

WHO Drug Information

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Announcement

**The 13th International Conference
of Drug Regulatory Authorities (ICDRA)
will be hosted by the Swiss Medicines
Agency SWISSMEDIC in collaboration with
the World Health Organization.**

**The ICDRA will take place
in Berne, Switzerland
from 16 to 19 September 2008.**

**Updated information will be provided regularly at:
<http://www.icdra.ch>**

or

<http://www.who.int/medicines/icdra/en/index/html>

Medicines for Tuberculosis

Emergence of extensively drug-resistant tuberculosis

Tuberculosis (TB) is generally treated with a course of four first-line drugs. However, if misused or mismanaged, resistance can develop and multidrug-resistant TB has emerged as a serious threat to the success of treatment programmes. Multidrug-resistant TB requires the use of second-line drugs that are less effective, more toxic, and costlier than the first-line isoniazid- and rifampicin-based regimens. With 425 000 new cases of drug resistant TB globally each year, resistance to drugs is a problem that is growing at a rapid pace.

Earlier this year, a WHO/US Centers for Disease Control prevention study was published documenting for the first time cases of tuberculosis that are extensively resistant to current drug treatments. Extensively drug-resistant (XDR)TB was identified in all regions of the world. Results of the survey showed that during the period 2000—2004, 20% of TB isolates were multidrug-resistant and 2% were extensively drug-resistant (XDR).

XDR TB could cause a future epidemic of virtually untreatable TB. Concerns about the emergence of XDR-TB have been heightened by reports and studies of high mortality rates in HIV-positive people with XDR-TB. This has led to warnings that XDR-TB could seriously threaten the progress being made in countries on TB control and the scaling up of universal access to HIV treatment and prevention.

New anti-TB drug regimens and better diagnostic tests are urgently needed for effective detection and treatment of drug-resistant TB. Using standard drugs to treat XDR-TB without knowing whether there is drug resistance could effectively condemn a patient to death. The emergence of XDR TB, coupled with increased use of second-line drugs, suggests that urgent measures are needed to establish population-based surveillance for resistance and to plan public health responses.

WHO Global Task Force on XDR-TB launched

At its first meeting in October 2006, a WHO Global Task Force outlined a series of measures that countries must implement to effectively combat XDR-TB. The Task Force has acted to establish teams that can respond to requests for technical assistance and be deployed at short notice to risk areas worldwide.

Along with a call for countries to strengthen TB control, it was agreed that control

of XDR-TB will not be possible without close coordination between all those concerned and, in particular, with HIV programmes. The Task Force also provided recommendations on:

- Drug-resistant TB surveillance methods and laboratory capacity measures.
- Implementing infection control measures to protect patients, health care workers and visitors (particularly those who are HIV infected).

- Access to second-line anti-TB and antiretroviral drugs for countries; communication and information-sharing strategies related to XDR-TB prevention, control, and treatment including co-management with antiretroviral therapy.
- Research and development of new TB drugs, vaccines and diagnostic tests.
- Management of XDR-TB suspects in high and low HIV prevalence settings.
- Accelerating access to rapid tests for rifampicin resistance, to improve case detection of all patients suspected of multidrug-resistant TB (MDR-TB) so that they can be given treatment that is as effective as possible. Rapid diagnosis is potentially life saving to those who are HIV positive.

Task Force members continue to coordinate with national and international partners involved in TB and HIV prevention, care and treatment to take the recommendations forward. They have also developed a plan to identify resources required to implement outcomes and accelerate the overall emergency response. The Task Force also recommends that national TB Programme priorities should focus on:

1. Adherence to WHO Guidelines for Programmatic Management of Drug Resistant TB.
2. Improve MDR-TB management conditions.
3. Enable access to all MDR-TB second-line drugs, under proper conditions.
4. Ensure all patients with HIV are adequately treated for TB and started on appropriate antiretroviral therapy.
5. Infection control and protection of health care workers with emphasis on high HIV prevalence settings.

6. Accelerate and widen implementation of recommended infection control measures in health care settings and other risk areas in order to reduce the ongoing transmission of drug-resistant TB, especially among those who are HIV positive.

The laboratory definition of XDR-TB was confirmed as: resistance to at least rifampicin and isoniazid from among the first line anti-TB drugs in addition to resistance to any fluoroquinolone, and to at least one of three injectable second-line anti-TB drugs used in TB treatment (capreomycin, kanamycin, and amikacin).

Future meetings are also planned on XDR-TB, including development of urgently needed new diagnostics, drugs and vaccines, and implications of antiretroviral therapy for HIV patients.

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Development of new drugs for tuberculosis

An analysis of the current drug pipeline for tuberculosis drugs has been published in a recent report by Médecins sans Frontières (MSF)* in support of its Campaign for Access to Essential Medicines. The analysis shows that greater investment is required to respond to extensively drug-resistant (XDR) TB emergence and

* The complete report "Development of new drugs for TB chemotherapy" is available at <http://www.accessmed-msf.org/documents/TBPipeline.pdf>

newer drugs will need to be available to patients as soon as possible, with accelerated development of those already in clinical trials.

Drugs making up the standard TB treatment regimen were developed in the 1950s and 1960s and the most commonly used TB test was developed over a century ago — it manages to detect TB in only about half of cases. In addition, existing TB drugs and tests are even less adapted for use in people who also have HIV/AIDS.

MSF considers that to respond to XDR-TB emergence, WHO will need to get newer drugs to patients as soon as possible by working with regulatory agencies and pharmaceutical companies to ensure fast-track clinical development and availability of new drugs under compassionate use. WHO will also need to promote development of more easy-to-use tests and urge major investment into research and development to ensure the availability of newer drugs that can shorten and improve treatment.

Current drug pipeline for tuberculosis chemotherapy

With approximately 9 million people developing active tuberculosis (TB) every year and 1.7 million deaths annually, TB is far from under control. Human immunodeficiency virus infection dramatically increases the risk of developing active tuberculosis and is driving the TB epidemic in Africa. HIV renders tuberculosis more difficult to diagnose due to higher incidence of sputum negative disease, and to treat due to interactions and side-effects.

The increasing spread of multidrug-resistant TB (MDR-TB) and the recalci-

trant nature of persistent infections pose additional challenges to treatment with currently available anti-TB drugs. The situation is exacerbated by the increasing emergence of extensively drug-resistant (XDR) TB.

The Global Alliance for TB Drug Development (TB Alliance)* has played a critical role in changing the TB research and development landscape and is associated with approximately half of all compounds or projects aimed to identify candidate compounds in development. The main criteria established by the TB Alliance to select drug candidates for further development are: shortening of the current treatment regimen, activity against MDR-TB, and lack of interactions with anti-retroviral drugs.

Among the major advances in basic research, molecular and genetic tools have become available for *Mycobacterium tuberculosis* and include targeted mutagenesis, array-based analysis of mutant libraries, techniques for conditional gene silencing, and global gene expression profiling. This has led to impressive improvements in the knowledge and understanding of the basic biology and physiology of *M. tuberculosis*.

Despite these positive changes there are still problems that need to be tackled. A critical question today is whether progress is sufficient to bring improved treatment to patients in the next few years. Most importantly, financial support will need to increase to ensure that any promising new compounds reach clinical development and trial. There will also need to be a sufficient number of promising compounds in the TB pipeline for a broadly effective new treatment combination to be developed. Many of the com-

* The non-profit Global Alliance for TB Drug Development comprises representatives of governments, nongovernmental organizations, professional organizations, academia, foundations, and industry. <http://tballiance.org>

pounds currently in the pipeline are either derivatives of existing compounds or they target the same cellular processes as drugs currently in use. Whilst analogues and derivatives are far quicker to develop, they may be subject to cross-resistance, as has been the case with the new rifamycins and quinolones.

Modern technologies and rational approaches to drug design such as creation of genomic libraries of *M. tuberculosis* conditional knock-out mutants for comprehensive target identification and validation, target-based drug discovery, or determination of three dimensional crystal structure of molecular targets, are still weakly implemented.

Even the more promising candidate compounds currently in clinical development were identified serendipitously. There is also an urgent need for rational approaches aimed at tackling the problem of mycobacterial persistence. The adaptations that allow *M. tuberculosis* to persist in the host despite a vigorous adaptive immune response likely contribute to the difficulty in curing TB with current chemotherapy.

If faster progress is to be achieved, then knowledge about *M. tuberculosis* metabolism and physiology needs to be translated into validated targets that can be used for screening of new lead compounds. The TB Alliance is associated with approximately half of all compounds or projects aimed to identify candidate compounds currently being developed. In order to analyse the pipeline, it is useful to group drug candidates currently in two main categories:

- Novel chemical entities.
- Compounds originating from existing families of drugs, where innovative chemistry is used to optimise the compounds.

Novel chemical entities

Diarylquinoline TMC207 (Johnson & Johnson)

Diarylquinoline TMC207 is a promising member of a new class of anti-mycobacterial agents. The target and mechanism of action is different from those of other anti-TB agents implying low probability of cross-resistance with existing TB drugs. This is further suggested by the fact that diarylquinoline TMC207 is able to inhibit bacterial growth when tested on MDR-TB isolates.

This compound has potent early bactericidal activity in the nonestablished infection murine mouse model, matching or exceeding that of isoniazid. Substitution of rifampicin, isoniazid or pyrazinamide with diarylquinoline TMC207, accelerated activity leading to complete culture conversion after 2 months of treatment in some combinations. In particular, diarylquinoline /isoniazid/pyrazinamide and diarylquinoline/rifampicin/pyrazinamide combinations cleared the lungs of TB in mice after 2 months. Diarylquinoline TMC207 is currently in phase IIa clinical trials.

Nitroimidazole PA-824 (Chiron Corp.-TB Alliance)

Nitroimidazole PA-824 is a new nitroimidazole derivative currently being developed by the TB Alliance. After activation by a mechanism dependent on *M. tuberculosis* F420 factor, PA-824 acts mainly by inhibiting the synthesis of cell wall components through molecular targets that are yet to be identified. In vitro, PA-824 showed high activity against drug-sensitive and drug-resistant *M. tuberculosis* strains, indicating that there is no cross-resistance with current TB drugs. Moreover, PA-824 exhibited bactericidal activity against both replicating and static bacteria in vitro. Although PA-824 was significantly more efficient

than isoniazid or moxifloxacin in clearing the infection during the continuation phase, it was not better than that of a rifampicin+isoniazid combination. However, when a 6-month treatment regimen containing PA-824 in combination with rifampicin, isoniazid and pyrazinamide was tested in mice, the PA-824 containing regimens were superior to the standard first line regimen in terms of more rapid reductions of the bacterial burden during treatment and lower rates of relapse after treatment. PA-824 entered phase I clinical trials in June 2005.

Nitroimidazole OPC-67683 (Otsuka Pharmaceuticals, Japan)

Little information about this compound is publicly available. It belongs to a subclass of mycolic acid inhibitors. In vitro, OPC-67683 showed high activity against drug-sensitive as well drug-resistant strains. No cross-resistance with any of the current first-line drugs was observed.

Moreover, OPC-67683 showed strong intracellular activity against H37Rv strain of *M. tuberculosis* residing within human macrophages and type II pneumocytes. When tested in mouse models for chronic tuberculosis, OPC-67683 showed a 6–7 fold higher activity compared to first line drugs isoniazid and rifampicin. No antagonist activity could be observed when OPC-67683 was used in combination with currently used anti-TB drugs in vivo.

Pyrrole LL-3858 (Lupin Limited, India)

Very limited information on the development of pyrroles as antimycobacterial agents is currently available. Pyrrole derivatives were found to be active against standard and drug-sensitive *M. tuberculosis* strains in vitro. Pyrrole derivative LL-3858 showed higher bactericidal activity than isoniazid when administered as monotherapy to infected mice. Pyrrole LL3858 is currently in Phase I clinical trials.

Pleuromutilins (GlaxoSmithKline–TB Alliance Partnership)

The pleuromutilins represent a novel class of antibiotics derived from a natural product. They interfere with protein synthesis by binding to the 23S rRNA. Despite the novelty of this class of compounds, recent studies have shown that cross-resistance might occur among pleuromutilins and oxazolidinones.

Pleuromutilins have been shown to inhibit the growth of *M. tuberculosis* in vitro. The goal of this project is the identification of a pleuromutilin derivative that is active against MDR-TB and allows shortening of the treatment schedule.

Dipiperidine SQ-609 (Sequella Inc.)

Dipiperidine SQ-609 is a novel compound structurally unrelated to existing anti-TB drugs. It kills *M. tuberculosis* by interfering with cell wall biosynthesis (precise mechanism unknown). Antimicrobial activity has been demonstrated in vivo in mouse models.

ATP Synthase Inhibitor FAS20013 (FASgene)

FAS20013 is a novel compound belonging to the class of β -sulphonylcarboxamides. The compound is very effective in killing MDR-TB organisms that are resistant to multiple drugs currently in use. A series of recent laboratory experiments indicates the superior effect of FAS20013 compared to current drugs in terms of its ability to “sterilize” TB lesions and kill latent TB. Therapeutic evaluation of FAS20013 has repeatedly shown its effectiveness in mice, and it appears to have no serious side effects.

Translocase I Inhibitor (Sequella Inc.)

Translocase inhibitors specifically inhibit mycobacterial translocase I, an enzyme required for bacterial cell wall synthesis. Preclinical evaluation of the compounds is planned.

InhA Inhibitors (GlaxoSmithKline–TB Alliance)

InhA, the enoyl reductase enzyme from *M. tuberculosis* catalyses the last step in the fatty acid biosynthesis pathway (FAS II). Frontline anti-tuberculosis drugs such as isoniazid (INH) target this enzyme. Drug resistance to INH results primarily from mutations in KatG, the enzyme that activates INH. Consequently, InhA inhibitors that do not require activation by KatG are attractive candidates for drug discovery. The main purpose for this screen is therefore to bypass the activation step and directly inhibit InhA. A possible limitation is that cross-resistance with isoniazid may occur.

Isocitrate Lyase Inhibitors (GlaxoSmithKline–TB Alliance)

The isocitrate lyase (ICL) enzyme has been shown to be essential for long-term persistence of *M. tuberculosis* in mice, but not required for bacilli viability in normal culture or hypoxic conditions. Inhibition of the two isoforms of isocitrate lyase present in *M. tuberculosis* blocks growth and survival of *M. tuberculosis* bacteria.

The absence of ICL orthologs in mammals should facilitate the development of glyoxylate cycle inhibitors as new drugs for the treatment for tuberculosis. Such a new drug is expected to be able to kill persistent bacteria and therefore have sterilizing activity and shorten treatment time. However, the structure of ICL active site is making the screening for inhibitors particularly lengthy and laborious.

Compounds originating from existing families of drugs

Other promising candidate anti-TB drugs include: Gatifloxacin, Moxifloxacin, Diamine SQ-109, Non-Fluorinated Quinolones, Nitrofuranyl amides, Picolinamide Imidazoles, Thiolactomycin Analogs, Dihydrolipoamide Acyltrans-

ferase Inhibitors, Methyltransferase inhibitors, and Quinolones.

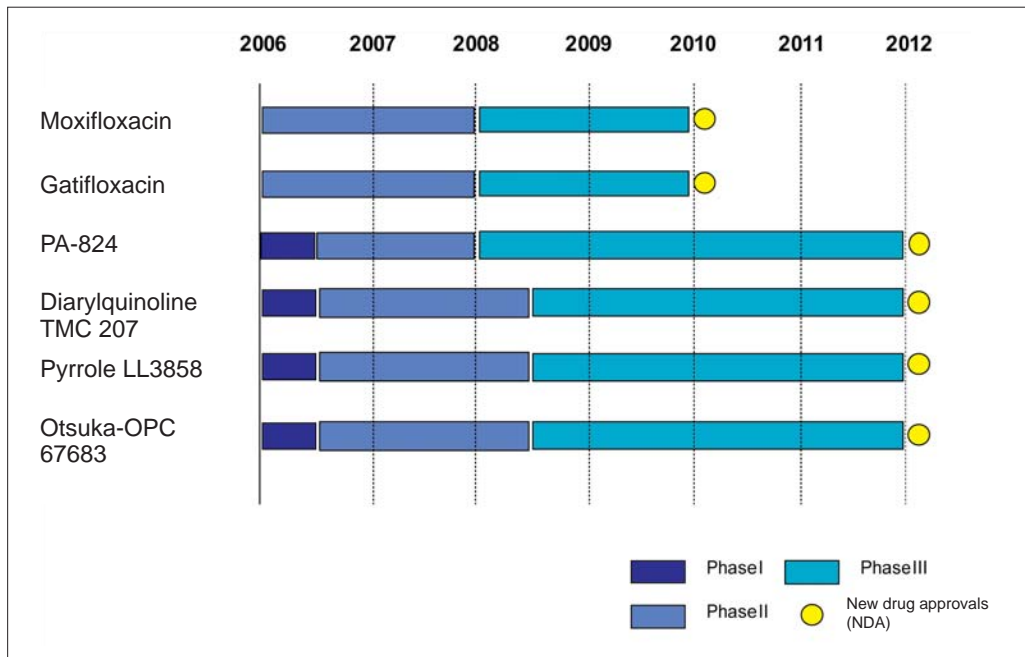
Timeline for development of candidate drugs

Clinical trials to register a TB drug represent a lengthy and expensive process that can take a minimum of six years, generally longer than for other infectious diseases. The greatest challenge in the design of TB clinical trials is in Phase III Trials. These trials are usually large scale, randomized clinical trials designed to show improvement or equivalent efficacy compared to the standard regimen among diseased patients.

Efficacy evaluation requires measurements of relapse rate during a 1–2 year follow-up after completion of the already lengthy 6-month treatment regimen. Relapse rate after chemotherapy is commonly accepted as the endpoint to determine the efficacy of a new therapy and to assess whether a new drug can improve sterilizing activity. Since relapse rates under random clinical trial conditions are often 3% or less, large numbers of patients are needed to demonstrate an improvement in relapse rate. This results in high drug development costs and long delays in introducing new medicines.

Regulatory agencies require that efficacy is demonstrated during phase III trials involving a combination of traditional and surrogate markers for activity. Since the identification of biomarkers could significantly streamline and accelerate clinical development, the TB Alliance has recently established a collaboration with BG Medicine Inc. to identify biomarkers for drug efficacy in TB treatment. Validated surrogate markers of relapse could provide evidence on the efficacy and the sterilising activity of a drug/regimen without requiring large numbers of patients.

Expected timelines towards approval for new candidate TB drugs



The current need for large number of patients recruited for Phase III clinical trials implies the need to conduct trials in countries with high TB incidence rates in order to ensure that a sufficient study population can be obtained. Phase III infrastructure is, in particular, poorly developed and might require additional coordination, regulatory support and specific funding to overcome gaps.

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Safety and Efficacy Issues

Teratogenicity of antiepileptic drugs

Prescribing for women with epilepsy is complicated by the potential teratogenicity of antiepileptic drugs. Current guidelines recommend that the most effective drug should be chosen before conception and prescribed at its lowest effective dose, ideally as monotherapy (1, 2). But which antiepileptic drug is safest in pregnancy? An editorial in the *British Medical Journal* reports on data now available from pregnancy registries set up in the late 1990s (3).

To date, the UK Epilepsy and Pregnancy Registry has recruited more than 3500 women, of whom 72% were given antiepileptic monotherapy. The overall rate of major congenital malformation in women given antiepileptic drugs during pregnancy was 4.2% compared with 3.5% in women with epilepsy who were not given such drugs (4). By three months of age, infants exposed to sodium valproate monotherapy during gestation had the highest frequency of major congenital malformation (6.2%), confirming similar findings from an Australian register (5). Lamotrigine monotherapy was associated with a 3.2% frequency of malformation, but in a multivariate analysis this frequency was not significantly different from that seen with valproate monotherapy. The risk with lamotrigine at doses above 200 mg a day was similar to that of valproate doses of 1000 mg/day. Carbamazepine was associated with the lowest frequency of major congenital malformation (2.2% for monotherapy). Polytherapy with antiepileptic drugs was associated with a significantly higher frequency of major malformation than monotherapy (6% v 3.7%).

The North American Pregnancy Registry found that valproate monotherapy was associated with a 10.7% frequency of major congenital malformation. This represents an increased relative risk of 7.3 compared with a control group from one US teaching hospital's malformation surveillance programme (6). The US registry had previously reported an increased risk of malformation in babies exposed to phenobarbital — an important finding as this antiepileptic drug is still widely used in many countries.

The potential for antiepileptic drugs to cause developmental delay in childhood is even more difficult to measure than major congenital malformation. A study (2) found that valproate monotherapy in pregnancy was associated with decreased verbal IQ when compared with carbamazepine or phenytoin monotherapy, and that this was dose related.

It was also reported that 30% of children exposed to valproate needed special educational support in school, compared with 36% of those exposed to monotherapy with other antiepileptic drugs. Similar results were reported in a Finnish study. A further study has, however, shown adverse neuro-developmental effects in children exposed to a variety of antiepileptic drugs during gestation, not only valproate. The neurodevelopment effects of antiepileptic drugs (NEAD) study is currently investigating behavioural outcomes in children exposed to antiepileptic drugs in pregnancy (www.neuro.mcg.edu/np/NEAD.htm).

It remains to be seen whether any of the newer antiepileptic drugs will prove to be less teratogenic.

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Meningococcal vaccine and Guillain Barré syndrome

United States of America — The Food and Drug Administration (FDA) and Centers for disease Control (CDC) have updated an October 2005 alert to consumers and health care providers regarding reports of Guillain Barré syndrome (GBS) following administration of Meningococcal Conjugate Vaccine A, C, Y, and W135 (Menactra®).

To date, a total of 15 confirmed cases of GBS among individuals 11–19 years of age occurring within six weeks of vaccination with Menactra® have been reported to the Vaccine Adverse Event Reporting System (VAERS). Two additional cases have been confirmed in persons 20 years of age and older. At this time, CDC and FDA cannot determine with certainty whether Menactra® does increase the risk of GBS in persons who receive the vaccine and, if so, to what degree.

In October 2005, reports indicating a possible association between Guillain-Barré Syndrome (GBS) and meningococcal conjugate vaccine (MCV4) (Menactra®) were made to the Vaccine Adverse Event Reporting System (VAERS). GBS is a serious neurologic disorder involving inflammatory demyelination of the peripheral nerves. During March 2005—February 2006, eight confirmed cases had occurred within 6 weeks (i.e., the time window of elevated risk noted for GBS after administration of other vaccines) after MCV4 vaccination. Nine additional GBS cases were reported to VAERS during March—September 2006. Although data suggest a small increased risk for GBS after MCV4 vaccination, the inherent limitations of VAERS and the uncertainty regarding background incidence rates for GBS require that these findings be viewed with caution.

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Panama mystery illness traced to diethylene glycol

Panama — Reports have been received of another incident of diethylene glycol (DEG) poisoning, this time in Panama. By 29 October 2006, a total of 82 persons — including 35 hospitalized and 38 fatal cases — had been affected by acute renal insufficiency syndrome after using suspected products, including topical skin creams and an expectorant syrup without sugar (1). The majority of reports have been of elderly patients. DEG is a highly toxic organic solvent that can cause acute renal failure and death when ingested. In this case, a material labelled as glycerin purportedly contained a mixture of 1% glycerol, 25% DEG and 75% unknown material (1).

This is yet another instance in a continuing litany of DEG poisonings. Although there are a number of high tech methods which can detect contamination or substitution, purity of glycerol and presence of propylene glycol can be tested by a relatively cheap technology such as refractometry (2, 3).

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Imatinib and cardiac dysfunction

Canada — Recent safety reports have been received on significant left ventricular ejection fraction reduction or congestive heart failure and use of imatinib mesylate (Gleevec®). Imatinib mesylate is indicated for the treatment of adult patients with Philadelphia chromosome-positive, chronic myeloid leukemia (CML) and for the treatment of adult patients with unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).

A recently published article in *Nature Medicine* reported ten patients treated with imatinib who developed significant left ventricular ejection fraction reduction and congestive heart failure (CHF). Although several of these individuals had pre-existing conditions including hypertension, diabetes and prior coronary artery disease, and had received other drugs, they were subsequently diagnosed with CHF.

The same article reports an animal study that examined the effects of imatinib mesylate on cardiac cells from the mouse. The authors hypothesize that development of cardiac dysfunction may be related to inhibition of Abl kinase which triggers the stress response in cardiomyocytes and induces cell death. In addition, recently obtained data from a pre-clinical carcinogenicity study of imatinib has demonstrated an incidental finding of cardiomyopathy in rats.

While the frequency of reported cardiac events remains less than 1% in the current prescribing information for imatinib, CHF and left ventricular dysfunction have occasionally been reported. Pending further information on this issue, it is recommended that:

- Any patients with known cardiac disease or risk factors for cardiac failure, should be monitored carefully.
- Any patient with symptoms or signs suggestive of congestive heart failure should receive timely and thorough evaluation and treatment.
- In patients with known underlying heart disease or in elderly patients, a baseline evaluation of left ventricular ejection fraction is recommended prior to initiation of therapy.

Reference: Communication from the licence holder 21 September 2006 on <http://www.hc-sc.gc.ca>

Online reporting of adverse reactions

Canada — Health Canada's MedEffect Web site has been updated to accept online transmittable reports of suspected adverse reactions (ARs) to health products marketed in Canada. Now, in addition to the previous reporting methods, health care professionals and consumers can submit reports of ARs online. Upon the online submission of a report, the system will generate a file that can be printed and stored electronically by the reporter. Information related to the identity of the patient and the reporter of the AR will be protected as per the Access to Information Act and the Privacy Act.

Underreporting of ARs is a well-known global issue. International studies have

estimated that only 1%–10% of all ARs are reported. Health professionals have identified barriers to reporting that relate to the inconvenience and lack of user-friendliness of reporting. The new user-friendly online AR reporting form will make the process more convenient and should contribute to increased AR reporting.

Reference: *Canadian Adverse Reaction Newsletter*. Volume 16, Issue 4, October 2006

SSRI–tricyclic antidepressant interaction

New Zealand — Prescribers are reminded of the potential for interactions to occur when a selective serotonin reuptake inhibitor (SSRI) antidepressant is co-prescribed with a tricyclic antidepressant (TCA). Concurrent use of SSRIs can elevate TCA plasma levels 2–4 fold, with resultant toxicity.

Reported symptoms include constipation, urinary hesitancy, seizures and delirium (1). Serotonin syndrome is another potential consequence of concurrent therapy. While TCAs and SSRIs can separately cause serotonin syndrome due to their serotonergic properties, this risk is increased when they are used together. Serotonin syndrome is a dose-dependent toxic state caused by excess serotonin within the central nervous system and is characterized by mental, autonomic and neuromuscular changes.

Clinical features include confusion, agitation, hyperactivity, sweating, tachycardia, ataxia, hypertonia and tremor. Prompt withdrawal of the suspect medicines and supportive care are key to the treatment of serotonin syndrome (2).

Extracted from Prescriber Update, Volume 27, Number 1, June 2006. at: <http://www.medsafe.govt.nz/pProfs/PUarticles.htm>

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1. Tricyclics, SSRIs and antidepressants. In Stockley IH (Ed). *Stockley's Drug Interactions 6th Edn*. 2003: Great Britain, p.845–850.
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Telithromycin: hepatic events and myasthenia gravis

Canada — Based on information in published case reports and post-market adverse event reports, the Canadian Product Monograph for telithromycin (Ketek®) has been revised to include information on severe and sometimes fatal hepatotoxicity and also includes updated information regarding syncope and use in patients with myasthenia gravis.

Acute liver failure including fulminant hepatitis and hepatic necrosis leading to liver transplant or death have been observed during or immediately after the completion of telithromycin treatment. Exacerbations of myasthenia gravis have led to death or life-threatening acute respiratory failure with a rapid onset, while syncope, usually associated with vagal syndrome, has been reported.

Alterations in hepatic enzymes have been commonly observed in clinical studies with telithromycin. Hepatitis and hepatocellular injury were observed infrequently. Most post-marketing cases of hepatic dysfunction were reversible after discontinuation. However, cases of severe hepatotoxicity, including necrosis, hepatic failure and death have occurred. In some of these cases liver injury occurred after administration of only a few doses of telithromycin and progressed rapidly. The mechanism underlying severe hepatocellular injury is unknown. Severe reactions, in some but not all cases, have been associated with serious underlying diseases or concomi-

tant medications. In light of this safety information, the Product Monograph has been revised to include the following recommendations:

- Telithromycin is contraindicated in patients with a previous history of hepatitis and/or jaundice associated with the use of this drug.
- Telithromycin is contraindicated in patients who are hypersensitive to telithromycin or to any macrolide antibiotic.

Physicians and patients should monitor for symptoms of hepatitis, such as fatigue, malaise, anorexia, nausea, jaundice, bilirubinuria, acholic stools, liver tenderness, hepatomegaly, or pruritus.

Telithromycin is not recommended for patients with myasthenia gravis. Patients should be cautioned about the potential effects of syncope.

Reference: Health Canada Endorsed Important Safety Information on Ketek® (telithromycin). 29 September 2006 at <http://>

BioGlue®: chronic inflammation

Canada — BioGlue® is the commercial name of a surgical adhesive composed of bovine serum albumin (BSA) and glutaraldehyde (1). The glutaraldehyde molecules covalently bond the BSA molecules to each other and, upon application, to tissue proteins at the repair site (2). BioGlue® was originally licensed for sale in Canada in 2000 for use in the repair of acute aortic dissections and pulmonary tissues. In 2003, its indication was expanded to include the repair of most other soft tissues. BioGlue® is indicated for use as an adjunct to standard methods of surgical repair (e.g., sutures, staples, electrocautery and patches) to bond, seal or reinforce soft

tissue (1). It may also be applied alone to seal or reinforce damaged parenchyma when other procedures are ineffective or impractical (1).

Health Canada has received 13 domestic reports of adverse incidents suspected of being associated with BioGlue® in 2004 and 2005. Seven of the reports described events consistent with ongoing inflammatory processes upon reoperation at sites where BioGlue® had been used months earlier. In 4 of the 7 cases, BioGlue® was suspected of contributing to a sterile discharge or persistent infection. In the other 3 cases, foreign-body reactions were reported that required the removal of BioGlue®-containing masses at the surgical site.

Severe, active inflammation surrounding a BioGlue® remnant with multiple granulocytes and histiocytes and a massive foreign-body reaction with numerous multinucleated giant cells has been reported at 3 months after BioGlue® application (3). Intense, focal acute and chronic nongranulomatous inflammation has also been observed at a site where persistent concretions of BioGlue® were identified 2 years after application (4).

Although “inflammatory and immune response” is listed among the possible complications in the device labelling, resorption times are not discussed (1) and additional long-term studies would help to evaluate these effects (2). The medical literature suggests that, even when BioGlue® appears to yield a clear benefit, it should be used sparingly and its toxic potential should be considered (2, 4).

Extracted from Canadian Adverse Reaction Newsletter. Volume 16, Issue 4, October 2006

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2. Furst W, Banerjee A. Release of glutaraldehyde from an albumin-glutaraldehyde tissue adhesive causes significant in vitro and in vivo toxicity. *Ann Thorac Surg* 2005;**79**(5):1522-9.

3. Erasmi AW, Sievers HH, Wolschlagel C. Inflammatory response after BioGlue application. *Ann Thorac Surg* 2002;**73**(3):1025-6.

4. Ngaage DL, Edwards WD, Bell MR, et al. A cautionary note regarding long-term sequelae of biologic glue. *J Thorac Cardiovasc Surg* 2005;**129**(4):937-8.

Beware the triple whammy!

Australia — The Australian Adverse Drug Reactions Committee (ADRAC) has previously warned prescribers about the ‘triple whammy’ — a combination of an ACE inhibitor (ACEI) or an angiotensin II receptor antagonist (A2RA), a diuretic and an NSAID (including a COX-2 selective NSAID), which may predispose vulnerable patients to renal failure (1–3). Risk factors include advanced age, pre-existing renal impairment and dehydration. In 2005, ADRAC received 21 reports of renal failure in patients who were exposed to the triple whammy. In a number of cases, precipitating factors included an acute illness, dehydration, digoxin toxicity or the recent addition of an NSAID to a patient already on an ACEI or an A2RA and a diuretic.

The National Prescribing Service (NPS) has recently released Indicators of Quality Prescribing in Australian General Practice: a manual for users, available from the NPS website. One of the process indicators is entitled Good prescribing (avoiding the ‘triple whammy’) and reinforces the message that risk of the triple whammy should be avoided if possible and extreme caution should be taken with ACEIs or A2RAs and NSAIDs in patients with renal impairment. There are now many combination products available that contain both an ACEI or an A2RA and a diuretic.

ADRAC advises that prescribers avoid the triple whammy wherever possible. However, if these drugs are necessary, prescribers should be alert for situations such as illness, dehydration or initiation of an NSAID, which may predispose patients on this combination to renal failure, and advise patients to seek medical advice during such episodes.

Extracted from Australian Adverse Drug Reactions Bulletin, Volume 25, Number 5, October 2006.

References

1. ADRAC, Thomas M. Diuretics, ACE inhibitors and NSAIDs - the triple whammy. *MJA* 2000; **172**: 184-5.
2. Boyd IW, Mathew TH, Thomas MC. COX-2 inhibitors and renal failure: the triple whammy revisited. *MJA* 2000; **173**: 274 (corr. *MJA* 2000; **173**: 504).
3. ADRAC. ACE inhibitor, diuretic and NSAID: a dangerous combination. *Aust Adv Drug React Bull* 2003; **22**: 14-15.

Colchicine: safe use is critical

New Zealand — Colchicine in overdose is extremely toxic and has resulted in fatalities. Prescribers are reminded that colchicine is now indicated as second-line therapy in the treatment of acute gout, after nonsteroidal anti-inflammatory drugs. Corticosteroids are recommended where both are contraindicated (1).

Due to the risk of dose-related serious adverse effects, the use of high doses of colchicine to treat acute gout is no longer appropriate, especially in elderly patients, patients with impaired hepatic or renal function, and patients who weigh less than 50 kg. The dosing interval for colchicine has been increased from 2–3 hourly to six hourly. For otherwise healthy adults the maximum dose of colchicine in the first 24 hours is 2.5 mg and the total dose given in an acute attack should not exceed 6 mg over four days. Further-

more, it is no longer considered safe or appropriate to continue dosing until gastrointestinal adverse effects occur (1).

Patients should be warned of the symptoms of colchicine toxicity and advised to immediately discontinue therapy and see their doctor if symptoms occur.

Extracted from Prescriber Update, Volume 27, Number 1, June 2006. at: <http://www.medsafe.govt.nz/pProfs/PUarticles.htm>

Reference

1. Medsafe Pharmacovigilance Team. Colchicine: Lower doses for greater safety. *Prescriber Update* 2005; **26**(2):26-27. <http://www.medsafe.govt.nz/profs/PUArticles/colchdose.htm>

Nitrofurantoin: monitor lung function in long-term use

New Zealand — An earlier article in *Prescriber Update* reported a case of fatal interstitial lung disease resulting from long-term nitrofurantoin therapy (1). The Centre for Adverse Reactions Monitoring continues to receive reports of acute and chronic pulmonary adverse reactions associated with nitrofurantoin. Acute pulmonary reactions typically have hypersensitivity-type features and occur 1–2 weeks after initiation of nitrofurantoin. Chronic pulmonary reactions mainly involve older persons, are often insidious in onset and associated with therapy of six months or longer. Interstitial lung disease and pulmonary fibrosis may develop so it is important to avoid any delay in the recognition of nitrofurantoin-induced lung changes.

The pulmonary function of patients undergoing prolonged nitrofurantoin therapy should be monitored. This involves careful vigilance for early features of emerging pulmonary toxicity which may be evidenced by cough or shortness of breath, indicating the need for prompt

withdrawal and further investigation including chest x-ray and spirometry. Patients should be informed of the warning symptoms and encouraged to report these early. Patients who have experienced pulmonary toxicity with nitrofurantoin should not be re-exposed.

Extracted from Prescriber Update, Volume 27, Number 1, June 2006. at: <http://www.medsafe.govt.nz/pProfs/PUarticles.htm>

Reference

1. Tatley M. Pulmonary reactions with nitrofurantoin. *Prescriber Update* 2002;**23**(2):24-25. www.medsafe.govt.nz/profs/PUarticles/nitrofurant.htm

Proton pump inhibitors and interstitial nephritis

New Zealand — Acute renal impairment caused by interstitial nephritis is a recognized complication of treatment with omeprazole. Presenting symptoms may be non-specific and include malaise, fever, nausea, lethargy, weight loss, rash and eosinophilia. Patients known to be taking omeprazole who exhibit these symptoms should undergo urine microscopy and assessment of renal function. If either or both are abnormal, omeprazole should be withdrawn pending nephrology assessment (1). Interstitial nephritis should also be considered if there is an unexpected rise in serum creatinine.

Since publishing information about omeprazole induced interstitial nephritis in 2000 (1), there have been 21 further cases reported to the Centre for Adverse Reactions Monitoring; nine were reported in 2005 alone. Interstitial nephritis has also been reported with pantoprazole (2) and lansoprazole (3); the Centre for Adverse Reactions Monitoring has received three such reports for pantoprazole. This reaction is thought to be rare but proton pump inhibitors are now believed to be the commonest cause of

interstitial nephritis in the Auckland region, perhaps due to their widespread use (4). This suggests that prescribers should be vigilant for this adverse reaction when using omeprazole or other proton pump inhibitors.

Extracted from Prescriber Update, Volume 27, Number 1, June 2006. at: <http://www.medsafe.govt.nz/pProfs/PUarticles.htm>

References

1. Savage R. Omeprazole-induced interstitial nephritis. *Prescriber Update* 2001; No.20 (Feb):11-13. www.medsafe.govt.nz/profs/PUarticles/omeprazole.htm

2. Pfizer New Zealand Ltd. Somac (pantoprazole) tablets data sheet 4 April 2005. www.medsafe.govt.nz/profs/Datasheet/s/somactab.htm

3. Wyeth (NZ) Limited. Zoton (lansoprazole) capsules data sheet 17 May 2002. www.medsafe.govt.nz/profs/Datasheet/z/zotoncap.htm

4. Simpson IJ, Marshall MR, Pilmore H, et al. Proton pump inhibitors and acute interstitial nephritis – report and analysis of 15 cases. *Nephrology* (In Press).

Package insert changes

Singapore — The Health Sciences Agency (HSA) has approved the following package insert changes in accordance with safety updates from January to March 2006.

1. Calcitriol (Calcijex®, Abbott)

Under “Precautions”, it is stated that use of vitamin D analogs and cardiac glycosides may result in cardiac arrhythmias. Its effects may be reduced in patients taking barbiturates or anticonvulsants. Corticosteroids may counter the effects of vitamin D analogs. Rare cases of hypersensitivity reactions including anaphylaxis and localised redness or pain at injection site have been reported.

2. Clarithromycin (Klacid®, Abbott)

Contraindicated with concomitant use of ergotamine or dihydroergotamine. Under warnings, clarithromycin should only be used in pregnancy after risk/benefit assessment. Pseudomonas colitis is possible with clarithromycin/macrolide therapy. It is cautioned that cross-resistance between clarithromycin and other macrolide drugs is possible. New drug interactions include HMG-CoA reductase therapy, cisapride, pimozide, quinidine, disopyramide, colchicine and ritonavir.

New ADRs include hypoglycaemia in patients on oral hypoglycaemic agents or insulin, leucopenia and thrombocytopenia, ventricular tachycardia, Torsades de Pointes, pancreatitis, convulsions and interstitial nephritis.

3. Ciclosporin (Gengraf®, Abbott)

New drug interactions documented with colchicine, quinopristin/dalfopristin, amiodarone, orlistat and St John's Wort. Ciclosporin potentially enhances the toxic effects of colchicine especially in patients with renal dysfunction. Close monitoring is required in patients concurrently taking digoxin or colchicine. Myotoxicity has been reported with concomitant administration with HMG-CoA reductase inhibitors.

4. Daunorubicin (Daunorubicin®, Pfizer)

Contraindicated in pregnancy. New safety information added to the sections on cardiac toxicity and bone marrow depression. Significant hepatic or renal impairment can enhance the toxicity of recommended doses of daunorubicin. A rise in blood urea or uric acid can also occur with rapid destruction of leukaemia cells. Monitoring is thus required. Drug interaction includes vaccines and live virus.

5. Fluticasone (Flixotide®, GSK)

Very rare cases of increased blood glucose levels reported. Ritonavir (a

CYP3A4 inhibitor) can greatly increase fluticasone propionate plasma concentrations resulting in markedly reduced cortisol concentrations, Cushing syndrome and adrenal suppression. Caution should be exercised when CYP3A4 inhibitors, e.g. ketoconazole, are coadministered with fluticasone.

6. Lidocaine, Prilocaine (Emla Cream®, AstraZeneca)

Patients with G6PD deficiency or congenital or idiopathic methaemoglobinaemia are more susceptible to drug induced methaemoglobinaemia. If eye contact occurs, loss of protective reflexes may allow corneal irritation and potential abrasion. Patients treated with anti-arrhythmic drugs class III (e.g. amiodarone) should be under close surveillance and ECG monitoring as cardiac effects may be additive. The results of intracutaneous injections of live vaccines (e.g. BCG) should be monitored as lidocaine and prilocaine have bacteriocidal and antiviral properties in concentrations above 0.5–2%. Caution should be exercised when using Emla® in pregnant women.

7. Nimesulide (Nidol®, IDS Pharmaceuticals)

Maximum dose is reduced to 100 mg twice daily. Some new contraindications include patients with a history of hepatotoxic reactions to nimesulide, cerebrovascular bleeding, severe coagulation disorders, severe heart failure, children under 12 years, third trimester of pregnancy and lactation. Avoid concomitant administration of hepatotoxic drugs and alcohol abuse. New drug interactions include valproic acid, lithium, methotrexate and ciclosporin.

8. Propafenone (Rytmonorm®, Abbott)

Drugs that inhibit CYP2D6, CYP1A2 and CYP3A4, might lead to increased levels of propafenone. Propafenone should be used with caution in nursing mothers.

New ADRs include hepatitis, anorexia, syncope, hepatocellular injury, jaundice and lupus syndrome.

New precautions added were: (1) Each patient should be evaluated electrographically and clinically prior to and during propafenone therapy to determine if the therapy is warranted; (2) Propafenone may worsen myasthenia gravis; (3) Propafenone may affect both the pacing and sensing thresholds of artificial pacemakers; (4) there is a predisposition of patients taking this class of drugs with significant structural heart disease to serious adverse events.

9. Ritonavir (Norvir®, Abbott)

Pancreatitis has been observed in patients receiving ritonavir, including those who developed hypertriglyceridaemia especially patients with advanced HIV. New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus and hyperglycaemia have been reported in HIV-infected patients receiving protease inhibitor therapy. In some cases, diabetic ketoacidosis occurred and in others, hyperglycaemia persisted despite removal of protease inhibitor.

Some new drug interactions include ritonavir with erectile dysfunction agents, herbal products and HMG-CoA reductase inhibitors. Cardiac and neurologic events have been reported when ritonavir has been coadministered with disopyramide, mexiletine, nefazodone, or fluoxetine. Some new ADR terms include myocardial infarction and menorrhagia.

10. Verapamil (Isoptin®, Abbott)

New contraindications include congestive heart failure, atrial fibrillation/flutter and concomitant Wolff-Parkinson-White syndrome. Use with caution in patients with first degree AV block, hypotension, bradycardia and severely impaired liver function. New ADRs include abdominal discomfort/pain, impotence and

galactorrhea. New drug interactions include quinidine, lithium, prazosin, midazolam, neuromuscular blockers, acetylsalicylic acid, ethanol, simvastatin/lovastatin and grapefruit juice.

11. Vinorelbine (Navelbine®, Orient Europharma)

Contraindicated in patients with neutrophil counts $<1500/\text{mm}^3$ or with current or recent severe infection. New precautions: (1) dose limiting neutropenia where treatment should be delayed till recovery if neutrophil count $<1500/\text{mm}^3$ and platelet count $<75000/\text{mm}^3$. (2) In severe liver impairment, dose should be reduced by 33% and haematological parameters closely monitored. (3) Combination of Navelbine® with other bone marrow toxic drugs (e.g. cisplatin) may exacerbate myelosuppressive adverse effects. A new list of ADRs has been added. Navelbine® should not be used in pregnant or lactating patients.

12. Fluoxetine (Prozac Dispensible®, Eli Lilly)

A new contraindication states that if fluoxetine has been prescribed chronically and/or at a high dose, a longer interval of discontinuation (>5 weeks) should be considered when switching to monoamine-oxidase inhibitors (MAOI). Serious and fatal cases of serotonin syndrome have been reported in patients treated with fluoxetine and MAOI in close temporal proximity. It is warned that there is a possibility of suicide in depression which may persist till significant remission occurs. Cases of suicidal ideation and behaviours have been reported during fluoxetine/antidepressant therapy or early after treatment discontinuation. Close supervision of high-risk patients is recommended.

Reference: Package insert amendments reflecting safety issues. *Adverse Drug Reaction News*. Vol.8 No.2 Page 4. at <http://www.hsa.gov.sg/cda/>

Leflunomide and peripheral neuropathy

Australia — Leflunomide is a disease modifying anti-rheumatic prodrug (DMARD) with immunosuppressive properties. It has been available in Australia since 2000 for the treatment of active rheumatoid arthritis.

To date, ADRAC has received 659 reports in association with leflunomide, 30 of which described neuropathy or peripheral neuropathy. Leflunomide was the sole suspected drug in 24 of these cases. Ages ranged from 33 to 90 years. The daily dose of leflunomide was 20 mg in 24 cases, 10 mg in 1, 30 mg in 1, and not stated in the remaining cases. The time to onset (n=21) ranged from 2 weeks to 20 months.

Most reports described insidious onset of bilateral sensory changes such as numbness, hypoaesthesia, paraesthesia, or painful burning sensations affecting the feet and (in a few cases) the hands. Clinical findings variously included reduced sensation to light touch and pin prick, decreased vibration sense distally, and in one case 'foot drop' was noted. Decreased or absent tendon reflexes were also noted in some cases.

Nine reports included the results of nerve conduction studies which supported a diagnosis of significant length-dependent sensory or sensorimotor neuropathy. Symptoms persisted and became worse with continued use of leflunomide in several cases.

Recovery was documented after withdrawal of leflunomide in 6 patients, 3 of whom were treated with 'cholestyramine washout' (which reduces the elimination half-life of the active metabolite of leflunomide from more than one week to about one day). At the time of

reporting, 15 patients had not recovered and the outcome was unknown for the remaining cases.

The cases reported to ADRAC are similar to those recently described by Martin et al (1). The temporal association of leflunomide with peripheral neuropathy and recovery on dechallenge suggest a causal relationship. The clinical features resemble the sensory peripheral neuropathy attributable to the vasculitic component of rheumatoid disease itself. Accordingly, the association may be difficult to recognise but prescribers should consider the possible role of leflunomide in patients who complain of sensory problems in the feet because in such cases the condition is potentially reversible if the drug is ceased.

Extracted from Australian Adverse Drug Reactions Bulletin, Volume 25, Number 5, October 2006.

Reference

1. Martin, K et al. Neuropathy associated with leflunomide: a case series. *Ann Rheum Dis* 2005; **64**: 649-50.

Ezetimibe and depression?

Australia — Ezetimibe (Ezetrol®) was registered in Australia in June 2003 for treatment of hypercholesterolaemia. Since then, ADRAC has received 265 reports of suspected adverse reactions associated with the use of this drug. Twelve of the reports describe depression (9) or depressed mood (3) in patients aged 60 to 82 years. In all cases, ezetimibe was the sole suspected drug. An unusual feature was the rapid onset of symptoms — within four days in 7 of the reports and at 4–6 weeks in another 3. In one report, the symptoms resolved after the dose was reduced from 10 mg to 5 mg daily, and another report described exacerbation of pre-existing depression after the second dose.

In 5 patients, symptoms abated on withdrawal of ezetimibe but recurred on rechallenge. One of these documented 2 positive rechallenges with identical time to onset and noted suicidal ideation after continued use of ezetimibe. In addition to the 5 reports of positive rechallenges 4 patients had recovered after ceasing ezetimibe and a further patient was recovering with antidepressant treatment after withdrawal of ezetimibe.

Reports of depression/depressed mood, as a proportion of total reports received, are higher for ezetimibe (4.5%) than for other hypolipidaemic agents: 3% for pravastatin (16/511) and simvastatin (86/2,784); 2.4% for atorvastatin (39/1,573) and fluvastatin (6/255); 1.9% for gemfibrozil (12/619); and for the database as a whole (1.4%).

The Ezetrol® product information does not mention depression as a finding in clinical trials of this medicine. Further, depression occurs commonly from other causes. However, the pattern of reporting suggests a possible causal association between ezetimibe and depression, particularly in elderly patients in the early phase of treatment, where careful monitoring is advisable. ADRAC will continue to monitor reports of depression in association with ezetimibe.

Reference: Ezetrol® (ezetimibe) Product Information. Merck Sharp & Dohme (Aust.) Pty Ltd (version dated Nov. 2005).

Sirolimus: acute rejection in renal transplant patients

Canada — Increased risk of rejection in *de novo* renal transplant patients receiving sirolimus (Rapamune®), mycophenolate mofetil, and corticosteroid, used in combination with interleukin-2 receptor antibody induction have been reported in an investigational setting. In this setting,

the term “*de novo*” refers to the use of this regimen from the time of transplantation.

Based on information from recent clinical trials, the use of sirolimus, mycophenolate mofetil (MMF), and corticosteroids, in combination with IL-2 receptor antibody (IL2R Ab) induction, is not recommended in the *de novo* organ transplant setting. Sirolimus is authorized solely for the prevention of renal transplant rejection. It is recommended that sirolimus be used initially in combination with cyclosporine and steroids.

The safety and efficacy of sirolimus as immunosuppressant therapy have not been established in liver or lung transplant patients, and therefore, such use is not recommended.

Reference: Health Canada Endorsed Important Safety Information on Rapamune® (sirolimus). 18 August 2006, <http://www.hc-sc.gc.ca>

Safety update for oseltamivir

United States of America — The manufacturer of oseltamivir phosphate (Tamiflu®) has advised health professionals of a recent revision to the product label as a result of adverse events reported during postmarketing clinical use. Oseltamivir is indicated for the treatment of uncomplicated acute illness due to influenza infection in patients 1 year and older who have been symptomatic for no more than 2 days. Oseltamivir is also indicated for the prophylaxis of influenza in patients 1 year and older.

The revised package insert now includes information and guidance on neuropsychiatric events following reports (mostly from Japan) of self-injury and delirium with the use of oseltamivir in patients with influenza. The reports were primarily among paediatric patients. The relative

contribution of the drug to these events is not known. Patients with influenza should be closely monitored for signs of abnormal behavior throughout the treatment period. In addition, the following statement has been added to the patient information:

People with the flu, particularly children, may be at an increased risk of self-injury and confusion shortly after taking oseltamivir and should be closely monitored for signs of unusual behavior. A health care professional should be contacted immediately if the patient shows any signs of unusual behavior.

Reference: www.fda.gov/medwatch. Tamiflu® complete product information at <http://www.rocheusa.com/products/tamiflu/pi.pdf>.

Darifenacin hydrobromide for overactive bladder: what clinical advantage?

Australia — Darifenacin hydrobromide (Enablex®) 7.5 mg and 15 mg prolonged-release tablets have been approved for overactive bladder.

The contraction of detrusor smooth muscle involves stimulation of muscarinic receptors by acetylcholine. Anticholinergic drugs have therefore been used to relax the bladder in patients with urge incontinence. These drugs have unwanted systemic effects so there is a need for a drug with an action that is more specific to the bladder. The M3 muscarinic receptor has been a target for drug development as it is thought to be the subtype responsible for bladder contraction.

Darifenacin is an anticholinergic drug which has a greater affinity for the M3 receptor than for other subtypes. Its action diminishes the frequency of detrusor contractions and increases bladder capacity.

Once-daily dosing is possible with the prolonged-release formulation. Peak plasma concentrations are reached seven hours after an oral dose, with a steady state reached in six days. Bioavailability depends on the patient's metabolism. Darifenacin is extensively metabolised in the liver and its pharmacokinetics are affected by moderate hepatic impairment. As the metabolism involves cytochrome P450 2D6 and 3A4, there are several potential drug interactions. The risk of adverse events may be increased by CYP2D6 inhibitors such as cimetidine, fluoxetine and paroxetine. Daily doses of darifenacin should not exceed 7.5 mg if the patient is taking an inhibitor of CYP3A4 such as itraconazole. The anticholinergic adverse effects of T T tricyclic antidepressants and drugs for Parkinson disease may be increased by darifenacin.

Compared with placebo, patients taking darifenacin complain more frequently of dry mouth and constipation. These adverse effects appear to increase with the dose. Other adverse effects include altered vision, dyspepsia and abdominal pain. Caution is needed if darifenacin is considered for patients with decreased gastrointestinal motility or at risk of urinary retention.

Darifenacin has been studied in people with overactive bladder. These people have urinary urgency, but not all of them have urge incontinence. The benefits of darifenacin may be less certain in these patients. Although it achieved statistical advantages over placebo, the absolute changes may be small. For example, a patient given darifenacin 15 mg will have one less micturition per day than a patient given a placebo. They may also have one less episode of urgency per day. Darifenacin does not decrease the number of times a patient is awoken by their overactive bladder significantly more than placebo (1).

Comparative studies are limited, but tolterodine has been included in a placebo-controlled trial of darifenacin. Unfortunately, a comparative analysis of the 15 mg dose of darifenacin was not carried out for all the outcomes. Darifenacin only achieved a statistical advantage over tolterodine for some outcomes if it was given at a daily dose of 30 mg. Darifenacin's selective action does not appear to give it a large clinical advantage.

Article drawn from: The Australian prescriber. Volume 29, Number 5, October 2006 at www.australianprescriber.com

Reference

1. Haab F, Stewart L, Dwyer P. Darifenacin, an M3 selective receptor antagonist, is an effective and well-tolerated once daily treatment for overactive bladder. *Eur Urol* 2004;**45**:420-9.

Tigecycline for serious infections

Australia – Tigecycline (Tygacil®) vials containing 50 mg lyophilised powder for reconstitution have been approved for complicated skin and soft tissue infections and complicated intra-abdominal infections.

Tigecycline is structurally related to the tetracycline class of antibiotics and is a derivative of minocycline. It has broad spectrum in vitro activity against Gram-positive, Gram-negative and anaerobic organisms and also tetracycline-resistant bacteria. Coverage includes multiresistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci. Tigecycline has poor activity against *Pseudomonas* species.

Tigecycline is not absorbed from the gut so it must be administered by slow

intravenous infusion. It is extensively distributed in the body and has a serum half-life of 40 hours. The tissue half-life is not known. Tigecycline is not extensively metabolised and so most of the drug is excreted unchanged in the urine and faeces.

The safety and efficacy of tigecycline were evaluated for the treatment of skin and skin-structure infections from pooled data of two trials totalling 1116 hospitalized adults. Soft tissue infections, abscesses and infected ulcers were the most common type of infections in these patients. Cure rates for tigecycline and vancomycin/aztreonam were similar in trials. Both treatments were equally effective in patients with underlying comorbidities such as diabetes mellitus and peripheral vascular disease (1).

The safety and efficacy of tigecycline were also evaluated for the treatment of complicated intra-abdominal infections, such as complicated appendicitis. Similar levels of drug efficacy were reflected in patients who were microbiologically evaluable (2). Although tigecycline has in vitro activity to multidrug resistant bacteria, there were limited data in these trials to support its use in patients with these infections. However, tigecycline was effective at eradicating MRSA in 25 out of 32 patients with complicated skin infections (1).

The most common drug-related adverse events reported by tigecycline recipients were nausea and vomiting. Overall there were 30 deaths in the tigecycline groups and 18 deaths in the control groups. One death of a tigecycline recipient, after septic shock, was possibly related to the study drug.

Tigecycline is not recommended for pregnant women or children. Tetracycline class effects, such as photosensitivity, may also occur in patients taking tigecycline.

Tigecycline provides an alternative antibiotic therapy for the treatment of serious infections in hospitalised adults. However, its effectiveness in treating multidrug resistant infections remains to be fully evaluated. Advice from an infectious disease specialist or bacteriologist should be sought before using tigecycline.

Article drawn from The Australian prescriber. Volume 29, Number 5, October 2006 at www.australianprescriber.com

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1. Ellis-Grosse EJ, Babinchak T, Dartois N, Rose G, Loh E. The efficacy and safety of tigecycline in the treatment of skin and skin-structure infections: results of 2 double-blind phase 3 comparison studies with vancomycin-aztreonam. *Clin Infect Dis* 2005;**41**:S341-53.
2. Babinchak T, Ellis-Grosse E, Dartois N, Rose GM, Loh E. The efficacy and safety of tigecycline for the treatment of complicated intra-abdominal infections: analysis of pooled clinical trial data. *Clin Infect Dis* 2005;**41**: S354-67.

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.

Rational Use of Medicines

The role of prescribed and defined daily doses in pharmacoepidemiology

In pharmacoepidemiological studies, it is important to use one single measurement for the volume of drugs prescribed, dispensed or consumed. For many years, the defined daily dose (DDD) has been the globally accepted standard unit for such assessments. A DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults (1). However, the DDD for a drug may deviate from the prescribed daily dose (PDD) (2–4). This may limit its usefulness unless the DDD/PDD ratio is known. Both DDD and PDD have been particularly useful in studying patient adherence since reports increasingly indicate that adherence to long-term drug therapy is low (5).

As an example, prescription refill adherence to corticosteroids used for asthma/chronic obstructive pulmonary disease (COPD) treatment has been found to be only 34% (6). This case provided the background for the study described below, where refill adherence was determined by comparing patient prescribed doses to data from pharmacies in Jämtland, Sweden (6). Although data bases of pharmacy records are preferred compared to prescription collection, many data bases only have information about drug volumes actually dispensed and not the prescribed doses. Furthermore, a large proportion of the prescriptions issued are not dispensed (7). When prescribed doses are not listed in the available data bases, dispensed drug volumes in DDDs can serve as a proxy for patient dosing and refill adherence, providing that the PDDs do not deviate from the DDDs to any great extent.

Asthma/COPD drugs: PDDs are critical to determining DDDs

The present study* was conducted with the aim of improving the rational use of medicines through application of DDDs and PDDs to data available concerning the treatment of asthma and COPD in Sweden. DDDs for different drug substances are available from the WHO Collaborating Centre of Drug Statistics Methodology (1). The prescribed doses for the dispensing of asthma/COPD drugs used in Sweden were obtained from

the pharmacy record data base of the County of Jämtland with approximately 120 000 inhabitants. The data base holds information on all drugs dispensed to a representative sample of 17 000 inhabitants (9, 10). Information relating to dispensing include: age and sex of the patient, dispensation date, name of the drug, its ATC-code, drug volume dispensed, and prescribed dose with code numbers for patients and prescribers. The identity of the patients and prescribers, as well as medical conditions, remain confidential.

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The study was carried out during the period 2000-2004. It included patients 20 years and older (since DDDs are based on adult doses). Patients were grouped in 10-year age groups. Drugs were selected from ATC code group R03 — drugs for inhalation and oral use (1). This includes:

- R03AC selective beta-2-adrenoreceptor agonists
- R03AK adrenergics and other drugs for obstructive airway disease; combination drugs for inhalation
- R03BA glucocorticoids
- R03BB anticholinergics
- R03C adrenergics for systemic use
- R03D other systemic drugs for obstructive airway disease.

Only prescriptions with precise posology/dosing instructions (e.g. one inhalation twice a day) were included. Consequently, all prescriptions with instructions such as “to be used when needed” were excluded.

For each 10-year age group of patients and for each ATC-group at the 5th level (e.g. R03AC02 for salbutamol) the PDD for each prescription was computed. The DDD-values for each drug were divided with the computed PDD value and the mean DDD/PDD ratio for each substance and for each 10-year age group was then calculated. For drugs with less than 20 registered prescriptions over the five year study period the DDD/PDD ratios were not determined.

For the period 2000–2004, 1812 patients 20 years and older were registered in the pharmacy record data base as having acquired R03 drugs from pharmacies in the county. The number of dispensations was 23 223. The DDD/PDD ratios for the different drug substances and the different age groups are presented in Table 1.

It was possible to calculate the DDD/PDD ratios for 15 of 18 asthma/COPD drugs.

For three drugs — the short acting adrenergics salbutamol (R03AC02) and terbutaline (R03AC03) and the combination product of salbutamol and ipratropium (R03AK04) — over 95% were prescribed to be used “when needed”. No DDD/PDD ratios were therefore determined for these drugs. For the youngest age group, 20–29 years, the number of prescriptions for 9 of the drugs was too low to make a determination of the DDD/PDD ratios meaningful.

PDDs were obtained from the pharmacy record data base of the same county. Data on R03 drugs from this data base (11) have previously been determined to correlate closely with data from the national register (8). The ratios are likely to be representative of the current situation in the rest of Sweden.

The DDD/PDD ratios for most drugs showed only small variations between the different age groups. For fluticasone there was a two-fold variation among the age groups with higher ratios for young and elderly patients. The reason for this is not clear. For ipratropium bromide the ratio increased by age. It is apparent that doctors prescribed lower doses of this anticholinergic drug to older patients, although no such recommendation is included in the specifications for the drug (12).

Of 15 drugs, the mean DDD/PDD ratios were close to 1 for 10. Two drugs, formoterol for inhalation and terbutaline for oral use, had DDD/PDD ratios of 0.7 and 0.6, respectively, showing that 1.4 and 1.6 DDDs were the average prescribed doses for these drugs. For three other drugs, fluticasone, ipratropium bromide, and theophylline the ratios were 1.7, 2.7 and 1.4 respectively, indicating that the average prescribed dose for

Table 1. DDD and PDD for asthma/COPD drugs in Sweden 2000–2004

ATC-code	Substance	Brand name	DDD/PDD ratios							Mean DDD/PDD ratio
			Age groups							
			20-29	30-39	40-49	50-59	60-69	70-79	80+	
R03AC02	Salbutamol	Ventoline ² inhalation	ND ¹	ND ¹	ND ¹	ND ¹	ND ¹	ND ¹	ND ¹	ND ¹
R03AC03	Terbutaline	Bricanyl inhalation	ND ¹	ND ¹	ND ¹	ND ¹	ND ¹	ND ¹	ND ¹	ND ¹
R03AC12	Salmeterol	Serevent	1	1.1	1	1.1	0.7	1.1	1	1
R03AC13	Formoterol	Oxis ²	0.5	0.5	0.8	0.9	0.9	0.7	0.7	0.7
R03AK04	Salbutamol + ipratropium bromide	Combivent	ND ¹	ND ¹	ND ¹	ND ¹	ND ¹	ND ¹	ND ¹	ND ¹
R03AK06	Salmeterol + fluticasone	Seretide	1.1	1	1.1	1.1	1	1	1	1
R03AK07	Formoterol + budesonide	Symbicort	0.7	0.8	0.8	1.1	1.7	0.8	0.7	0.9
R03BA01	Beclo-metasone	Becotide ²	0.8	ND ¹	0.5	0.7	1	1	0.8	0.8
R03BA02	Budesonide	Pulmicort	0.8	0.9	1	1.1	1.1	1	1	1
R03BA05	Fluticasone	Flutide	ND ³	2.6	1.1	1.1	1.9	1.1	2.4	1.7
R03BA07	Mometasone	Asmanex	ND ³	ND ³	ND ³	1.2	0.8	ND ³	ND ³	1
R03BB01	Ipratropium bromide	Atrovent	ND ³	1	1.2	3.3	2.6	3.4	4.8	2,7
R03BB04	Tiotropium bromide	Spiriva	ND ³	1	1	1.1	1	1	1	1
R03CC02	Salbutamol oral	Ventoline	ND ³	ND ³	ND ³	ND ³	1	ND ³	ND ³	1
R03CC03	Terbutaline oral	Bricanyl	ND ³	ND ³	ND ³	ND ³	0.5	0.6	ND ³	0.6
R03CC12	Bambuterol	Bambec	ND ³	ND ³	ND ³	ND ³	1	ND ³	ND ³	1
R03DA04	Theophylline	Theo-Dur ²	ND ³	ND ³	ND ³	ND ³	1.6	1.2	ND ³	1.4
R03DC03	Montelukast	Singulaire	1	1	1	1	1	1	1	1

1. Not determined since over 95 % did not have dosing instructions.

2. This is the most common brand but others were also used.

3. Not determined due to low number of prescriptions.

fluticasone was about 0.6 DDDs, for ipratropium bromide about 0.4 DDDs and for theophylline 0.7 DDDs. The ratios for oral terbutaline and for theophylline were only determined in two age groups due to the low number of prescriptions. The values are therefore uncertain.

Unfortunately, the study remained limited to Swedish data because published PDD data for R03 drugs from other countries is unavailable. However, the study drugs are widely used internationally and dosing recommendations are based on similar documentation in many countries. Approximately 70% of total sales of drugs in Sweden are from transnational pharmaceutical companies (13). Given the multinational nature of the pharmaceutical industry, the DDD/PDD ratios presented are therefore likely to be of relevance to other countries.

It was concluded from the study that for the majority of asthma/COPD drugs prescribed in Sweden, DDDs agree with the PDDs. For the cited drugs, the DDDs can therefore be used to estimate patient dosing and to evaluate to what extent patients have access to continuous therapy over a defined period of time.

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Topics of Current Interest

Development of medicines for neonates

The development of safe and effective medicines for newborn babies requires stronger cooperation between researchers, developers and regulators. This was one of the main conclusions of a workshop, organized by the European Medicines Agency (EMA) on 11 October 2006.

Highlighting EMA's commitment to stimulate multidisciplinary cooperation in the development of medicines for children, the workshop brought together some 70 experts from academia and learned societies, industry and regulatory authorities, and also healthcare professionals involved in looking after and treating newborn and premature babies.

The participants discussed the impact of organ immaturity and the rapid changes in the first days and weeks of life when investigating medicines for neonates. The outcome of the workshop — together with a series of concept papers on the impact of brain, liver, kidney, heart and lung immaturity prepared by the Agency's Paediatric Working Group will form the basis of a future EMA guideline on this issue. Other aspects covered during the workshop included formulations appropriate for neonates, ethical aspects in relation to the conduct of clinical trials in newborn babies, novel study design methods and safety and pharmacovigilance aspects.

The workshop was organized in the framework of the entry into force of the new European legislation on medicines for children which will introduce incentives

aimed at stimulating research, development and authorization of medicines for children. It is expected that this will result in an increase of clinical trials in children, including neonates. The workshop provided a platform for a multidisciplinary scientific dialogue among European experts to identify appropriate measures to encourage high-quality research into medicines for neonates, while also putting in place safeguards and precautions to protect this highly vulnerable patient population.

Notes

1. The proceedings of the conference are available on the EMA website at <http://www.ema.europa.eu>
2. The EMA Paediatric Working Party (PEG) has prepared four concept papers focusing on organ immaturity in neonates. The Concept Paper on the *Impact of Brain Immaturity when investigating medicinal products intended for Neonatal use*, the Concept Paper on the *Impact of Lung and heart Immaturity when investigating medicinal products intended for Neonatal use* and the Concept Paper on the *Impact of Liver Immaturity when investigating medicinal products intended for Neonatal use*. A Discussion Paper on *Renal Immaturity when Investigating Medicinal Products for Paediatric Use* has also been published.

3. On 4 October 2006, the European Commission released a draft document on *Ethical Considerations for Clinical Trials Performed in Children*. Recommendations of the Ad Hoc Group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use.

Reference: EMA Press Release, Doc. Ref. EMA/416788/2006, 25 October 2006. <http://www.ema.europa.eu>.

Plan for paediatric essential medicines

With millions of children dying every year from treatable diseases, United Nations agencies have devised a plan aimed at increasing children's access to essential medications. WHO and UNICEF held a joint meeting in Geneva in August 2006 to form a strategy to expand access to paediatric formulations and improve the medicines and prescribing guidelines for the entire range of infant and child care needs.

Some 10 million children die every year, many of them from diarrhoea, HIV and AIDS, malaria, respiratory tract infection or pneumonia. Effective treatments for these illnesses exist, but there is a lack of treatment guidelines and paediatric formulations.

Under the plan, UNICEF's supply division said it would work with industry to promote the development of paediatric formulations for HIV and AIDS medications. It also promised to work towards painless remedies, better-tasting medications and new mini-tablets to treat other diseases, as well as to emphasize the importance of climate zone considerations in creating and distributing new formulations.

WHO will work towards ameliorating the cost of many medicines, especially for children in resource-poor settings

Reference: UN Agencies present plan to bring essential medicines to children New York, 14 August 2006 at <http://www.who.int/mediacentre/news/releases/2006/pr42/en/index.html> and <http://www.unicef.org/>

200 African scientists join forces

Over 200 African scientists from 23 countries met in September 2006 at an international conference to engender

greater regional research partnership to combat the most neglected diseases such as sleeping sickness, kala azar and malaria. Since the first meeting of the Drugs for Neglected Diseases initiative (DNDi) in 2003, significant progress has been made. Clinical research platforms for leishmaniasis and sleeping sickness have been established on the continent, and African scientists have contributed to the clinical trials of a new drug for malaria.

However, new drugs and diagnostics are desperately needed: Only 1.3% (21 out of 1556) of new drugs developed over 30 years have been for neglected tropical diseases and tuberculosis, even though these diseases account for 12% of the global disease burden.

DNDi is a not-for-profit drug development initiative established in 2003 by five publicly-funded research organizations (Kenya Medical Research Institute, Indian Council of Medical Research, Oswaldo Cruz Foundation Brazil, Malaysian Ministry of Health, and the Institut Pasteur), the WHO Tropical Diseases Research Programme (TDR), and Médecins Sans Frontières. DNDi aims to develop 6 to 8 new, improved and field-relevant drugs by 2014 for neglected diseases.

DNDi is currently conducting two large, multicentre clinical trials. The first on paromomycin, a treatment for leishmaniasis in Africa, and the second for co-administration of nifurtimox-eflornithine for sleeping sickness. The new treatments are expected to be available to patients within 3 years. DNDi supports training of members in various aspects of clinical trials, thus building expertise in clinical research for both diseases so that new treatments and diagnostics can be effectively evaluated and registered by scientists from the endemic regions.

Another focus group meeting at the conference is on fixed-dose artesunate-

based combination therapies (FACT) for chloroquine-resistant malaria. DNDi and its partners will bring the new, easier to use artesunate-amodiaquine combination to patients in Africa.

Reference: <http://www.who.int/mediacentre/news/releases> or amsevcsik@dndi.org

New strategy to fight tropical diseases

WHO and a group of more than 25 partner organizations has unveiled a new strategy to fight some of the most neglected tropical diseases that destroy the lives and health of poor people by combining treatment regimens for different diseases, but which require common resources and delivery strategies for control or elimination.

The approach is set out in a newly published manual, *Preventive Chemotherapy in Human Helminthiasis*, and focuses on how and when a set of low-cost or free drugs should be used in developing countries to control diseases caused by worm infections. Drugs that are effective against a broad range of worm infections will simultaneously prevent or treat the four most common diseases caused by worms: river blindness (onchocerciasis), elephantiasis (lymphatic filariasis), schistosomiasis, and soil-transmitted helminthiasis. Significant opportunities also exist to integrate these efforts with the prevention and control of diseases such as trachoma.

The second key component of the strategy brings together dozens of agencies, NGOs, pharmaceutical companies and others into a coordinated assault on neglected diseases. These organizations are integrating their expertise and resources to deliver the manual's protocols for wide-scale drug use.

More than one billion people are afflicted by these diseases. Their impact can be measured in the impaired growth and development of children, complications during pregnancies, underweight babies, significant and sometimes disabling disfigurements, blindness, social stigma, and reduced economic productivity and household incomes. These effects can now be dramatically reduced by scaling up interventions using effective drugs of proven quality — the majority donated by companies or costing less than US\$ 0.40 per person per year.

Reference: WHO Press Release, 26 October 2006 at <http://www.who.int/mediacentre/news/releases>

ICH efforts to improve processes

The International Conference on Harmonization (ICH) Steering Committee and its expert working groups met in Chicago, USA, from 21–26 October 2006.

ICH aims to collaborate with accredited Standards Development Organizations to leverage the development of technical standards for ICH e-Initiatives. This decision follows the outcome of a series of discussions on improving the efficiency of the ICH process that started at the Steering Committee meeting in May, 2005. Additionally it is likely that the resulting standards would be taken up by many non-ICH countries and organizations.

Expanding ICH standards would fulfill ICH's vision of the future development of more efficient processes and increased uniformity of drug development requirements globally without compromising the quality, safety, and efficacy standards expected by practitioners and patients.

In order to keep pace as science evolves and with a view to reduce, refine and replace animal testing, expert groups were convened during the meeting to revise the guidelines on *Genotoxicity* and the *Non-clinical Safety Studies for the Conduct of Human Clinical Trials*. The groups had very productive discussions and worked on significant revisions of the guideline requirements.

Quality experts from both the chemical and biotech areas held a Quality Strategy Session to identify those areas in pharmaceutical quality which need to be addressed across all products at ICH level towards the goal of achieving harmonized submissions. Discussions will continue at the next ICH meeting.

A draft guideline on *Pharmacogenomics (E15)* reached Step 2. This document will describe harmonized terminology for use in regulatory documentation.

ICH also adopted a new topic entitled *Development Safety Update Reports (E2F)* which will harmonize the requirements for annual clinical trial reporting in the three regions.

The Gene Therapy Discussion Group has also finalized the Document on *Inadvertent Germline Transmission* which presents scientific principles to address the risk of inadvertent germline integration during development of a gene therapy product. The group also made progress on two new Considerations Documents on Vector/Viral Shedding and Oncolytic Viruses.

The next ICH Steering Committee Meeting will be held in Brussels, Belgium, from 7–10 May 2007.

Reference: ICH Steering Committee Meeting. Press Release. *Leveraging ICH Efforts to Increase Globalization*. <http://www.ich.org>

Anticounterfeiting Taskforce develops strategy

The World Health Organization (WHO) and its partners have officially launched the International Medical Products Anti-counterfeiting Taskforce (IMPACT) at a meeting in Germany on 15 November 2006. IMPACT is made up of WHO Member States and more than 20 other major stakeholders, including Interpol, the World Customs Organization, patient and health professional organizations, and associations representing pharmaceutical manufacturers and wholesalers.

Counterfeiters and their allies engage in elaborate conspiracies to disguise activities. They establish fictitious businesses and front companies; exploit weaknesses in border control; use false documents to obtain pharmaceutical ingredients and manufacturing equipment to replicate genuine products. In sum, their actions are meant to disguise the extent of the crime and this makes detection and reporting extremely difficult.

Following the launch, IMPACT has proposed a global plan to combat counterfeit medical products. As a first step, it has released a preliminary report on estimates of the number of counterfeit products thought to be circulating on world markets.

Until now, the number of counterfeit medicines has generally been estimated at approximately 10% of the global medicines market. As the capacity to collect and analyse information improves, a better understanding of the situation is possible. A rapid overview of the situation shows that counterfeiting is greatest in those regions where regulatory and legal oversight is weakest.

Most developed countries with effective regulatory systems and market control

currently have a very low proportion of counterfeiting, i.e. less than 1% of market value. However, indicators do point to an increase in the prevalence of counterfeit medicines even in developed countries.

Many developing countries of Africa, parts of Asia, and parts of Latin America have areas where more than 30% of medicines on sale can be counterfeit. Other developing markets, however, have less than 10%; overall, a reasonable estimate is between 10% and 30%. Many of the countries which were part of the Soviet Union have a proportion of counterfeit medicines which is above 20% of market value. Medicines purchased over the Internet from sites that conceal their actual physical address are counterfeit in over 50% of cases.

In addition to the huge differences sometimes recorded between regions, variations can also exist within countries — city versus rural areas, city versus city — and can also be time-sensitive. The difficulty of capturing data furthermore reflects the complexity of a situation that, by its very nature, is informal and illegal and where the evidence itself is consumed.

Overview of country reports

Angola: According to the head of the National Department of Intellectual Copyright Crime of the Economic Police, approximately 70% of medicines used by the population may be forgeries.

Cambodia: A Cambodian Health Ministry survey conducted in 2002 revealed that 13% of drugs on the domestic market were counterfeit or substandard, especially antimalarial drugs and antibiotics.

China: China's Research and Development-based Pharmaceutical Association estimates that about 8% of over-the-counter drugs sold in China are counterfeit.

Colombia: According to the Association of Colombian Pharmaceutical Industries (ASINFAR), it is estimated that out of a total US\$1300 million in annual medicines sales, almost 5 percent stem from contraband, counterfeiting or adulteration.

Dominican Republic: The Public Health Department has reported that 50% of pharmacies operate illegally and that, according to statistics, 10% of the medicines that arrive in the country are fake. Some of the medicines found had expired over 10 years ago!

El Salvador: INQUIFAR, the Association of Pharmaceutical Companies, has denounced the widespread availability of counterfeit drugs on the domestic market. According to a local drug manufacturer, the commercialization of counterfeit medicines currently causes economic losses of around US\$40 million per year to the country's pharmaceutical industry.

India: Indian pharmaceutical companies have suggested that in major cities, one in five strips of medicines sold is fake. They claim a loss in revenue of between 4% and 5% annually. The industry also estimates that spurious drugs have grown from 10 to 20% of the total market.

Indonesia: The International Pharmaceutical Manufacturers Group (IPMG) in Indonesia has estimated that pirated drugs constitute 25% of Indonesia's US\$2 billion pharmaceutical market. According to IPMG, fake drugs hit foreign pharmaceutical companies' profits and pose a potential serious public health threat.

Kenya: A random survey by the National Quality Control Laboratory (NQCL) and the Pharmacy and Poisons Board found that almost 30% of drugs in Kenya are counterfeit. Some of the drugs have been described as no more than just chalk and water being marketed as original pharmaceutical products. According to figures

from the Kenya Association of Pharmaceutical Industries, counterfeit pharmaceutical products account for approximately US\$130 million annually in sales in the country.

Lebanon: The chief of Lebanon's National Health Commission (NHC), has estimated that 35% of pharmaceuticals available in the Lebanese market are counterfeit products.

Mexico: During 2004, federal agents seized — in two regions — approximately 60 tons of stolen, expired and counterfeit pharmaceuticals. There is concern in the pharmaceutical industry at the rapid growth in sales of counterfeit and contraband products. Reportedly, the penetration of these illegal products is about 10% of the pharmaceutical market.

Nigeria: The National Agency for Food, Drug Administration and Control (NAFDAC) announced that the prevalence of counterfeit drugs has dropped to 16% at the beginning of 2006.

Peru: Some US\$66 million of counterfeit and adulterated pharmaceuticals are sold in Peru every year. In the capital alone, there are 1800 stores devoted to this illegal business. The General Directorate of Medicines, Supplies and Drugs (DIGEMID) of the Department of Health seized around 460 000 adulterated and expired medicines in 2005.

The Association of Pharmaceutical Laboratories of Peru (ALAFARPE) estimates that the illegal pharmaceuticals trade in the country represents around US\$ 40 million. This figure includes medicines that enter the country as contraband, are expired, counterfeit, adulterated, with altered or missing labels or stolen from warehouses of the Ministry of Health, the armed forces, and police.

Around 200 pharmacies operate in downtown Lima with neither registration nor authorization issued by the Ministry of Health. According to the Municipal Health Department, they sell 40% contraband pharmaceuticals and 12% adulterated or expired goods supplied by clandestine laboratories. During 2004, the Ministry of Health seized ten tons of adulterated pharmaceuticals.

Philippines: In 2003, the former director of the Bureau of Food and Drug (BFAD), has estimated that 30% of drug store outlets visited by food and drug deregulation officers carry and sell counterfeit drugs.

Russia: The Federal Service for Health Sphere Supervision (FSHSS) reported that 10% of all drugs on the Russian market were counterfeit. However, other sources estimate that the real figure could be much higher.

Reference: <http://www.ho.int/medicines>

Regulatory Action and News

Bevacizumab approved for lung cancer

United States of America — The Food and Drug Administration (FDA) has approved use of bevacizumab (Avastin®) in combination with carboplatin and paclitaxel for initial systemic treatment of patients with unresectable, locally advanced, recurrent or metastatic, non-squamous, non-small cell lung cancer. Approval was based on an improvement in survival time when bevacizumab was added to a standard chemotherapy regimen. Lung cancer is the leading cause of cancer-related death in men and women.

The most serious adverse events associated with bevacizumab, including some fatal cases, were gastrointestinal perforation, wound healing complications, haemorrhage, blockage of arteries, abnormally high blood pressure, albumin deficiency in blood and congestive heart failure. The most common adverse events included weakness, abdominal pain, headache, diarrhoea, nausea and vomiting.

Bevacizumab, in combination with intravenous 5-fluorouracil-based chemotherapy, was previously approved for first- or second-line treatment of patients with metastatic cancer of the colon or rectum.

Reference: *FDA News*, P06-166. 12 October 2006

Risperidone for irritability associated with autism

United States of America — The Food and Drug Administration (FDA) has approved risperidone (Risperdal®) orally disintegrating tablets, an adult antipsy-

chotic drug, for the symptomatic treatment of irritability in autistic children and adolescents. The approval is the first for the use of a drug to treat behaviours associated with autism in children. These behaviours are included under the general heading of irritability, and include aggression, deliberate self-injury, and temper tantrums.

Risperdal® has been approved since 1993 for the short-term treatment of adults with schizophrenia, and since 2003 for the short-term treatment of adults with acute manic or mixed episodes associated with extreme mood swings. The most common side effects of the use of risperidone included drowsiness, constipation, fatigue and weight gain.

Reference: *FDA News*, P06-163. 6 October 2006.

New treatment for chronic hepatitis B

United States of America — The Food and Drug Administration (FDA) has approved telbivudine (Tyzeka®) for the treatment of adults with chronic hepatitis B (HBV), a serious viral infection that can cause lifelong infection, scarring of the liver (cirrhosis), and eventually liver cancer, liver failure, and death.

Telbivudine is not a cure for hepatitis B, and long-term treatment benefits of this drug are not known. Use of telbivudine has not been shown to reduce the risk of transmission of HBV to others through sexual contact or blood contamination.

The most common side effects were elevated creatinine phosphokinase, upper respiratory tract infection, fatigue, headache, abdominal pain and cough. Also,

after several weeks to months of telbivudine use, some patients developed symptoms ranging from transient muscle pain to muscle weakness. Those who developed muscle weakness experienced significant improvement in their symptoms when telbivudine was discontinued.

Patients should only stop Tyzeka after a careful discussion with their doctor. As has happened with other forms of treatment for hepatitis B, some patients who discontinued telbivudine experienced a sudden and severe worsening of their hepatitis B. Therefore, patients who discontinue telbivudine should be closely monitored by their doctor for at least several months. Some cases of lactic acidosis and severe enlargement and accumulation of fat in the liver, including fatal cases, have been reported among drugs in this class.

Reference: *FDA News*, P06-175. 25 October 2006.

Influenza virus vaccine composition: 2007 southern hemisphere

World Health Organization — It is recommended that vaccines to be used in the 2007 season (southern hemisphere Winter) contain the following:

- an A/New Caledonia/20/99(H1N1)-like virus;
- an A/Wisconsin/67/2005(H3N2)-like virus (The currently used vaccine viruses are A/Wisconsin/67/2005 and A/Hiroshima/52/2005.); and
- a B/Malaysia/2506/2004-like virus.

As in previous years, national control authorities should approve the specific vaccine viruses used in each country. National public health authorities are responsible for making recommendations regarding the use of the vaccine.

WHO has published recommendations on the prevention of influenza. Most of the population is likely to have been infected with influenza A(H1N1), influenza A(H3N2) and influenza B viruses. As a consequence, 1 dose of inactivated influenza vaccine should be immunogenic for individuals of all ages except young children. Previously unimmunized children should receive 2 doses of inactivated vaccine, with an interval of at least 4 weeks between doses.

Reference: *Weekly Epidemiological Record*, 2006,**81**:390

Sitagliptin phosphate for diabetes

United States of America — The Food and Drug Administration (FDA) has approved sitagliptin phosphate (Januvia®), the first diabetes treatment in a new class of drugs known as DPP-4 inhibitors that enhances the body's own ability to lower elevated blood sugar.

FDA approved Januvia® for use in addition to diet and exercise to improve blood sugar levels in patients with type-2 diabetes, alone or in combination with two other commonly prescribed oral diabetes medications, metformin or a PPAR (peroxisome proliferator-activated receptor gamma) agonist, when either of these drugs alone, along with diet and exercise, do not provide adequate blood sugar control.

Sitagliptin phosphate was examined in a total of 2719 patients with type-2 diabetes, in studies lasting from 12 weeks to more than a year. The most common side effects in clinical studies were upper respiratory tract infection, sore throat, and diarrhoea.

Reference: *FDA News*, P06-169 17 October 2006.

Dronedarone marketing application withdrawn

European Union — The European Medicines Agency (EMA) has been formally notified by manufacturer of the decision to withdraw the application for a centralized marketing authorisation for the medicinal product dronedarone hydrochloride (Multaq®).

The indication applied for was rhythm and rate control in patients with atrial fibrillation or atrial flutter (abnormalities of the heartbeat), to maintain normal sinus rhythm or to decrease ventricular rate.

At the time of the withdrawal, it was under review by the Agency's Committee for Medicinal Products for Human Use (CHMP). In its official withdrawal letter, the company stated that the withdrawal of MULTAQ® was due to the fact that the additional clinical data requested by the CHMP cannot be provided within the timeframe of the current procedure.

Reference: European Medicines Agency. Ref. EMA/354409/2006, 8 September 2006. <http://www.emea.europa.eu>

Repaglinide marketing authorization extension request withdrawn

European Union — The manufacturer of repaglinide (NovoNorm® and Prandin®) 0.5 mg, 1 mg and 2 mg tablets has notified the European Medicines Agency (EMA) of its decision to withdraw the application for an extension of the marketing authorization to include use of NovoNorm® or Prandin® in combination with a thiazolidinedione, such as rosiglitazone or pioglitazone, for the treatment of type-2 diabetes. Both products are currently indicated for use in patients who have non-insulin-dependent diabetes (type-2 diabetes).

EMA's Committee for Medicinal Products for Human Use (CHMP) had submitted a provisional opinion that NovoNorm® or Prandin® in combination with a thiazolidinedione could not be approved.

Reference: EMA Press Release, <http://www.emea.europa.eu> and www.emea.europa.eu/humandocs/Humans/EPAR/novonorm/novonorm.htm and <http://www.emea.europa.eu/humandocs/Humans/EPAR/prandin/prandin.htm>.

Abetimus marketing authorization request withdrawn

European Union — The manufacturer of abetimus sodium (Riquent®) has notified the European Medicines Agency (EMA) of its decision to withdraw an application for a centralized marketing authorization. Abetimus sodium was designated as an orphan medicinal product for the treatment of lupus nephritis on 20 November 2001.

At the time of the withdrawal, it was under review by the Agency's Committee for Medicinal Products for Human Use (CHMP). Additional clinical data requested by the CHMP to support the application cannot be provided within the timeframe of the current application procedure.

Reference: EMA Press Release, EMA/410861/2006, 13 October 2006 <http://www.emea.europa.eu>

Imatinib mesilate: revised indications

European Union — The manufacturer of imatinib mesilate (Glivec®), 50 mg and 100 mg capsules and 100 mg and 400 mg film-coated tablets, has notified the European Medicines Agency (EMA) of its decision to withdraw the application for a change to the marketing authorization.

The change would have included treatment of aggressive systemic mastocytosis in adults. Imatinib mesilate was designated as an orphan medicinal product for the treatment of mastocytosis on 26 August 2005. The Committee for Medicinal Products for Human Use (CHMP) considered that the limited data provided did not support a positive benefit-risk balance.

Glivec® is currently indicated for the treatment of adult and paediatric patients with Philadelphia chromosome positive chronic myeloid leukaemia, adult patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia, adult patients with Kit-positive unresectable and/or metastatic malignant gastro-

intestinal stromal tumours, and adult patients with dermatofibrosarcoma protuberans.

During its meeting on 16–18 October 2006, the CHMP recommended an extension of the marketing authorization for Glivec® to include treatment of myelodysplastic syndromes and myeloproliferative diseases, as well as treatment of adult patients with hypereosinophilic syndrome and chronic eosinophilic leukaemia.

Reference: EMEA Press Release, EMEA/423844/2006, 23 October 2006. <http://www.emea.europa.eu> and www.emea.europa.eu/humandocs/Humans/EPAR/glivec/glivec.htm.

Recent Publications, Information and Events

Vigiflow Online for pharmacovigilance

The validation of Vigiflow case report management system has now been completed and version 3.0 was successfully released in February 2006.

The Vigiflow web-based software allows seamless electronic transmission of adverse drug reaction (ADR) reports in (ICH) E2B format from healthcare professionals to their designated reporting centres and onwards to the WHO database or other destinations such as the European medicines Agency (EMA) or the Food and Drug Administration (FDA).

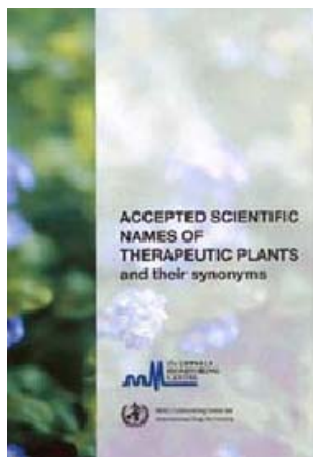
The majority of reports so far submitted to the WHO database via Vigiflow have been received from Switzerland, Brazil, Ghana and Morocco — all active members of the WHO Programme on International Drug Monitoring — are using it to send in their ADR reports, plus eight other member national centres.

Vigiflow offers significant benefits, including:

- Streamlined reporting.
 - Report download for local storage.
 - Multilingual.
 - Built-in statistics and data retrieval.
 - Cost-effective and time-saving.
 - User guide and online help available.
- Reference:** The Uppsala Monitoring Centre.
<http://www.who-umc.org>

Scientific plant names and synonyms

The Uppsala Monitoring Centre's work on herbal synonyms in the form of lists of accepted scientific names and their latin and vernacular synonyms has now been published.



Reference: The Uppsala Monitoring Centre.
<http://www.who-umc.org>

Pharmaceutical inventory control software

The latest release of mSupply v1.94 pharmaceutical inventory control software has been announced. New features include:

- a French version under construction.
- better PDF generation support
- support for direct printing to label printers
- lots of new reports
- sends reports directly to Excel®
- improvements to dispensary mode
- demonstration available on <http://www.msupply.org.nz/download>
- user guide <http://www.msupply.org.nz/files/>

mSupply remains free for use in single-user mode if you are in a developing country or your organization is not-for-profit.

Reference: <http://www.msupply.org.nz> or <http://sussol.net>

Reporting adverse reactions and continuing education

In collaboration with the Canadian Medical Association (CMA), Health Canada has developed a continuing medical education (CME) course entitled *Physician Reporting of Adverse (Drug) Reactions*. A number of reference resources are available via hyperlinks to Health Canada's MedEffect Web site.

Future steps for the online course include posting on Health Canada's MedEffect Web site and pilot testing in the medical undergraduate curriculum. If successful, this initiative will result in the course being

made available to all undergraduate medical programmes in the country.

Outside the medical community, the development of the online AR course has generated interest and requests for similar education initiatives from other health professions and consumers.

An online module for naturopathic doctors has been posted on MedEffect (with a link from the Canadian Association of Naturopathic Doctors website to the learning centre section of MedEffect) and will be integrated into the Canadian College of Naturopathic Medicine's curriculum this fall. Another online module and corresponding guidebook to assist consumers and patients on how to report ARs to their health care professional or Health Canada will be made available on the MedEffect Web site.

Reference: *Canadian Adverse Reaction Newsletter*. Volume 16, Issue 4, October 2006.

Good governance in medicines procurement

Huge amounts of money are spent every year on pharmaceutical products; a market so large that it is extremely vulnerable to corruption. The World Health Organization (WHO) has launched a new initiative to assist governments to promote greater transparency in medicines regulation and procurement. As a first step, WHO is establishing an international expert group.

Before reaching patients, medicines change hands several times in the production and distribution chain. Apart from the loss of resources and the danger posed to patients' lives, corrupt practices also allow the entry into the medicines chain of counterfeit and substandard products, further endangering the health of communities.

Corruption may take on different forms such as bribery, soliciting payment from

suppliers, favouritism in selecting members of committees or in recruiting staff, theft and embezzlement in the distribution chain and health care facilities.

To combat the problem, WHO plans to strengthen regulatory authorities and procurement practices by:

- Stimulating legislative reform that will establish laws against corruption with enforcement and punitive measures.
- Promoting standardized systems of checks and balances to limit or prevent abuse by making publicly available the criteria, structures and procedures to select regulatory and procurement staff and medical products.
- Encouraging ethical practices through behaviour change activities and staff training.

WHO will compile a data base of best practices and successful experiences already tried and tested in countries to promote good governance in the public pharmaceutical sector. A two-day meeting to determine strategies and set up the new initiative took place at WHO, Geneva, on 30–31 October 2006.

Reference: *WHO sets up network to combat corruption in medicines procurement.* Note for the Media, WHO/32. 30 October 2006 and <http://www.who.int/medicines/areas/policy/goodgovernance/home/en/index.html>

WHO public hearings on innovation and intellectual property

All parties with an interest in the upcoming Intergovernmental Working Group on Public Health, Innovation and Intellectual Property have been invited to present their views to a web-based public hearing organized by the World Health Organization (WHO).

WHO has encouraged individuals, civil society groups, government institutions, academic and research institutions, the private sector and other interested parties to contribute to the open hearings which took place between 1 and 15 November. The initiative provided an opportunity for everyone, including the general public, to contribute to developing a solution to a major public health challenge – how to enhance innovation, research and development to address diseases predominantly affecting poor populations.

The developing world continues to bear the highest burden of disease but represents only a small part of the treatment market. While having to cope with a high incidence of infectious diseases, developing countries are also seeing a rapid growth in non-communicable and chronic diseases. Many of the benefits of modern science are not reaching the poor, in particular women and children, who are among the most vulnerable populations.

The web-based hearings come a few weeks before the start of formal discussions between Member States at an Intergovernmental Working Group on Public Health, Innovation and Intellectual Property, taking place in Geneva from 4-8 December. The group will discuss a global strategy and plan of action to enhance research and development to respond to public health challenges.

The parameters of the Intergovernmental Working Group were set out in WHA Resolution 59/24, which was based on recommendations of the Commission on Public Health Innovation and Intellectual Property (CIPIH). Contributors to the public hearings are invited to consult the resolution and the CIPIH report at: http://www.who.int/gb/ebwha/pdf_files/WHA59/A59_R24-en.pdf and <http://www.who.int/intellectualproperty/documents/thereport/en/>

Reference: WHO public hearings: on public health, innovation and intellectual property. <http://www.who.int?medicines>

Pharmaceutical Forum: better information, access and prices

The European Commission has set up the Pharmaceutical Forum to find practical solutions to some of the key structural and public health issues affecting the pharmaceutical industry. The Pharmaceutical Forum brings together Member States, the pharmaceutical industry, public health and patient groups in a voluntary process brokered by the Commission to achieve the benefits of Europe-wide cooperation in areas which are partially governed by national law.

Europe needs to look urgently at the structural issues affecting the competitiveness of the industry and respond to these challenges. The purpose of the Pharmaceutical Forum is to push forward to deliver concrete results by June next year. The progress report just adopted sets out a series of proposals for further action.

Information to patients

The Forum has identified ways to improve quality and access to information, such as:

- Developing a model package of information for patients on diseases (using diabetes as a first example).
- Considering areas for harmonization of EU wide action on information on medicines.
- Improving patient access to good quality health information.

Control of expenditure

Several factors have generated significant changes in the pricing and reimbursement mechanisms of most Member States during recent years, including rising expenditure on medicines, inequity

and lack of early access to medicines and innovative products. The Forum seeks to identify, explore and exchange information and data on alternative mechanisms. With the objective of finding a balance between controlling expenditure, improving access to medicines and rewarding innovation.

Assessing the effectiveness of medicines in comparison with other treatment options

The Forum's report makes a series of recommendations on how to support relative effectiveness systems to help contain pharmaceutical costs as well as stimulating innovation. Relative effectiveness assessment systems identify the most clinically efficiency and cost-effective medicines, and will help set a fair price for these medicines.

Reference: *European Union Press Release*, IP/06/1282, Brussels, 29 September 2006 at http://ec.europa.eu/enterprise/phabiocom/comp_pf_en.htm

Pharmacy education symposium: multidisciplinary practice

Registration is now open for the Fourth Pharmacy Education Symposium: Teaching for multidisciplinary practice to be held in Italy in July 2007.

Programme summary

Day 1: Teaching and learning in a traditional environment.

Day 2: Teaching and learning in an experiential environment.

Day 3: Teaching and learning in a virtual environment.

Reference: Pharmacy Education Symposium website at www.vcp.monash.edu.au/prato2007

Pharmaceutical policy analysis conference in 2007

A conference on pharmaceutical policy analysis, including sociocultural, economic, regulatory and epidemiological aspects of pharmaceuticals and international health will be held from 19–21 September 2007, in Zeist, Netherlands. Everybody who comes to the conference will be asked to submit a paper which will be discussed in groups during the conference. The first stage of attending is to submit a 300 word abstract.

Pharmaceutical policy analysis is increasingly acknowledged as an important driver of evidence-based policy making on pharmaceuticals. In a world with ample diversity in perspectives and opinions about how to prioritize and regulate pharmaceutical policies, and where to intervene in daily practice, robust data and valid research methodologies can, and should, make a difference. However, despite all the enthusiasm and support for pharmaceutical policy research, the scientific quality of the field is yet rather limited in terms of impact on policy makers and visibility in high-impact journals. The objectives of the Conference on Pharmaceutical Policy Analysis are to:

- Build knowledge on the basis of a discussion of Pharmaceutical Policy Analysis papers submitted and reviewed in advance of the meeting.
- Focus on methods for Pharmaceutical Policy Analysis as a long-term outcome to fuel the field.
- Create commitment to deliver publications in high-impact journals.

The theme for the conference will be broadly interpreted to encourage submission of a range of papers on various topics related to international policy

aspects of pharmaceuticals. These could include: prioritizing in and barriers to pharmaceutical innovation. Drug utilization aspects, regulatory issues, economic questions, cross-cultural aspects of medicines' efficacy, safety and usage, quality indicators, methods of pharmaceutical policy analysis, effectiveness of rational use interventions, promotional practices, role of consumers, access to medicines, and international health. Ultimately, it will be the quality of the papers which determines the content of the meeting.

Reference: Enquiries and abstracts to Pieter Stolk: pharmapolicy2007@pharm.uu.nl. P.O. Box 80082, 3508 TB Utrecht, Netherlands.

Final guidance on quality systems

The US Food and Drug Administration (FDA) has released the final version of their *Guidance for industry: quality systems approach to pharmaceutical CGMP regulations*. This version finalizes the draft which was published in October 2004. The October 2nd *Federal Register* announcement notes that the Agency considered all comments received on the draft as they established the final version; however no substantive changes were made.

The final version contains a number of clarifying edits. The guidance is intended to encourage the use of modern quality management system principles by the regulated industry and to foster innovation and continuous improvements in pharmaceutical manufacturing. Alternative approaches may be used so long as they satisfy the requirements of the applicable statutes and regulations.

Reference: *The Federal Register*, Vol. 71, No. 190; pp. 57980 and 57981. 2 October 2006. <http://www.fda.gov/cder/guidance/index.htm> or <http://www.fda.gov/ohrms/dockets/default.htm>.

Newly available guidance documents

The following guidance documents are now available on the US Food and Drug Administration website:

- Fixed Dose Combinations, Co-Packaged Drug Products, and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment of HIV
- Investigating Out-of-Specification Test Results for Pharmaceutical Production

- Current Good Manufacturing Practices (CGMPs)
- Bar Code Label Requirements—Questions and Answers
- Compliance
- Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations

Reference: <http://www.fda.gov/cder/guidance/index.htm>