinib mesylate approved for paediatric leukaemia

United States of America — The Food and Drug Administration (FDA) has announced the approval of imatinib mesylate (Gleevec ®) tablets for the treatment of paediatric patients with Philadelphia chromosome positive (Ph+) chronic myeloid leukaemia (CML) in chronic phase — a rare, life-threatening form of cancer that accounts for approximately two percent of all leukaemia in children.

Imatinib mesylate is indicated for children whose disease has recurred after stem-cell transplant or who are resistant to interferon alpha therapy. This drug was approved under the accelerated approval programme. As of yet, there are no controlled trials demonstrating clinical benefit, such as improvement in disease-related symptoms or increased survival. Subsequent studies after approval will be conducted to confirm that the drug has improved survival or other clinical benefits in paediatric patients.

In addition to its original approved indication for CML refractory to other treatments in adults, and expansion to use as a first line treatment for CML, imatinib mesylate was also previously granted accelerated approval for the treatment of gastrointestinal stromal cancer in February 2002. Accelerated approval for paediatric use is based on extrapolation of results from adults with CML together with good responses in a small number of children. As a condition of approval, the manufacturer has agreed to conduct paediatric studies after approval to gain greater insight into the drug's use in children.

The most frequently reported adverse events reported with the use of imatinib mesylate are nausea, vomiting, diarrhoea, edema (sometimes severe), and muscle cramps. A considerable reduction in white blood cells and platelets was also reported.

Reference: *FDA News*, P03–43 (2003).

Drug-eluting stent for clogged heart arteries

United States of America — The Food and Drug Administration (FDA) has approved the first drug-eluting stent for angioplasty procedures to open clogged coronary arteries. In most cases, a stent is left permanently in the artery to keep the vessel open after angioplasty. The new stent slowly releases a drug, and has been shown in clinical studies to significantly reduce the rate of re-blockage that occurs with existing stents.

Drug-eluting stents may have a substantial impact on the occurrence of re-blockages for patients with heart disease. Each year 800 000 angioplasty procedures are performed in the United States to open clogged coronary arteries. In approximately 15%–30% of patients, the artery becomes clogged again (a condition called restenosis) within a year, and it must be treated again with a procedure such as angioplasty or bypass surgery.

The product is the Cypher Sirolimus-Eluting Coronary Stent (Cypher Stent)®. It is a tiny metal mesh tube that is covered with the drug sirolimus. The Cypher stent provides a mechanical scaffold to keep the vessel open while the drug is slowly released from the stent to prevent the build-up of new tissue that re-clogs the artery. In studies conducted by the firm, the stent reduced the rate of restenosis by about two-thirds.

FDA approved the stent based on a review of laboratory and animal tests and two clinical studies of safety and effectiveness conducted by the manufacturer, as well as a review of manufacturing procedures for this new combination product. In the SIRIUS study, 1058 patients received either the Cypher Stent® or an uncoated stainless steel stent. The patients in the SIRIUS study had blockages of 15 mm to 30 mm long in arteries that were 2.5 mm to 3.5 mm wide. Results were similar for both types of stents in the weeks immediately following the procedure, but after nine months the patients who received the drug-eluting stent had a significantly lower rate of repeat procedures than patients who received the uncoated stent (4.2% versus 16.8%). In addition, patients treated with the drug-eluting stent had a restenosis rate of 8.9%, compared to 36.3% of patients with the uncoated stent. The combined occurrence of repeat angioplasty, bypass surgery, heart attacks and death was 8.8% for drug-eluting stent patients and 21% for the uncoated stent patients.

The RAVEL study, a smaller study of 238 patients was similar to the SIRIUS study, but evaluated patients with shorter blockage of the coronary artery. That study also showed significant reductions in repeat procedures and restenosis. This smaller study was the basis for the product's approval in Europe, and supported the product's approval in the United States. While the RAVEL study suggested that the Cypher Stent® showed promise, it was not large enough to assess the patients most likely to benefit from the device.

Patients who are allergic to sirolimus or to stainless steel should not receive a Cypher Stent®. Caution is also recommended for people who have had recent cardiac surgery and for women who may be pregnant or who are nursing. Patients who receive the drug-eluting stent will likely need to take certain kinds of anti-platelet drugs for at least several months.

The FDA is requiring the manufacturer to conduct a 2000-patient post-approval study and continue to evaluate patients from ongoing clinical trials to assess the long-term safety and effectiveness and to look for rare adverse events.

Reference: *FDA News*, P03–31 (2003). Accelerated approval for the treatment of gastrointestinal stromal cancer in February, 2002.

Pegvisomant for acromegaly

United States of America — The Food and Drug Administration (FDA) has approved pegvisomant (Somavert®) for the treatment of acromegaly, a potentially life threatening disease triggered by an excess of growth hormone. Pegvisomant, the first in a new class of drugs called growth hormone receptor antagonists, is approved for patients who have had an inadequate response to existing therapies.

Acromegaly causes headaches, profuse sweating, swelling, joint disorders, changes in facial features, and enlarged hands, feet and jaw. If untreated, patients with acromegaly often have a shortened life span because of heart and respiratory diseases, diabetes mellitus and cancer. In clinical studies, the most commonly reported side effects with pegvisomant were injection site reactions, sweating, headache and fatigue. Patients should have tests to monitor their liver function during the first six months of therapy with pegvisomant.

Reference: *FDA News*, P03–22 (2003).

Aspects of Quality Assurance

Fixed-combination medicines: an Australian perspective

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In Australia, the Therapeutic Goods Act 1989 provides for a national system of controls for the regulation of therapeutic goods, including both medical products and medical devices. The Therapeutic Goods Act 1989 is administered by the Therapeutic Goods Administration (TGA), a Division of the Department of Health and Ageing of the Australian Government. The TGA is located in Canberra and undertakes a number of activities in administering the regulation of therapeutic goods in Australia. These include pre-market assessment of products, pharmacovigilance, enforcement of standards, enforcement of good manufacturing practice (GMP) requirements, manufacturing licensing and maintenance of a register of approved goods.

In carrying out its duties, the TGA adopts a risk-based assessment approach whereby higher-risk medicines, such as those available on prescription, are fully assessed for quality, safety and efficacy pre-market whereas goods considered to pose a low risk have an emphasis on quality and safety before market entry. Examples of low-risk goods include simple vitamin preparations where it is considered that there is not only an inherent low risk from use of the product but also that claims made about benefits of the product are restricted.

In undertaking the assessment of higher-risk medical products, the TGA adopts international guidance documents where possible. This is done to reduce the compliance costs for the industry and to ensure that international best-practice is followed. In particular, since 1992, the TGA has adopted many European Guidelines and International Conference on Harmonization (ICH) Guidelines. TGA's policy on fixed-combination medicinal products is strongly influenced by the European approach to fixed-combination medical products as contained in EudraLex – the rules governing medicinal products in the European Union — Rules 1998 (3c) 3a 10a, pp.175–180.

Fixed-combination medicinal products cover the entire spectrum of medicinal products — though often people tend to think of fixed-combinations as a relatively new introduction. Many traditional formulations, for example multi-vitamins and minerals or the oral contraceptive pill, are in fact, fixed-combination medicinal products. Therefore, there should be a wealth of experience around the world in the use of these products. Nevertheless, there are some important factors to consider when assessing a new fixed-combination medicinal product.

Firstly, it is important to assess the potential advantages of fixed-combination medicinal products. These include an improvement in effectiveness of treatment, safety profile and simplification of therapy. There may also be cost advantages if a fixed-combination product can be manufactured and sold for less than a combination of individual products.

But there are also potential disadvantages. As the dosage is fixed in the combination, the doses of the individual substances cannot be easily adjusted to meet the needs of the individual patient. There may be unnecessary exposure to the second medicine for some patients and the combination may lead to additional adverse events. It is also not always true that costs will be reduced by a second agent if use of a single agent alone could have satisfactorily treated the patient.

It is therefore important that when considering a new fixed-combination medicine, there be a justification as to why that particular fixed-combination is acceptable and appropriate. This justification needs to address issues relating to the benefit and risk of the combination. Possible justifications for fixed-combination products could be that it is more effective. Examples of this

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could include better control than from either medicine used alone at the same or higher dose.

Combinations should also be rational so that medicines complement each other in their actions or potentiate the beneficial effects of each other. It is also important that combinations be rational in terms of the condition to be treated.

Commonly used fixed-combination products include widely-used cold and flu' remedies. These often consist of an analgesic, anti-pyretic, a decongestant agent and perhaps an anti-histamine. The combination is logical for self-medication for many patients as the symptoms that are to be treated in these self-limiting conditions often co-exist. In contrast, if a product was to be developed that simultaneously treated the symptoms of a respiratory tract infection and managed diabetes, the combination would not be rational. Although there will be a small sub-set of patients with diabetes at any point in time who also have the symptoms of an upper respiratory tract infection, the majority of people with an upper respiratory tract infection are not those with diabetes. The addition of the other treatment would lead to an unnecessary exposure to a medicine.

Justifications may also be based on grounds of safety. There may be reduced side-effects if two medicines are used at lower doses than one medicine used alone at a higher dose. This is an entirely acceptable reason for using a fixed-combination. It may also be that fixed-combinations can lead to a reduction in adverse effects if one of the drugs in the combination reduces the adverse effects of the other medicine. Although, ideally, we would wish to see patients treated with medicines with no adverse effects, this is not always possible. Where alternative treatments with less adverse effects cannot be found, a combination that leads to a reduction in adverse effects may be important.

Probably the weakest justification on grounds for a fixed-combination is improved compliance. This is often cited as a rationale and is intuitively plausible but rarely in the experience of the Australian regulator do submissions contain data to support claims of improved compliance. It is certain that some patients are compliant with therapies but it is not known if someone who complies with taking several medicines every few hours will be less or more compliant if they only have to take the medicines once or twice a day. Similarly, if someone is not compliant when given clear instructions on taking medicines every four hours, it is not certain that their compliance will increase because they are required to take a combination medicine daily.

Development of fixed-combination medicinal products

In developing a fixed-combination product, it is important that the sponsor addresses certain criteria and the regulatory agency assesses the combination to ensure that these criteria are met. As always, the quality of the pharmaceutical product must be acceptable. It is also important that there be a logical combination of medicines in relation to pharmaceutics. As previously discussed, a combination of therapies for conditions that rarely co-exist or that have no obvious connection to each other is not rational or desirable.

The pharmacodynamics and pharmacokinetics of the drugs used in the combination must be fully explored as part of development. Indeed, an interaction between the two products may in itself be a rationale for the combination. It is important to establish the role of each medicine, alone and in combination. Interactions can and do occur within fixed combinations and with other medicines used commonly in the target patient group. The potential effects on the pharmacokinetics of both medicines must be investigated and understood before the product can be approved for marketing.

Efficacy

The indication for which the product is intended to be approved should be rational. Ideally, the ingredients of the product should be used in the same conditions, but use in usually concurrent conditions may be acceptable as discussed above. Conservatively, it has generally been recommended by many regulatory agencies that combination products be used as add-ons to single therapy. This would seem to be sensible as using a single therapy to control a condition is less likely to lead to over-prescribing, unnecessary adverse events and increased costs. However, there may be circumstances in which it is possible to demonstrate optimization of treatment with a combination as first-line treatment. These would be circumstances where a condition is important and serious, where either drug used singly at higher doses had significant adverse events or costs, and it was demonstrated that there was a low rate of success of treatment with one product alone.

The amount of information that the regulatory agency should require to demonstrate efficacy for a fixed-combination will vary. If two products have a long history of safe and effective use in combination, then it may be possible for documentation to be substantially bibliographic or based on a significantly reduced data set, relying on previous reviews of the individual products and published literature and other experience of use in combination. This would occur, for example, if two products were commonly taken at the same time each day and were used in the same patient group. Nevertheless, even given this circumstance, it is important that there be evidence of effectiveness. If effectiveness for the products used in combination is not greater that the effectiveness for one of the products used alone, then it is important this be identified for there is little additional benefit to be gained from such a fixed-combination and it is not desirable that it be approved for registration.

If a new combination of medicines is proposed, then it is important that a more substantial product development programme be undertaken and that similar information relating to the combination at varying doses in the intended patient group be generated as if the product was a new single entity. It is particularly important that the dose be well established. A fixed-combination allows the opportunity for the dose to be minimized and adverse events reduced. In order for this to happen, it is important that the minimally effective dose of the medicines, used alone and in combination, be established.

It is also important that the maximal dose response information is available. This is important because, if a minor increase in dose of one component of the fixed-combination leads to an improved dose response, then development of a fixed-combination using marginally lower dose of that substance may not be a rational development. It is also important, when comparing a fixed combination, to look at effective doses of either medicine alone and other reference therapies used for the treatment of the condition. It may also be important to compare the fixed-combination with placebo in some cases.

Safety

As for any product, it is important that there be as much evidence as possible about performance in terms of safety of the medicine. For this reason, there should be some animal experience for the use of both medicines, singly and in combination, and human data should be available from use of the medicines, both singly and in combination. Again, if the products have a long history of concomitant use, documentation may be abridged.

Summary

Fixed-combination products can offer significant benefits to consumers and health systems. It is important in assessing the place of a fixed-combination product to consider the justification of the combination, as well as information on it's quality, safety and effectiveness in patient management.

Recent Publications and Sources of Information

International Travel & Health

The latest edition of International Travel and Health has been completely redesigned to reflect better knowledge about the risks to which travellers are exposed and the precautions needed to protect their health. With new material and a revised structure, the book offers guidance on the full range of health risks likely to be encountered at specific destinations and associated with different types of travel. Information is intended to help the medical profession be fully alert to potential risks and provide appropriate advice, whether concerning recommended vaccinations, protections against insects and other disease vectors, or safety in different environmental settings.

Details cover effectiveness of mosquito nets and advice on when and how to treat diarrhoea. The book concludes with a country by country list of required vaccinations, togehter with pertinent information on the malaria situation for every country or territory of the world.

International Travel and Health 2003, ISBN 92 4 258028 7. Available from: Marketing and Dissemination, World Health organization, 1211 Geneva 27, Switzerland. e-mail: bookorders@who.int

Affordability of medicines

In developing countries, most medicines are paid for out-of-pocket by individual patients rather than through social security systems. High prices are therefore a barrier to use of medicines and health products. Too little is known about the prices that people pay for medicines in poor and developing countries.

Medicines Prices: a new approach to Measurement, the accompanying workbook and database provide a new approach to measuring the price of medicines in response to the need for a standard approach to measuring medicines prices. The work proposed can be reliably carried out by academic centres, consumer groups, or government departments.

A survey is based on a methodology to evaluate thirty key medicines and results raise questions about the relationship between procurement prices and the final price to patients and affordability. The impact of policy changes on the price of medicines can also be assessed using this tool.

Medicines prices: a new approach to measurement. 2003 edition. Working draft for field testing and revision. Available from: Marketing and Dissemination, World Health organization, 1211 Geneva 27, Switzerland. e-mail: bookorders@who.int

Drugs and money

Society attaches great importance to better health, and has witnessed a rising demand for health care. The rapid growth of expenditure on medicines is of particular concern and it has attracted considerable political attention, partly because it seems most amenable to economic control.

The World Health Organization first launched a study on “Drugs and Money” in 1983, on the feasibility of measures to control the growth of expenditure on medicines. This culminated in a critical overview of the effectiveness of older cost-containment schemes while also paying attention to innovative ventures. The report was widely used and repeatedly updated, and this is now its seventh edition.

This latest edition provides policy-makers and regulators with a compact and practical review of the various approaches used to contain the costs of pharmaceutical services and drug treatment. The true art of good housekeeping in this field is clearly to ensure that drugs continue to benefit society, while eliminating every form of waste of public funds. This book also addresses issues concerning the organization, standards and delivery of health care. Unlike earlier editions of Drugs and money, this volume also devotes considerable attention to the special problems of developing countries and those where the economy is currently in transition.

Drugs and money. Prices, affordability and cost containment. Available from: Marketing and Dissemination, World Health organization, 1211 Geneva 27, Switzerland. e-mail: bookorders@who.int

ABPI launches online clinical trials register

An online register of industry-sponsored clinical trials has been launched by the Association of the British Pharmaceutical Industry (ABPI). So far, the register includes details of 65 trials sponsored by five companies.

Since 2001, the ABPI has encouraged member companies to register clinical trials involving United Kingdom patients that form part of a licensing application for a new medicine. Participating countries are asked to register their phase III trials within three months of any product receiving its first licence in a major market. Ongoing trials can also be included.

Trial information listed on the website includes details of the sponsor company, design and methodology used, trial intervention method, planned and actual sample size, start and end date, and whether trial data have been published. Trial results are not given.

The website can be accessed through PJ Online at http://www.pjonline.com/links on a read-only basis.

Reference: *The Pharmaceutical Journal*, **270**: 640 (2003).

Expert Committee on Drug Dependence Report

The Thirty-third report presents recommendations from the Expert Committee on Drug Dependence which is responsible for reviewing information on dependence-producing drugs and assessing the need for international control by the UN Commission on Narcotic Drugs. It is important to balance the need for preventing diversion of therapeutic substances with abuse potential against the need to ensure access for therapeutic use. WHO has developed a formal procedure for its review of dependence-producing psychoactive substances which is described in the first part of the report.

This is followed by a critical review of five psychoactive substances (amfepramone, amineptine, buprenorphine, delta-9-tetrahydrocannabinol and tramadol). The report also discusses the substances that were pre-reviewed by the Committee, four of which (ketamine, zopiclone, butorphanol and khat) were recommended for critical review at a future meeting. The final section discusses the problems of the terminology used in reporting abuse-related adverse drug reactions and describes how confusion affects the reporting of adverse effects using as an example the selective serotonin reuptake inhibitors (SSRIs).

WHO Expert Committee on Drug Dependence. *Thirty-third report. WHO Technical Report Series, No. 915 (2003). Available from: Marketing and Dissemination, World Health organization, 1211 Geneva 27, Switzerland. e-mail: bookorders@who.int*

Biomedical research in human subjects

The Council for International Organizations of Medical Sciences (CIOMS) has published the revised International Ethical Guidelines for Biomedical Research Involving Human Subjects. This is the third revision of the guidelines, first issued in 1982, and consists of 21 core guidelines with commentaries. Appendices include the World Medical Association's Declaration of Helsinki.

The scope of the guidelines reflects the changes, advances and controversies that have characterized biomedical research ethics recently. The Guidelines are also designed to be of use in defining national policies on ethics, applying ethical standards and establishing or improving ethical review. A particular need is to consider the implications for research of the specific conditions and needs of different communities and countries.

International Ethical Guidelines for Biomedical Research Involving Human Subjects. Available from: Marketing and Dissemination, World Health organization, 1211 Geneva 27, Switzerland. e-mail: bookorders@who.int