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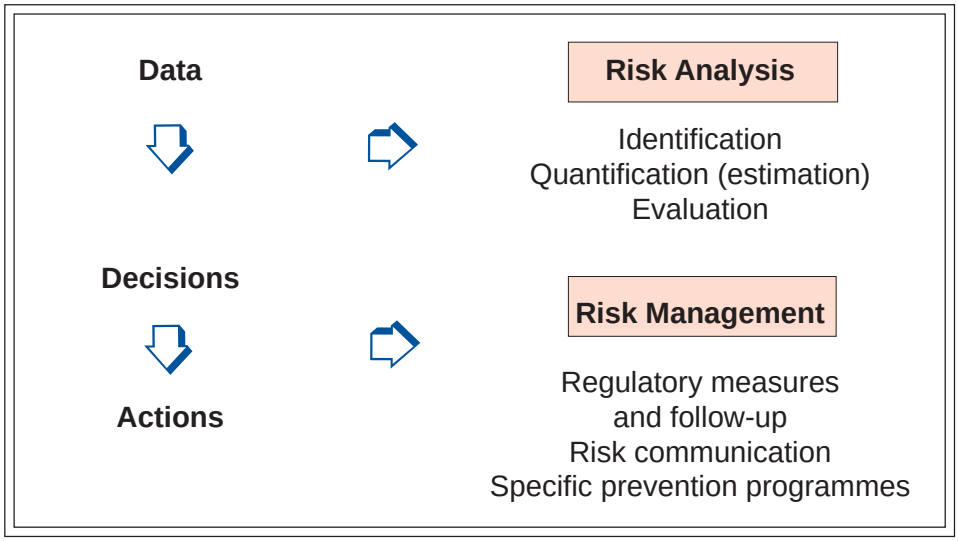
Safety and Efficacy Issues

Improving pharmacovigilance practice beyond spontaneous reporting*

Pharmacovigilance is a public health practice aimed at analysing and managing the risks of medicinal products once they have been marketed. According to this definition, pharmacovigilance can be divided into two distinct phases: risk analysis and risk management. Risk analysis concerns the identification, quantification (or estimation) and evaluation of risks in a stepwise manner, while risk management concerns the implementation and follow-up of the adopted regulatory measures, communication of risks to health professionals and/or the population at large, and setting up specific preventive strategies (1, 2). Risk analysis is data-driven whereas risk management is action-driven, and the decisions taken constitute the bridge between these two areas (figure 1).

In the realm of pharmacovigilance, the identification of risks is normally achieved through spontaneous reporting schemes — the bedrock of any drug surveillance strategy. However, the identification of a risk should be followed by its proper quantification, which means, firstly, measurement of the strength of the association between the drug and the suspected adverse drug reaction (ADR) as a way to confirm or refute the causal relationship and, secondly, the estimation of the impact of such a risk in the exposed population. Finally, identification is made of effect modification factors (sometimes referred to as risk factors). Although the number of spontaneous reports complemented with consumption or sales data may provide a first estimation of risk (e.g. reporting rates), the limitations of such a simple approach are well-known and include variable underreporting, selective reporting, lack of adjustment for confounding factors, difficulty in assuming a daily dose, etc. These limitations are particularly relevant when different drugs are to

Figure 1. Steps in pharmacovigilance



**Presentation made by Francisco J. de Abajo, Division of Pharmacoepidemiology and Pharmacovigilance, Spanish Agency for Medicines and Healthcare Products, at the Eleventh International Conference of Drug Regulatory Authorities (ICDRA), 16–19 February, Madrid, Spain*

be compared. An appropriate quantification will normally require the performance of valid epidemiological studies.

Experience shows, however, that too often regulatory authorities pass directly from risk identification to risk evaluation and take important decisions solely on the grounds of spontaneous reports. According to a recent study (3), from January 1990 to December 1999, 22 new chemical entities were withdrawn from the Spanish market (and most of them from the European market as well) for primary safety reasons; in 15 (68%) of them the decision was based in case reports, in 3 (14%) the decision was based on both case reports and clinical trials and in 4 (18%) the decision was based on epidemiologic studies.

Many decisions in pharmacovigilance could, of course, be warranted on the basis of individual case reports. For instance, when the causal relationship can be easily established (e.g. anaphylactic shock), or the suspected ADR can reasonably be linked to the drug and represents a serious issue prompting application of the precautionary principle. However, the importance placed upon case reports in risk analysis may be excessive. A good number of pharmacovigilance signals can only be properly assessed with the help of pharmacoepidemiologic studies. Do highly-active antiretroviral drugs increase the risk of myocardial infarction (4)? Does use of SSRIs increase the risk of serious bleeding disorders (upper gastrointestinal or intracranial haemorrhages) (5, 6)? Is the use of dinoprostone (PGE_2) as a labour inducer associated with increased risk of postpartum disseminated intravascular coagulation (7)? Spontaneous reports raised the signal in all these examples, but a rational decision had to await completion of formal studies.

The above data pinpoint an important issue for regulatory authorities: pharmacovigilance practice is not optimal because risk quantification is rarely achieved through appropriate epidemiological studies. The reason for this shortcoming is probably twofold: a prevailing conception of pharmacovigilance as just monitoring individual case reports; and a lack of efficient data sources to perform the studies in the timeframe required for a meaningful pharmacovigilance risk analysis — whose units are normally months, not years.

Regulatory authorities are not comfortable with this status quo and may need to progress in at least two directions in order to improve pharmacovigilance practice. Firstly, by providing or reinforcing the training in epidemiological methods among pharmacovigilance teams and, secondly, by supporting the development of permanent and efficient data sources that may allow the performance of epidemiological studies to assess signals raised by spontaneous reports or any other source (Table 1).

Efficient data could be drawn from automated healthcare databases (either requiring record-linkage or stand-alone databases), but may also be permanent registries for specific diseases potentially associated with drugs (ideally according to a case-control scheme), product-specific or patient-specific large and long-term cohorts. Although some progress has been made in the past, a greater and generalized emphasis is needed for the proliferation of these efficient data sources. Multisite databases studies will be

Table 1. Ways to improve pharmacovigilance practice: the role of drug regulatory authorities

1. Reinforce training of the pharmacovigilance team in epidemiological methods.
2. Support the development of permanent and efficient data sources (e.g. healthcare automated databases) that may be useful for risk identification and, particularly, for risk quantification.
3. Identify and evaluate the potential usefulness for pharmacovigilance of the existing national data sources (e.g. registries of specific diseases, hospital discharge databases).
4. Reserve a specific budget for funding ad hoc studies when a signal of public health importance is raised.

necessary in the future to identify risks emerging in the early postmarketing phase, where even the largest databases are underpowered. Health authorities have much to say in this development, in particular when databases potentially useful for pharmacovigilance are managed in the public sector, as frequently occurs in Europe. Confidentiality issues have sometimes been argued to impede access to relevant clinical information and this is a hurdle we have to overcome.

In line with the above mentioned ideas, the Spanish Agency for Medicines and Healthcare Products has set out a programme of funding aimed at supporting academic initiatives like a case-control surveillance of blood dyscrasias in the Barcelona area (8), a register of serious liver injuries provided by a nationwide network of hepatology units coordinated by the University of Malaga (9), or the long-term follow-up of rheumatologic patients treated with anti-TNF products managed by the Spanish Society of Rheumatology (10). In addition, the Agency has assumed the challenge of setting up a database (called BIFAP) using clinical records from general practitioners (11), taking the General Practice Research Database from the United Kingdom as a reference (12). Up to now, the BIFAP database includes information from over one million patients provided by more than 800 primary healthcare physicians (general practitioners and paediatricians) on a voluntary basis, and it is currently in the clinical validation phase. One of the important advantages of this database is that health data are anonymous, ensuring confidentiality of patient identity.

Sometimes the study we need is not an aetiology-oriented one but merely a drug utilization enquiry. In a good number of pharmacovigilance crises the misuse component plays a fundamental role: for instance, the cerivastatin case with the highly prevalent concomitant use of gemfibrozil and the habit of using high doses from the very beginning of treatment. Early detection of such misuse (or off-label use) problems may help to prevent risk situations. None the less, efficient and valid data sources that complement spontaneous reporting are necessary as well. To this aim, we are planning the establishment of a network of community pharmacies to provide our agency with information on the qualitative aspects of drug utilization (dose, duration, patient characteristics, concomitant use of drugs, etc). The information provided will also be useful to assess the impact of regulatory measures

Often, we have requested the pharmaceutical industry to be pro-active over drug safety issues and not merely reactive. A shift in approach is now required from drug regulators. Since the 1960s, health authorities have understood that spontaneous reporting of individual cases could be an important tool for detecting drug safety problems and have taken important steps to set up national pharmacovigilance schemes. Forty years later, we have learned that for a risk analysis to be scientifically sound we need pharmaco-epidemiological studies and newer and more efficient data sources to make these feasible. In the 1960s, health authorities took the lead and did not pass the responsibility of drug surveillance to the pharmaceutical companies. In the same manner as health authorities devote a budget to support spontaneous reporting schemes, they should also reserve a budget for epidemiological studies to be performed, either on their own or in collaboration with independent researchers.

Pharmacovigilance is a cooperative and worldwide effort. It is clear that the developed countries have a greater responsibility in setting up newer data sources and promoting better pharmacovigilance practice. But the developing countries should also be prepared for this progress by acquiring at least the necessary training in order to keep up with the pace of modern pharmacovigilance.

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Spironolactone and ACE inhibitors: link to hyperkalaemia

Heart failure affects approximately 5 million persons annually in Canada and the United States (1). Medications are the mainstay of therapy, and in the past two decades there has been a shift away from the use of diuretics and cardiac glycosides toward use of angiotensin-converting–enzyme (ACE) inhibitors, beta-adrenergic antagonists, and aldosterone antagonists (1). Published in September 1999, the Randomized Aldactone Evaluation Study (RALES) demonstrated that treatment with spironolactone substantially reduced morbidity and mortality in patients with severe heart failure (2). Spironolactone is inexpensive and generally well tolerated, but it can provoke life-threatening hyperkalaemia when combined with ACE inhibitors (3–6).

In 1994, among patients treated with ACE inhibitors and recently hospitalized for heart failure, the spironolactone-prescription rate was 34 per 1000 patients, but it increased immediately after publication of the RALES trial to 149 per 1000 patients by late 2001. A population-based time-series analysis to examine trends in the rate of spironolactone prescriptions and the rate of hospitalization for hyperkalaemia in ambulatory patients before and after the publication of RALES has recently been reported in the *New England Journal of Medicine* (7). The study links prescription-claims data and hospital-admission records for more than 1.3 million adults 66 years of age or older in Ontario, Canada, for the period 1994 – 2001. As compared with expected numbers of events, there were 560 additional hyperkalaemia-related hospitalization and 73 additional hospital deaths during 2001 among older patients with heart failure who were treated with ACE inhibitors.

The study found that publication of the RALES trial results was associated with an abrupt increase in the rate of prescriptions for spironolactone among older patients in Ontario who were treated with ACE inhibitors, regardless of whether or not they had previously been hospitalized for heart failure. This finding suggests that a major clinical trial can significantly influence prescription practices in the absence of direct marketing forces from the pharmaceutical industry. Considerable increases in the rates of hospital admission for hyperkalaemia and subsequent in-hospital death were also noted. Findings also indicate that spironolactone-related hyperkalaemia is a much greater problem in everyday practice than in the setting of a clinical trial.

The authors of the analysis believe there are at least six possible reasons why hyperkalaemia is a more common occurrence in clinical practice than it was in the carefully controlled setting of RALES.

- monitoring of patient potassium levels is insufficient (8);
- baseline attributes that predispose patients to hyperkalaemia (e.g., diabetes mellitus) are neglected (9, 10);
- conditions that develop during therapy (e.g., renal dysfunction) are overlooked;
- inappropriate prescribing of high doses of spironolactone (11) or other medications contributes to hyperkalaemia (12).

- increase in dietary potassium intake by patients during treatment.

- Finally, extending the RALES findings to patients who do not have left ventricular systole dysfunction.

Although the study was observational in nature and cannot prove causality, the relationship between the publication of RALES, the surge in spironolactone use, and the increase in hyperkalaemia-related admissions is temporally compelling, biologically plausible, and consistent with existing evidence (4–6, 8, 11, 13). Closer laboratory monitoring and more judicious use of spironolactone may reduce the occurrence of this complication.

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Pulmonary toxicity with long–term nitrofurantoin

Nitrofurantoin is indicated for the treatment of urinary tract infections (1, 2). To date, the Australian Drug Reactions Advisory Committee (ADRAC) has received 576 reports of suspected adverse reactions to nitrofurantoin, with pulmonary reactions described in 142 reports (25%), including 46 reports received since the last ADRAC publication on the subject in 1995 (3). Forty of the reports of pulmonary reactions related to long-term use and were consistent with pulmonary fibrosis or interstitial pneumonitis. The most common presenting symptoms were dyspnoea or cough, but some had hypersensitivity features (fever, rigours, pruritus, rash, or eosinophilia).

The reports usually involved elderly females, probably reflecting usage. The nitrofurantoin doses were 50–300 mg/day (recommended daily dose for prophylaxis 50–100 mg). Some reports described severe pulmonary reactions with exposure as low as 50 mg/day for 8 months. The longest time to onset was 16 years. Recovery by the time of reporting was documented in 12 cases, but some patients showed indications of persistent lung damage. Two patients died as a result of pulmonary toxicity.

Pulmonary toxicity of nitrofurantoin should be considered when treatment is extended for > 6 months, especially if the patient is elderly. Patients should be made aware of the possibility of pulmonary toxicity, and advised to report dyspnoea or persistent cough. If pulmonary reactions occur, nitrofurantoin should be immediately stopped. Although cessation may be followed by regression of symptoms, the resolution of pulmonary injury arising from long-term use may be incomplete.

Extracted from Australian Adverse Drug Reactions Bulletin, Volume 23, Number 4, August 2004.

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Cardiac valvulopathy and pergolide

Pergolide is a dopamine agonist and ergot derivative indicated for the adjunctive treatment of Parkinson disease. An association has recently been identified between pergolide and valvular heart disease (1). This evidence has been subsequently supported by a study which found cardiac valvulopathy in 26 of 78 patients (33%) with Parkinson disease who were treated with pergolide, but in none of 18 patients who had never been treated with ergot-derived dopamine agonists (2). There was a trend to more severe disease with greater exposure to pergolide. The mitral valve was affected in most (20) of the patients and smaller numbers had restriction of the aortic and tricuspid valves. Mean systolic pulmonary artery pressures were significantly higher in the pergolide recipients versus the control group. Pergolide was discontinued in only six of the patients with restrictive valvular heart disease and improvement had occurred in two of them six months after discontinuation of pergolide.

Pergolide-related valvulopathy involves fibro-restrictive lesions of the cardiac valves and is typically associated with valve regurgitation. Other ergot derivatives, such as methysergide and ergotamine, and the appetite-suppressants fenfluramine and dexfenfluramine (withdrawn worldwide in 1997), are known to cause a similar cardiac valvulopathy (3, 4). Valvulopathy associated with the carcinoid syndrome and with ergot derivatives including pergolide is attributed to high serotonin levels. Fenfluramine and dexfenfluramine also cause pulmonary hypertension and along with pergolide interact with the serotonin 5-HT_2B receptor (2).

The Australian Drug Reactions Advisory Committee (ADRAC) has not yet received any reports of valvular heart disease with pergolide, possibly reflecting lack of recognition of the association. Although cabergoline is also an ergot derivative, there are, at present, no associated reports of valvulopathy to ADRAC or in the published literature.

Before pergolide is prescribed, patients should be advised of the risk of valvulopathy. Prescribers should conduct a thorough baseline clinical cardiovascular examination including a check of patient history, and perform regular follow-up checks of patients taking pergolide. Echocardiography should be considered if a murmur is detected. Consideration should be given to discontinuation of pergolide if new-onset valvular disease is confirmed.

Extracted from Australian Adverse Drug Reactions Bulletin, Volume 23, Number 4, August 2004

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Tramadol–warfarin interaction

Some individuals are susceptible to interaction between tramadol and warfarin. The Australian Drug Reactions Advisory Committee (ADRAC) has received 11 reports of this interaction leading

to an increase in INR (international normalized ratio) or a haemorrhagic event. The median onset time after addition of tramadol to stabilized warfarin therapy was 4 days. Five reports describe rapid recovery within 1–4 days of withdrawal of tramadol with or without reduction in the dose of warfarin. Two patients, aged 76 and 88 years, died of haemorrhagic stroke. In one of these patients, both tramadol and warfarin were continued for six days after an INR of 5.0 was measured. Four cases of interaction between tramadol and warfarin have been reported in the English language literature (1–3) and the interaction is included in the Australian product information for products containing tramadol. It is unclear whether the interaction occurs with injectable tramadol.

A pharmacodynamic study has been conducted of the effect on INR of giving tramadol to 19 individuals stabilized on phenprocoumon (a coumarin anticoagulant with properties similar to warfarin) (4) Two of the individuals had clinically significant increases in INR to 6.0 and 7.3, respectively, while they were taking tramadol, but the mean difference in INR for all participants did not reach statistical significance. The mechanism of the interaction is unclear, but these results suggest that the interaction may be associated with a variation in metabolism present in a small proportion of the population. With a total of 4.2 million PBS prescriptions for oral tramadol and 11 reports of tramadol-warfarin interaction (c.f. 827 total reports for tramadol), this would appear to be an uncommon event in those taking both medications.

Prescribers are advised to monitor INR in the first few days for up to a week after adding tramadol to warfarin therapy.

Extracted from Australian Adverse Drug Reactions Bulletin, Volume 23, Number 4, August 2004.

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Fluoroquinolones and warfarin interactions

Fluoroquinolones are primarily used to treat respiratory and urinary tract infections, prostatitis, septicaemia, and skin, soft-tissue, bone and joint infections (1–6). Cases of increased anticoagulant activity have been reported in patients taking warfarin concurrently with fluoroquinolones (7, 8). The proposed mechanisms of this interaction are displacement of warfarin from protein-binding sites, reduction in gut flora that produce vitamin K and its clotting factors, and decreased warfarin metabolism (9). Most fluoroquinolones are inhibitors of cytochrome P450-mediated metabolism and may therefore be responsible for toxicity of other co-administered drugs by decreasing their clearance, especially drugs with a narrow therapeutic index such as warfarin (10).

As of January 2004, Health Canada received 57 reports of suspected coagulation disorders associated with fluoroquinolones and warfarin. Ten cases involved ciprofloxacin, 13 gatifloxacin, 16 levofloxacin, 12 moxifloxacin and 6 norfloxacin. None of the cases of coagulation disorders involved ofloxacin (marketed in Canada in December 1990). The 57 reports involved 46 patients 60 years of age and older. Forty-nine reports were considered serious, with 16 involving adverse reactions resulting in hospital admission. Four patients (aged 70 to 90 years) taking ciprofloxacin (1), gatifloxacin (2) and levofloxacin (1) died. Causality assessment of these cases is difficult because of confounding factors or the complexity of the cases. In 15 of the reports, the INR had been stabilized with warfarin before the fluoroquinolone therapy was started.

Health Canada continues to receive reports of suspected interactions between fluoroquinolones and warfarin. Possible risk factors for this interaction include the infectious disease and its accompanying inflammatory process, other concomitant drugs, and the age and general health status of the patient (5). Certain fluoroquinolones may enhance the effects of warfarin or its derivatives during concomitant administration of these drugs (2–6). The prothrombin time and INR should be monitored closely, especially in elderly patients, and the anticoagulant dose adjusted accordingly.

Extracted from Canadian Adverse Reaction Newsletter, Volume 14, Issue 3, July 2004

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Suspected interactions with anticoaglants

In September 2003 the United Kingdom Committee on Safety of Medicines highlighted the possible interaction between warfarin and cranberry juice and advised patients taking warfarin to limit or avoid drinking cranberry juice (1). They had received 8 reports since 1999 of a possible interaction that led to changes in the international normalized ratio (INR) or bleeding: in one case the patient died, in four cases there was an increase in INR or bleeding, in two cases the INR was unstable, and in one case the INR decreased (2). In the fatal case, the patient's previously stable INR increased to > 50 (therapeutic INR 2.0-3.0) following 6 weeks of cranberry juice consumption (2). The patient died of a gastrointestinal and pericardial haemorrhage. In another case a patient with a prosthetic mitral valve was taking warfarin. A persistently elevated INR was noted 2 weeks after he began to drink cranberry juice (almost 2 L/d). Subsequent surgery led to postoperative bleeding complications (3).

In theory, the interaction between warfarin and cranberry juice is biologically plausible: warfarin is predominantly metabolized by cytochrome P450 (CYP2C9), and cranberry juice contains flavonoids, which inhibit CYP enzymes (1, 2). In the United States, the National Center for Complementary and Alternative Medicine at the National Institutes of Health, will investigate cranberry-drug interactions as part of a larger cranberry research initiative (4).

Suspected interactions have also been documented between anticoagulants and herbal products such as devil's claw, ginkgo biloba, Panax ginseng, green tea, papain (papaya extract), St. John's wort (5, 6), dong quai, dan shen (6, 7) and certain brands of quilinggao (7). Vitamins (e.g., A, E, C and K) (8, 9) fish oil supplements (10), and food products (e.g., soy milk) (11) may also interact with anticoagulants. Given warfarin's narrow therapeutic margin, patients should be aware of which drugs, natural health products and food products may be associated with interactions.

Extracted from Canadian Adverse Reaction Newsletter, Volume 14, Issue 3, July 2004

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Dura mater graft: association with Creutzfeldt–Jakob disease

Tutoplast Dura® mater is commercially processed dura mater obtained from human donors (1). Regulated as a medical device, Tutoplast Dura® mater was available in Canada between January 1982 and April 2002 for use in various surgical treatments, including neurosurgery (1). In June 2003, a 59-year-old Canadian woman presented with slight memory loss, decreased level of consciousness, myoclonus, focal seizures, decreased ability to speak and nystagmus. The patient had received a graft in 1992 during a surgery for excision of a benign brain tumour. Investigations showed hydrocephalus and surgery sequelae on MRI, and electroencephalography changes not typical for Creutzfeldt-Jakob disease (CJD). She died in July 2003. Autopsy confirmed classical CJD.

Worldwide there has been only one documented case of CJD associated with the use of Tutoplast Dura® (2). Health care providers should be aware of the possibility of iatrogenic CJD in recipients of dura mater grafts in whom neurological signs and symptoms develop. The incubation period can be 20 years or more. Appropriate infection prevention and control precautions should be taken for recipients of dura mater grafts when they present a risk of transmitting the CJD agent (3).

Extracted from Canadian Adverse Reaction Newsletter, Volume 14, Issue 3, July 2004

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Leflunomide: serious multisystem adverse effects

Leflunomide is an effective disease-modifying agent (DMARD) for rheumatoid arthritis (1). Its use has been associated with significant and serious adverse reactions involving haematological, hepatic, immune, dermatological and respiratory systems. It is a pro-drug activated by metabolism in the gut wall and liver, and excreted by the renal and biliary systems (2). The long half-life of leflunomide may delay resolution of some of these reactions (3, 4) . However, regular monitoring and patient education of early warning signs can reduce morbidity.

It is estimated that between 500 and 1500 patients in New Zealand have been prescribed leflunomide up to the end of 2003 (5). The adverse reactions report include:

- Elevated hepatic enzymes, neutropenia, thrombocytopenia and diarrhoea.
- Sepsis leading to multi-organ failure and death (concomitant medicines were methotrexate, ketoprofen and triamcinolone).
- Hypersensitivity pneumonias, resulting in life-threatening respiratory compromise.
- Multiple bullous eruptions occurring within three weeks of starting leflunomide, and resolving upon discontinuation.

Despite the serious adverse reaction profile of leflunomide, it is an effective DMARD. As with all medicines use of leflunomide requires an assessment of its risk and benefits on an individual patient basis. Prescribers should be aware that the concomitant use of other immuno-

modulating agents may have an additive effect, not only on improving symptoms of acute rheumatoid arthritis but also on the frequency and severity of adverse reactions.

To minimize the risk of serious blood and liver adverse reactions, all patients taking leflunomide should have their haematological and liver function monitored. Ongoing monthly monitoring is recommended if methotrexate is used concurrently (6).

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Myopathy with statins: importance of CK levels

Reports of myopathy and rhabdomyolysis with statins are a reminder to prescribers to measure creatine kinase (CK) levels in patients presenting with muscle pain or weakness. The risk of myopathy may be increased by high doses of statins, especially in patients with co-morbidities, or in the presence of interacting medicines such as diltiazem.

While the statins are effective in providing protection from coronary and cardiovascular events, they are known to cause myopathy (usually dose-related) and, rarely, rhabdomyolysis (1). A clinical diagnosis of myopathy is made when there is muscle pain or weakness accompanied by a creatine kinase (CK) level more than ten times the upper limit of normal. Rhabdomyolysis is a severe form of myopathy with muscle breakdown leading to myoglobinuria, which may result in renal failure and death (2).

The Centre for Adverse Reactions Monitoring (CARM) in New Zealand has received eight recent reports (including two fatalities) of rhabdomyolysis occurring in patients taking between 20 mg and 80 mg of a statin daily. Six of these patients were taking simvastatin which, along with atorvastatin, is fully funded in New Zealand and therefore prescribed more often than the other available statins (i.e. fluvastatin and pravastatin).

It is advisable to monitor patients for signs and symptoms of muscle pain, tenderness or weakness, particularly during both the initial months of statintherapy and subsequent dose increases (3, 4). Creatine kinase measurements must be performed when symptoms occur. Patients with additional risk factors (e.g., diabetes, older age, hypothyroidism, liver or renal disease (1, 5) merit closer monitoring as they may be more at risk of rhabdomyolysis (3). Statin treatment should be discontinued immediately if an elevated CK level is found. i.e., CK >10 x upper limit of normal (6), or where myopathy is suspected or diagnosed (3, 4).

The risk of myopathy or rhabdomyolysis with simvastatin alone is dose related and this risk is increased with concomitant fibrates, as they alone can cause myopathy (3). The risk is also increased when simvastatin and atorvastatin (both CYP 3A4 substrates; fluvastatin and pravastatin are not (7) are used concomitantly with potent CYP 3A4 inhibitors (e.g., erythromycin, itraconazole, amiodarone, verapamil) (3, 4). Diltiazem, a weaker inhibitor of CYP 3A4, is frequently prescribed with a statin. Diltiazem increases the risk of rhabdomyolysis to 1% when given with simvastatin 80 mg daily (3). However, fatal rhabdomyolysis has been reported in two New Zealand patients taking diltiazem whose simvastatin doses were increased to 40 mg and 60 mg daily, respectively. Both had significant comorbidity (8).

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Inhaled corticosteroids and skin atrophy

Inhaled corticosteroids can cause skin atrophy. This adverse effect may be exacerbated by sun exposure, possibly via a cumulative mechanism. The risk of skin atrophy can be minimized by using the lowest possible maintenance dose of inhaled steroid, as well as protecting the skin from sun exposure.

Inhaled corticosteroids have an essential role in the management of asthma. Inhalation allows high concentrations of corticosteroids to reach target sites within the lung while keeping systemic exposure to a minimum (1). Although the safety profile of inhaled corticosteroids is generally superior to that of oral corticosteroids, systemic adverse effects still occur. A number of studies (2, 3) confirm that inhaled corticosteroids, even at low doses, (4) can cause skin atrophy (5) and purpura. The mechanism appears to involve a reduction in collagen synthesis (4). Collagen changes were also found in pre-pubertal children receiving inhaled budesonide (6). A meta-analysis (3) of 27 studies found that marked adrenal suppression mostly occurred with doses of inhaled corticosteroid above 1500 mcg/day (750 mcg/day for fluticasone propionate).

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Dermatological adverse drug reactions

The skin is the organ most frequently affected by adverse drug reactions (ADRs). In 2003, dermatological ADRs accounted for 46% of all adverse reactions reported to the Pharmacovigilance Unit of the Health Sciences Authority, Singapore. Most of the reported dermatological ADRs were the non-serious types such as urticaria, erythema and rashes. However there were a significant number of serious and potentially life-threatening reactions such as toxic epidermal necrolysis (TEN) and Stevens Johnson syndrome (SJS).

Analysis of local ADR reports
Between January 1997 and May 2004, the Pharmacovigilance Unit has received 35 reports of TEN and 111 reports of SJS. The top ten suspected causative drugs are:

Name	Reports
Carbamazepine	24
Cotrimoxazole	21
Phenytoin	14
Amoxicillin	12
Allopurinol	11
Coamoxiclav	8
Ceftriaxone	6
Mefenamic acid	5
Ciprofloxacin	4
Cloxacillin	4

Other drugs implicated include the following:

Anti-infectives: ampicillin, bacampicillin, cefadroxil, cefalexin, ceftazidime, cefuroxime, chloramphenicol, clindamycin, dapsone, doxycycline, erythromycin, imipenem/cilastatin, levofloxacin, lincomycin, methisoprinol, metronidazole, moxifloxacin, nitrofurantoin, ofloxacin, rifampicin, spiramycin, sulfadiazine, tetracycline and trimethoprim

Anti-inflammatory agents: Acetylsalicylic acid, celecoxib, diclofenac, etoricoxib, ibuprofen, isoniazid, mefenamic acid, nimesulide and piroxicam

Antiepileptics: gabapentin, lamotrigine and phenobarbitone

Analgesics: chlormezanone/paracetamol, codeine/promethazine, orphenadrine/ paracetamol and paracetamol

Cardiac drugs: amlodipine, captopril, hydrochlorothiazide, losartan and perindopril

Others: alendronate, amitriptyline, atropine/ diphenoxylate, glucosamine, hydroxychloroquine, mesalazine, omeprazole, prochlorperazine, ticlopidine, tolbutamide, trichloroethylene and trifluoperazine

Further analysis of the data revealed that the patients' ages ranged from 1 to 89 years. More females were reported to suffer from these ADRs: 79 females compared to 59 males.

Reference: Health Science Authority of Singapore website at: http://www.hsa.gov.sg

Table 1: Comparison of toxic epidermal necrolysis and Stevens Johnson syndrome

	TEN	SJS
Estimated incidence	0.4 – 1.2 cases per million population per year	1.2 – 6 cases per million population per year
Possible causes	95% drug-induced	33% cases are drug-induced 15% due to infections
Mortality	44% (major cause: sepsis)	< 5%
Description	Fever (higher) Influenza-like syndrome 1-3 days before development of lesions Discrete red macules, lesions of the skin and mucous membranes of conjunctiva, oral cavity and/or genitalia > 30% of epidermis involved Pulmonary complications Anaemia, lymphopenia, neutropaenia Mild elevations of liver enzymes	Fever Influenza-like syndrome 1-3 days before development of lesions Discrete red macules, lesions of the skin and mucous membranes of conjunctiva, oral cavity and/or genitalia < 10% of epidermis involved May evolve into TEN

Visual disturbances with COX–2 inhibitors

Acute, temporary, and sometimes severe visual disturbances have been reported with celecoxib and rofecoxib use. The eyesight changes appear to be completely reversible on withdrawal of the COX-2 inhibitor. Similar events have occurred with non-specific nonsteroidal anti-inflammatory agents (NSAIAs). In patients who develop acute visual disturbance while on a COX-2 inhibitor or NSAIA, prompt withdrawal is recommended followed by monitoring for resolution of symptoms.

The Pharmacovigilance Centre in New Zealand has received nine reports of visual changes — blurred vision, abnormal vision, scintillating scotomata, visual field defect and temporary blindness — associated with the use of celecoxib and rofecoxib. Six of the reports were for celecoxib (from a total of 726 reports), and three for rofecoxib (out of 487 reports) (1). In all but one, duration to onset from first taking the COX-2 inhibitor was within four weeks. The eyesight changes were bilateral in eight of the cases. To date, there have not yet been any reports received for the newer COX-2 inhibitors.

The World Health Organization (WHO) adverse reactions database contains similar reports for celecoxib and rofecoxib. There is one other published report (2) of visual disturbance with celecoxib; and two reports (3, 4) of visual disturbance associated with ibuprofen involving a total of four patients, suggesting that visual changes can also occur with the nonspecific nonsteroidal anti-inflammatory agents (NSAIAs).

Blurred vision, cataract, conjunctivitis, eye pain and glaucoma are listed as adverse effects in the celecoxib data sheet (5); while blurred vision is included in the rofecoxib data sheet (6).

There is evidence that the cyclo-oxygenase enzymes COX-1 and COX-2 are involved in the regulation of retinal blood flow (7). Interference with the action of these enzymes by either COX-2 inhibitors or conventional NSAIAs may therefore cause acute, temporary disturbance of vision. The clinical picture seen in the reported cases is consistent with this mechanism, although there may be other possible explanations.

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Clopidogrel, haemorrhage and haematological disorders

Clopidogrel is indicated for the prevention of myocardial infarction and stroke in patients with atherosclerosis and, in combination with acetylsalicylic acid, for the treatment of acute coronary syndrome. It inhibits platelet aggregation, with activity persisting for as long as seven days.

Haemorrhagic events have been described in 28% of the reports received by the Australian Drug Reactions Advisory Committee (ADRAC) in association with clopidogrel (130 of a total of 460 reports). Clopidogrel was the only suspected drug in 27 cases and another 27 cases were attributed to clopidogrel plus acetylsalicylic acid alone (see Table 1). In 63 (48%) of the cases, the patient was taking clopidogrel plus two or more other drugs which are known to cause bleeding (anticoagulants, thrombolytics, platelet inhibitors, NSAIDs). Of the 130 reports, 18 had a fatal outcome.

In a randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE), the rate of any bleeding

Table 1: ADRAC reports of haemorrhage with clopidogrel

Suspected drug(s)	No. of cases	No. of fatal cases
Clopidogrel alone	27	(1)
Clopidogrel + acetylsalicylic acid alone	27	(1)
Clopidogrel + one other drug*	25	(4)
Clopidogrel + > 2 other drugs*	63	(12)
Total reports of haemorrhage	130	(18)

** Anticoagulants, thrombolytics, platelet inhibitors, NSAIDs*

disorder with clopidogrel was 9.3% (15% severe) (1). The risk of bleeding events had been reduced in this study by discontinuing anticoagulants and antiplatelet drugs before randomization. Further, an early report from the MATCH study of high-risk stroke patients indicates that adding acetylsalicylic acid to clopidogrel doubled the risk of life-threatening bleeds from 1.3% to 2.6% ($p<0.001$) (2). In addition to increasing the risk of haemorrhage, the ADRAC data suggest that concurrent use of more than two drugs with the potential to cause bleeding increases the likelihood of fatality (19% of reports with > 3 suspected drugs had a fatal outcome, see Table 1).

Blood dyscrasias, with a total of 80 reports to ADRAC, are another common reaction type with clopidogrel. Table 2 compares the number of these reports for clopidogrel and ticlopidine. Considering usage, ticlopidine is associated with a much higher rate of reporting of agranulocytosis, neutropenia and thrombocytopenia than clopidogrel (3). ADRAC has received one report of the life-threatening thrombotic thrombocytopenic purpura (TTP), involving disseminated platelet aggregation, with each drug (4, 5). Clopidogrel has largely replaced ticlopidine, because of its greater safety in relation to bone marrow suppression and TTP.

Allergic cutaneous reactions, particularly urticaria, rash and puritus, are also a common adverse effect of clopidogrel (141 reports).

Prescribers should be aware of the risk of haemorrhagic complications with clopidogrel, especially when it is used in combination with other antithrombotic agents.

Extracted from Australian Adverse Drug Reactions Bulletin, Volume 23, Number 4, August 2004

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Table 2: Reports of haematological disorders with clopidogrel and ticlopidine

Haematological disorders	Clopidogrel	Ticlopidine
Neutropaenia	14	26
Agranulocytosis	4	22
Other leukopaenia	4	6
Thrombocytopaenia	42	19
Thrombocytopaenic purpura	4	5
Pancytopaenia	1	2
Anaemia	19	4
Total reports	460	181
Total PBS prescriptions (million, Australia)	4.0	0.16

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Reports of diarrhoea with carvedilol

Carvedilol is a non-cardioselective beta-blocker with alpha blocking activity (1). It is indicated for the management of essential hypertension, angina pectoris and as adjunctive therapy in chronic heart failure (2). The New Zealand Centre for Adverse Reactions Monitoring (CARM) has received four reports of diarrhoea with carvedilol (Dilatrend®).

In three of the reports, severe diarrhoea developed within a week; and in the fourth case, the diarrhoea was moderate and began during the first month of carvedilol treatment. The doses of carvedilol ranged from 6.25 mg to 25 mg daily. All the individuals experienced improvement in their symptoms on stopping the medicine. In Australia, eleven cases have been reported to the Adverse Drug Reactions Unit (3).

Diarrhoea is a recognized adverse effect of the beta-blockers as a class, (1) and there are cases documented in the literature (4). Diarrhoea is a possible, but not dose-related, side effect of beta-blocker therapy. If the diarrhoea is severe or persistent, withdrawal of the beta-blocker is recommended but this must be gradual to avoid harmful cardiovascular sequelae.

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Herbal remedy containing glibenclamide

Singapore — A female patient was hospitalized recently for diabetic ketoacidosis, characterized by lethargy, polyuria and polydipsia. The patient had apparently defaulted follow-up with her doctor and stopped taking her anti-diabetic medications when she started taking a Jamu product, Kenis Pil® about 3 years ago. The product was labelled to contain herbal ingredients and claimed to cure symptoms of diabetes.

However, on testing and analysis, the product was found to be adulterated with glibenclamide. Based on a recommended intake of 10 tablets 3 times daily, the patient was consuming 0.9 mg of glibenclamide daily. Also, the patient's diabetic condition was not controlled thus resulting in diabetic ketoacidosis. Unsupervised use of glibenclamide poses a high risk to patients. Doses have to be adjusted in elderly patients and those with moderate to severe renal and liver impairments.

Reference: 29 July 2004. . Health Sciences Agency, Singapore. http://hsa.gov.sg

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.

Vaccines and Biomedicines

Safety of vaccine products under development

The Global Advisory Committee on Vaccine Safety (GACVS) is an expert clinical and scientific advisory body to WHO established to deal independently and with scientific rigour to vaccine safety issues of global importance (1). The GACVS held its tenth meeting in Geneva on 10–11 June 2004 and, among other issues discussed, it devoted time to review safety issues for products that are likely to be submitted for regulatory review in the near future. The full set of conclusions and recommendations from the Committee are published on the GACVS web site at http://www.who.int/vaccine_safety/en (2).

Safety of adjuvants

During the meeting, presentations were made on the current status of the scientific development of a number of novel adjuvants. Current WHO requirements for production, quality control, preclinical and clinical evaluation of vaccines and adjuvants published in the WHO Technical Report Series (3–5) were reviewed. Other guidelines and guidance relevant to adjuvants in vaccines were discussed (6, 7).

During the past decade, a large number of novel adjuvants have been developed and evaluated clinically (8–11). Those considered by the Committee included oil-based emulsions such as MF59 and Montanide ISA 720®, immunostimulators such as monophosphoryl lipid A, CpG oligonucleotides, saponins such as QS21, and mucosal adjuvants based on bacterial exotoxins that have been developed for nasal and oral delivery. Several of these adjuvants are already contained in licensed vaccines, and others are likely to be submitted for regulatory approval in coming years. The availability of novel adjuvants will have an important impact on the scientific development, efficacy, safety and quality of new vaccines developed for conditions such as HIV, tuberculosis, malaria, or leishmaniasis. Increasingly, adjuvants will be developed to facilitate vaccine delivery to different sites in the body, such as mucosal surfaces.

The Committee concluded that WHO will have an important role in facilitating dialogue between the scientific community, industry and regulatory agencies, in establishing standards through publication in the Technical Report Series, and ensuring a consistent regulatory approach in this complex area. Adverse events attributable to adjuvants need to be documented and reviewed, and the information made available. That is another important role for WHO. Since many of the new adjuvants are likely to be used in vaccines for conditions endemic in developing countries, it is important to involve scientists from those countries. Systems for safety monitoring and the necessary training will also be required.

In considering a framework for safety studies of adjuvants, attention was drawn to the limitations of animal models in predicting adjuvant safety. A number of the traditional methods and interpretations used in animal studies of (non-vaccine) drug safety are unlikely to apply in the specialized field of adjuvant safety. Nevertheless, animals cannot be dispensed with in the early consideration of a safety profile. No single experimental animal can provide the answer, nor do conventional dose-increment safety studies adequately address the immunological aspects of adjuvant safety (including tolerance effects, hypersensitivity and generation of autoimmunity). Validated animal models for adjuvant safety testing do not exist, yet they will be required for future vaccine research and development. Short-term and long-term safety evaluation and prediction are important, as is the evaluation of the pharmacokinetics of the adjuvant alone. WHO might promote research and further develop guidelines on adjuvant safety.

Safety testing of new adjuvants, once combined with a vaccine, necessitates improved and consistent standards for safety monitoring boards, post-marketing signal generation and evaluation, and surveillance of adverse immunological events. This includes unexpected safety issues. Phase IV studies should accommodate adverse reactions that cannot be anticipated from the biological actions of the vaccine and its adjuvant, including the rare and unusual adverse reactions that are not detected in animal work or in small

pre-registration human studies. For this, clear case definitions are needed. All this requires a new clinical, scientific and regulatory approach, with attention to the short- and long-term safety of adjuvants.

It was suggested that WHO might serve as a repository for safety reports and as a forum for dialogue and guidance for the technical and scientific standards for adjuvants and their safety; for setting standards for such work, and for defining principles governing regulatory issues in adjuvant safety. The GACVS might collate such information, which should be evaluated and made widely available. Updates on vaccine safety issues that are regularly considered by the Committee can be found on the GACVS web site at http://www.who.int/vaccine_safety/en.

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Dengue vaccine safety update

Dengue virus is a flavivirus with four serotypes and type-specific protective immunity. At least eight vaccines against dengue virus infection are currently under development; two are at the stage of phase II clinical evaluation. Sensitization to severe dengue illness through pre-existing immunity is a serious safety concern for vaccination. Such sensitization has been observed in the course of sequential dengue epidemics by different virus strains in Cuba. From this and other data, the relative risk of severe disease following secondary heterotypic infection has been estimated to be 15–80.

The occurrence of dengue haemorrhagic fever (DHF) in infants of immune mothers, as well as data from in vitro models, provides additional indication of a possible sensitization to severe DHF as a result of immunity. While host genetic as well as viral virulence factors might contribute to severe DHF, viral load (infectious pressure) and concentration of antibody also appear to play a role.

One of the implications of sensitization to DHF is that dengue vaccines need to elicit a balanced immunity to all four dengue serotypes. The 4–5 year follow-up of a tetravalent vaccine currently under clinical evaluation has not revealed a risk of severe disease among vaccine recipients (1), but available information is still limited. It will be important to study the early immune response and its kinetics, and the relationship of these to vaccine-induced memory (2). Long-term follow-up is required (3). The seroepidemiology of dengue fever should be determined in order to evaluate dengue vaccine safety before and after general introduction of the vaccine, with special attention to the impact of herd immunity.

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Development of vaccines for SARS and avian influenza

A joint workshop has been held between the Ministry of Science and Technology of China and the World health Organization on development of vaccines against SARS and avian influenza. The event took place in China in March 2004 and was attended by over 60 international experts. Discussion took place on various aspects of vaccine programmes on SARS, influenza, HIV, Japanese encephalitis and malaria.

Progress on SARS vaccine development

China has achieved much progress towards the development of the first-ever vaccine against SARS. Preclinical, laboratory-based studies involving animals have been carried out, and an application has been made to the State Food and Drug Administration (SFDA) for authorization to begin a Phase I clinical trial of this vaccine, which may begin as early as April or May 2004.

China has invested considerable effort and resources in the quest to develop a SARS vaccine, marshalling the large scientific research potential of the country. It normally takes several years from pre-clinical testing through pharmaceutical and clinical development to availability of a vaccine for the general human population. China has mobilized its scientific forces with great energy to put SARS vaccine on the fast track and a vaccine could be available within two to three years. In the meantime, there will be a need for sustained surveillance, early diagnosis of suspected cases, effective case management and outbreak containment activities.

Developing an avian influenza vaccine for humans

Measures continue to be applied to curb the ongoing outbreaks of highly pathogenic avian influenza in poultry in the Asia-Pacific region, and international efforts are under way to develop an avian influenza vaccine for humans.

In China, as in other countries affected by these outbreaks, efforts have focused on the isolation and characterization of viruses – an essential first step before embarking on vaccine development. China is sharing live virus isolates with WHO international reference laboratories as part of this effort.

Development of an avian influenza virus prototype for a possible vaccine is on schedule and the "prototype virus" could be available before the end of 2004. It would then be offered to various vaccine manufacturers around the world to produce clinical batches for Phase I testing in human volunteers.

Vaccine development in China

Ensuring vaccine quality, procurement and supply is a continuous process. The strengthening of the national regulatory authority is essential to ensure the quality of locally produced and/or imported vaccines. This will help ensure their quality, potency and safety. China State Food and Drug Administration and WHO have agreed to working together in assuring vaccine quality of the highest international standards.

Reference: http://www.who.int/vaccine_research/diseases/sars/events/2004/03/en/

Regulatory and Safety Action

Potential effects of SSRIs and other antidepressants on newborns

Canada — Health Canada is advising that newborns may be adversely affected when pregnant women take selective serotonin re-uptake inhibitors (SSRIs) and other newer antidepressants during the third trimester of pregnancy. The advisory is intended to increase awareness among mothers and physicians of the possible symptoms that may occur in the newborn, so that symptoms can be recognized and addressed quickly and applies to the following SSRIs: bupropion (whether used for depression or for smoking cessation), citalopram, fluoxetine, fluvoxamine, mirtazapine, paroxetine, sertraline and venlafaxine.

International and Canadian reports reveal that some newborns whose mothers took these medications during pregnancy have developed complications at birth requiring prolonged hospitalization, breathing support and tube feeding. Reported symptoms include: feeding and/or breathing difficulties, seizures, muscle rigidity, jitteriness and constant crying. In most cases, the newer antidepressant was taken during the third trimester of pregnancy. These symptoms are consistent with either a direct adverse effect of the antidepressant on the baby, or possibly a discontinuation syndrome caused by sudden withdrawal from the drug.

When treating depression in pregnant women, physicians and patients should carefully consider the potential risks and benefits of the various treatment options for both the mother and the unborn baby. To date, there is little evidence-based information on how best to treat depression during pregnancy. However, physicians may consider slowly decreasing the dose of these medications in the third trimester. It is very important that patients do NOT stop taking these medications without first consulting their doctor.

The frequency of symptoms may vary with each drug. In the case of two of the newer antidepressants — bupropion and mirtazapine — discontinuation problems appear to be less than with the other drugs. In the case of mirtazapine, there are only two reports. The manufacturers of these medications will update their labelling with new precaution information.

Reference: Health Canada Advisory, 2004–44. 9 August 2004 available on http://www.hc-sc.gc.ca

Deregulation of 371 OTC products

Japan — Until now, regulations identify pharmaceutical products as prescription-only and over-the-counter medicines for sale in pharmacies and drug stores. Other parapharmacy products, or "quasi-drugs" —defined as having mild action on the body — are available in convenience stores and general sales outlets.

In order to give manufacturers and importers wider access to the general public, and opportunity to establish or expand brands, deregulation of 371 over-the-counter products to "quasi drugs", together with relaxed advertising and promotional requirements, have been announced. This action, based on expert recommendations, will affect products in 15 categories. Manufacturers and importers planning to make the switch to "quasi-drugs" are given one year to comply with new packaging and labelling requirements.

Reference: Ministry of Health, Labour and Welfare http://www.mhlw.go.jp

Critical path initiative: standardizing trial data

United States of America — The Food and Drug Administration (FDA) has announced development of the Study Data Tabulation Model (SDTM) (1) for sponsors of human drug clinical trials. It is expected that this will lead to greater efficiencies in clinical research and FDA reviews of new drug applications (NDAs). The SDTM represents an important step to accelerate research through the use of standards and health information technology. In addition, the adoption of the standard is consistent with the FDA's Critical Path initiative because it will help automate the largely paper-based clinical trials research process and foster

easier communication and collaboration among clinical researchers.

By providing a consistent framework and format for clinical trial information, this standard is expected to enhance data integration opportunities and thereby help to reduce data management barriers for sharing the latest clinical trial data. FDA's Critical Path initiative is focused on identifying problems and potential solutions so that the safety and effectiveness of breakthroughs can be evaluated as quickly and inexpensively as possible (2).

The SDTM standard will be added to other specifications involving regulatory submissions in electronic format. FDA is currently exploring approaches to require the use of the STDM standard for regulatory submissions (3, 4).

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4. *FDA News*, P04-73. 21 July 2004

Fixed dose combination drug products approved for HIV

United States of America — The Food and Drug Administration (FDA) has announced the approvals of abacavir/lamivudine (Epzicom®) and tenofovir disoproxil/emtricitabine (Truvada®), two fixed-dose combination treatments for HIV-1 infection. Control of HIV/AIDS generally requires simultaneous use of three or more drugs from different classes. Combination products bring together different HIV/AIDS drugs in a single medication or co-package and help make treatment regimens less complicated for patients to follow.

Abacavir/lamivudine and disoproxil/emtricitabine are indicated for use in combination with other antiretroviral drug products from different classes such as non-nucleoside reverse transcriptase inhibitors or protease inhibitors for the treatment of adults with HIV-1 infection.

The Epzicom® approval is based on a large well-controlled clinical study which showed that abacavir dosed once daily had a similar antiviral effect as abacavir dosed twice daily both in conjunction with lamivudine and with efavirenz, another antiretroviral drug. The approval of Truvada® is based on data demonstrating therapeutic equivalence between the combination product and the individual products.

Reference: *FDA News*, P04-75. 2 August 2004.

Acetylcysteine labelling changes

Singapore — Changes have been made to the labelling for acetylcysteine (Parvolex®) including the addition of new sections on carcinogenicity and mutagenicity, impairment of fertility, use in lactation, paediatric use, use in the elderly and use in renal/hepatic impaired patients. Acetylcysteine should be used with caution in patients with a history of oesophageal varices and peptic ulceration (acetylcysteine induced vomiting may increase the risk of haemorrhage).

New ADR terms have been added: flushing, vomiting, dyspnoea, nausea, hypotension, angio-oedema, anxiety, hypertension, malaise, rigours, urticaria, cyanosis, tachycardia, chest pain, extrasystole, face oedema & oedema periorbital.

Reference: 31 May 2004. Health Sciences Agency, Singapore. http://hsa.gov.sg

Rituximab and hepatitis B reactivation

Canada — Rituximab (Rituxan®) is indicated for the treatment of patients with relapsed or refractory low grade or follicular, CD20-positive, B cell non-Hodgkin lymphoma and patients with CD20-positive, diffuse large B-cell non-Hodgkin lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) chemotherapy. It is estimated that over half a million treatments have been administered worldwide. Since rituximab was introduced to the market, the manufacturer has continued to gather information on safety and efficacy and has reviewed recent post marketing and clinical safety reports.

- Hepatitis B virus (HBV) reactivation, occasionally with fulminant hepatitis, hepatic failure, and death has been reported in some patients with haematologic malignancies.

- Persons at high risk of HBV infection should be screened before initiation of rituximab.
- Carriers of hepatitis B and patients with evidence of having recovered from hepatitis B infection should be closely monitored for clinical and laboratory signs of active HBV infection and for signs of hepatitis during and up to one year following therapy.
- Very rare cases (less than 1 adverse event per 10000 treated patients) of hepatitis B reactivation in association with rituximab therapy were reported internationally.

Persons at high risk of HBV infection should be screened before initiation of rituximab. Carriers of hepatitis B, and patients with evidence of having recovered from hepatitis B infection, should be closely monitored for clinical and laboratory signs of active HBV infection and for signs of hepatitis during and up to one year following rituximab therapy.

Reference: Health Canada, 27 July. http://www.hc-sc.gc.ca 2004

Rosuvastatin and Asian subjects

Singapore — The manufacturer of rosuvastatin (Crestor®) has submitted a labelling amendment to indicate information on a twofold increase in median AUC after a single dose (40 mg) of rosuvastatin given to Chinese patients in Singapore compared to western Caucasian patients. This observation was similarly reported in Japanese subjects residing in Japan. The label update approved by Health Sciences Agency (HSA) is as follows:

Pharmacokinetic studies show an approximately two-fold elevation in median AUC comparing western Caucasians and Japanese subjects residing in Japan. Preliminary data from a pharmacokinetic study conducted in Chinese subjects living in Singapore suggests a similar response to that seen with Japanese subjects. However, limited studies in other Asian patients have been inconclusive. The contribution of environmental and genetic factors to these observed differences has not been determined. Crestor® 40 mg should only be used for patients who do not achieve their treatment goal on 20 mg and should be used with caution.

It is advisable to start rosuvastatin at 10 mg daily. Rosuvastatin should be prescribed with caution in patients with predisposing factors for myopathy, such as renal impairment, advanced age and hypothyroidism, or situations where an increase in plasma levels may occur. Patients with renal or liver dysfunction should also be closely monitored. Patients who develop any signs or symptoms suggestive of myopathy should have their CK levels measured.

Reference: 31 May 2004. Update on pharmacokinetic data of Rosuvastatin and local Chinese subjects. Health Sciences Agency, Singapore. http://hsa.gov.sg

Trazodone, interactions and CYP 3A4 metabolism

Canada — The manufacturer of trazodone hydrochloride (Desyrel®), indicated for the symptomatic relief of depressive illness, has advised health care professionals of important safety information concerning drug interactions with CYP 3A4 inhibitors including ketoconazole, ritonavir, indinavir, and a CYP3A4 inducer, carbamazepine.

The Canadian labelling has been updated to state that in vitro drug metabolism studies suggest that there is a potential for drug interactions when trazodone is given with drugs that alter metabolism by CYP3A4, leading to adverse effects including nausea, hypotension and syncope.

Reference: Communication from Bristol-Myers Squibb Canada, 30 June 2004, available on http://www.

Phenol: new labelling data

Singapore — Oily phenol injection is now contraindicated for use in patients hypersensitive to phenol or almond oil, in neonates and children. Labelling changes for products containing phenol include new sections on clinical trials, carcinogenicity and genotoxicity, use in paediatrics and possible interference with laboratory test results.

Although limited data did not show an increase in frequency of malformation or other direct harmful effects on the human foetus when pregnant women were exposed to the drug, oral administration of phenol to rats and mice resulted in embryonic and foetal resorptions. The clinical relevance of these findings is unclear, but it is advised that phenol should not be used in pregnant women.

A new list of ADR terms has been added including local ulceration, sterile abscess, haematuria, haematospermia, epididymitis, chronic cystitis, urolithiasis, seminal vesicle abscess, urinary perineal fistula, dysuris, transient incontinence, pyrexia, impotence and prostatic abscess. Necrotizing fascitis and retroperitoneal sepsis have also been reported.

Reference: 31 May 2004. . Health Sciences Agency, Singapore. http://hsa.gov.sg

Docetaxel for early stage breast cancer

United States of America — The Food and Drug Administration (FDA) has approved docetaxel (Taxotere®) for use in combination with doxorubicin and cyclophosphamide for the adjuvant (post surgery) treatment of patients with operable, node-positive breast cancer, of which more than 300 000 women are diagnosed worldwide each year.

The FDA based its decision on results from a second interim analysis of the Breast Cancer International Research Group (BCIRG) study, which demonstrated that women with node-positive, early stage breast cancer who received a Taxotere®-based chemotherapy regimen (TAC) after surgery experienced a significant 25.7 percent reduction in their risk of relapse.

Docetaxel is currently approved in the United States to treat patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy, and patients with unresectable locally advanced or metastatic non-small cell lung cancer (NSCLC) in combination with cisplatin, who had not received prior chemotherapy. It also is approved for patients with unresectable locally advanced or metastatic NSCLC after failure of prior platinum-based chemotherapy.

Among patients receiving docetaxel the most common severe adverse events were low blood cell count, fatigue, diarrhoea, and mouth and throat irritation. The most common non-severe side effects include hair loss, numbness, a tingling and/or burning sensation, dyspnoea, rash, nail changes, nausea, vomiting, and muscle pain. Less common severe or potentially life threatening side effects include fluid retention, infections, and allergic reactions. Patients 65 years of age or older may experience some side effects more frequently.

Reference: Communication from Aventis, http://www.taxotere.com/

Imiquimod approved for keratosis

United States of America —The Food and Drug Administration (FDA) has announced approval of imiquimod (Aldara®) for the treatment of superficial basal cell carcinoma (sBCC). Superficial basal cell carcinoma is usually treated by surgical removal. Imiquimod should only be used for treatment of sBCC when surgery is medically less appropriate, because the chances of effectively treating sBCC are generally greater with surgery.

The safety and effectiveness of imiquimod were established in two double-blind controlled studies of approximately 364 patients. Basal cell carcinoma affects at least 800 000 Americans each year. The superficial type of basal cell carcinoma usually occurs on the arms, legs or on parts of the body such as the chest or back. imiquimod has not been approved for treatment of sBCC on the face.

Patients have experienced skin reactions at the treatment site, including redness, swelling, a sore or blister, peeling, itching, and burning.

Reference: *FDA news*, P 04-66 15 July 2004.

Cetuximab for metastatic colorectal cancer

United States of America — The manufacturer has announced approval of cetuximab (Erbitux®), an antibody for use in combination with irinotecan in the treatment of patients with metastatic colorectal cancer who are refractory to irinotecan-based chemotherapy and for use as a single agent in the treatment of patients with metastatic colorectal cancer who are intolerant of irinotecan-based chemotherapy. Colorectal cancer is the third leading cause of cancer death in the USA The effectiveness of cetuximab is based on objective response rates. Currently, no data are available that demonstrate an improvement in disease-related symptoms or increased survival.

Severe infusion reactions, rarely fatal and characterized by rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and hypotension, have occurred. Most reactions are associated with first infusion. Severe cases of interstitial lung disease, which was fatal in one

case, occurred in less than 0.5% of patients. Dermatologic toxicities, including acneform rash, skin drying and fissuring, and inflammatory or infectious sequelae were reported. Sun exposure may exacerbate these effects.

Other serious adverse events in clinical trials were fever, sepsis, kidney failure, pulmonary embolus, dehydration and diarrhoea.

Patients should be screened for EGFR expression using immunohistochemistry to determine if they are appropriate candidates for treatment.

Reference: Communication from Bristol-Myers Squibb Company, 29 June 2004 on http://www.ERBITUX.com.

Tiotropium approved for bronchospasm

United States of America — A new treatment for obstructive pulmonary disease, tiotropium bromide (Spiriva HandiHaler®), has been approved by the Food and Drug Administration. Tiotropium, an antimuscarinic agent, is indicated for the treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), chronic bronchitis and emphysema. Tiotropium is an antimuscarinic agent or anticholinergic which inhibits M3-receptors at the smooth muscle leading to bronchodilation.

Approval was based on six phase III trials, enrolling a total of 2663 subjects with COPD and a history of smoking greater than 10 pack-years. Adverse events associated with the use of tiotropium may include (but are not limited to) dry mouth, arthritis, coughing, influenza-like symptoms, sinusitis. As an anticholinergic drug, tiotropium must be used with caution in patients with narrow angle glaucoma (eye disease), prostatic hyperplasia (abnormal growth of prostate), or bladder-neck obstruction as it may potentially worsen symptoms and signs of these conditions.

Reference: http://www.spiriva.com.

European antimicrobial expert group established

European Union — The Committee on Veterinary Medicinal Products has established a Scientific Advisory Group on Antimicrobials to provide expertise on matters relating to antimicrobial substances. The Group will also advise on critical aspects, trends and any related situation with regard to antimicrobial resistance in Europe. Its mandate and workplan are published on the website of the European Medicines Agency (EMEA) at http://www.emea.eu.int.

Reference: Press Release, 16 July 2004 on http://www.emea.eu.int

Ciclesonide: novel asthma treatment

Australia — The Therapeutic Goods Administration has approved ciclesonide (Alvesco®) a new-generation inhaled corticosteroid with novel release and distribution properties for the treatment of asthma in adults and adolescents 12 years of age and older. According to the Global Initiative for Asthma (GINA) more than 300 million people worldwide suffer from asthma and prevalence is increasing by approximately 50 percent every decade, with worldwide deaths at more than 180 000 annually.

A new drug application for ciclesonide has also been submitted to the US Food and Drug Administration for the treatment of persistent asthma (regardless of severity) in adults, adolescents and children four years of age and older. The most frequently reported adverse events seen in US clinical trials were nasopharyngitis, headache and upper respiratory tract infection.

Concurrent with the submission, the manufacturer has initiated a Phase III, 12-month trial to further profile the safety and tolerability of high doses of ciclesonide in adult patients with moderate to severe asthma. This trial will characterize the occurrence of lens opacity ocular events, as sometimes seen in patients who are treated with high doses of inhaled corticosteroids.

Reference: Altana Press Release, Bad Homberg, 27 February 2004. http://www.altanapharma.com

HIV Medicines

Assessment reports on WHO prequalified HIV medicines now publicly accessible

More HIV/AIDS medicines have been added to the World Health Organization (WHO) prequalification list (1, 2). At the same time, the product assessment reports on quality and bioequivalence of triple fixed-dose combination (FDCs) antiretrovirals already prequalified will be made public. The new products being added to the list are: lamivudine (150 mg tablet) from a newly prequalified generic manufacturer and the antifungal, fluconazole in three different strengths (50 mg, 150 mg, 200 mg capsules) also from a generic manufacturer. The new listing therefore expands the range of choice for those programmes wishing to use lamivudine. The current prequalified list now offers five different manufacturers for lamivudine — including innovator and generic products; and seven fluconazole products in four different strengths from two generic manufacturers.

In keeping with the 2004 World Health Assembly resolution, WHO has taken measures to make public the assessment reports resulting from its prequalification process. WHO therefore joins the European Medicines Agency (EMEA) in making such reports publicly accessible, with WHO providing reports on generic medicines in addition. The public assessment reports include information on product compliance with international standards for quality, safety and efficacy as well as bioequiva-lence for generic products (1). This information will be particularly useful to developing country regulatory authorities, procurement agencies and nongovernmental organizations.

The WHO public assessment reports (WHOPARs) will assist in establishing the acceptability and appropriateness of a medicine. and will provide indirect professional development and capacity building to regulators in countries that do not have sufficient regulatory capacity to fully assess products and determine their acceptability before licensing.

With the objective of providing greater transparency, the prequalification project will also make available the findings resulting from inspections carried out at production sites according to good manufacturing practices (1, 3).

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Efficacy of dual antiretroviral regimen in mother–to–child transmission of HIV

In industrialized nations, the use of HAART (highly active antiretroviral therapy) in pregnant women along with an optimal package of interventions, including cesarean section and formula feeding, has reduced the rate of mother-to-child transmission of HIV-1 from about 25% to between 1 and 2%. In developing countries, where HAART and complex antiretroviral regimens are unavailable and avoidance of breast-feeding is not a realistic option, short-course zidovudine, administered from weeks 32 through 36 of pregnancy, and single-dose nevirapine are the most frequently employed regimens to reduce the risk of peripartum transmission.

Two studies have recently been commented in the *New England Journal of Medicine* (1). The first, a study carried out in Thailand (2), has recently demonstrated that adding single-dose nevirapine to a course of zidovudine beginning at 28 weeks of pregnancy, in women who do not breast feed, can achieve results equivalent to the best reported from any region. A similar short course of zidovudine had previously been estab-

lished as the standard regimen in Thailand, reducing the rate of mother-to-child transmission of HIV-1 from 25 to 6.5 % (3). In the current study, the rate was further reduced from 6.3 % among 348 women who, like their infants, received the standard regimen alone to 1.1 % among 353 women who received the standard regimen plus a single intrapartum dose of nevirapine, with a single dose of nevirapine also given to their infants soon after birth.

In recently updated recommendations (see page 243), WHO recommends this approach as the most efficacious regimen for the prevention of peripartum mother-to-child transmission of HIV-1 for women who do not require antiretroviral treatment for themselves, and the Thai government has accepted this regimen as the standard of care. The rate of mother-to-child transmission was 2.1 % among 333 women who received the standard regimen plus intrapartum nevirapine while their infants received placebo, and this rate did not differ significantly from the rate of 1.1 percent among the women who, with their infants, received a single dose of nevirapine.

One of the chief concerns regarding the use of antiretroviral agents for the prevention of mother-to-child transmission of HIV-1 is that the drugs in these regimens could be less efficacious in subsequent pregnancies and in subsequent clinical management of the infection in the mothers or in their infants who become infected despite prophylaxis. The possibility of selection for HIV-1 variants that are resistant to antiretroviral agents has been a major worry, particularly with respect to nevirapine, because a single mutation can induce high-level resistance to nevirapine as well as to other nonnucleoside reverse-transcriptase inhibitors (NNRTIs) (1).

In another study (4) resistance mutations to nucleoside reverse-transcriptase inhibitors (which include zidovudine) were detected 10 days after delivery in 5 % of mothers, and among the women who had received intrapartum nevirapine, 32 % had at least one mutation that conferred resistance to NNRTIs. The development of nevirapine resistance after a single dose of the drug is affected by a number of factors, including maternal viral load and CD4 cell count, making comparisons between studies difficult (5).

However, the study showed that at least half of the women who received intrapartum nevirapine and who subsequently had clinical indications for treatment had a good response to subsequent nevirapine-containing HAART. The findings suggest that women who receive single-dose nevirapine alone or in combination regimens for the prevention of mother-to-child transmission of HIV-1 and in whom NNRTI resistance mutations develop may be less likely than women who do not receive intrapartum nevirapine or have resistance mutations to have maximal viral suppression when NNRTI-based treatment is initiated soon after delivery.

Additional studies with longer follow-up to investigate and quantify the clinical implications are urgently required, as is research into alternative antiretroviral agents for the prevention of mother-to-child transmission of HIV-1. The problem of resistance is likely to be heightened in African countries that are introducing programmes for the national provision of antiretroviral agents (6).

It is recognized that these study results (4) are not a reason to abandon single-dose nevirapine for the prevention of mother-to-child transmission of HIV-1. Single-dose nevirapine is a regimen of striking simplicity, efficacy, and affordability. None the less, implementation of even this basic regimen has been hampered by failing health systems in many countries in Africa. Overcoming these barriers and choosing optimal antiretroviral regimens are therefore simultaneous priorities.

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Monitoring of antiretroviral safety and efficacy

Many countries in Africa are introducing combinations of antiretrovirals (ARV) as part of WHO's 3 by 5 Strategy to provide antiretroviral treatment to 3 million people by 2005. Most of the first-line drugs are now available as multisource generics.

As with many of the newly registered products, there is still limited experience with the operational use of antiretrovirals in general, especially in developing country settings, including moinitoring of safety and efficacy.

A workshop has been organized by WHO in South Africa from 1–10 September for HIV programme managers and officials responsible for pharmacovigilance in Kenya, Malawi, Nigeria, Mozambique, Tanzania, South Africa, Uganda and Zambia with the aim of introducing a common system of safety monitoring. Links with WHO will also provide access to the WHO database of adverse drug reactions and technical expertise to assist in early implementation of pilot projects in these countries.

It is hoped that the initiative can later be expanded to include workshops in other countries.

Reference: *World Health Organization website at http://www.who.int/medicines*

Essential Medicines

Neglected Diseases

Over the last few decades, progress in science has enabled increasingly sophisticated medicines to be developed to cure a wide variety of diseases. Some infectious tropical diseases, however, have been progressively marginalized by research programmes in both private and public sectors. These "neglected diseases", such as leishmaniasis, trypanosomiasis and Chagas disease have a devastating impact on the world's poor – but because they affect only the poor, they do not constitute a market lucrative enough to attract investment in research and development of new drugs.

The **Drugs for Neglected Diseases Initiative** (DNDi) is a not-for-profit association established in partnership with Médecins Sans Frontières, Oswaldo Cruz Foundation/Far Manguinhos, the Indian Council of Medical Research, Institut Pasteur, the Ministry of Health of Malaysia, and the Kenya Medical Research Institute, with WHO as a permanent observer. DNDi's vision is to improve the quality of life and the health of people suffering from neglected diseases by developing new drugs or new formulations of existing drugs for patients suffering from these diseases. This will be carried out through identifying opportunities and initiating and coordinating drug research and developmenrt (R&D) projects.The DNDi website is at: http://www.dndi.org

A portfolio for research and development

Neglected diseases such as leishmaniasis, trypanosomiasis, Chagas disease and malaria have a devastating impact on the world's poor. DNDi is addressing this lack of new, improved drugs for these treatable, infectious tropical diseases with an alternative model of research and development. DNDi's strength lies in its collaborative model: using existing research and capacity for drug development in different parts of the world and pulling it together to build each project. This model matches patients' needs with gaps identified in the drug development pipeline.

Currently available treatments for neglected diseases leave a great deal to be desired and do not address patients' needs. People suffering from tropical diseases are still taking drugs that are hugely toxic or ineffective because of parasite resistance. It is clear that patients in developing countries afflicted by neglected diseases urgently need new treatments that are safe, efficient, short course, easily administered, reasonably priced and accessible.

At the end of its first year, the DNDi has constituted a balanced portfolio of nine projects that fill identified gaps in the drug development pipeline for neglected diseases: at the early discovery stage, at the stage before drugs enter clinical development, and at the point where drugs should reach patients but do not.

Four long-term projects identify new lead compounds that can eliminate parasites causing trypanosomiasis and/or leishmaniasis, and one focuses on combining existing anti-leishmanial drugs. The remaining four are short-term projects, working with existing drugs at the end of the pipeline: for instance, the registration of paromomycin, an old antibiotic, for visceral leishmaniasis in Africa (in collaboration with the Institute of One World Health and WHO/TDR); the evaluation of nifurtimox, a drug used for Chagas disease, in combination with eflornithine to treat second stage sleeping sickness (in collaboration with WHO/TDR and Bayer); and two fixed-dose artesunate combination therapies (FACT) of artesunate/amodiaquine and artesunate/ mefloquine against chloroquine-resistant malaria in Africa and Asia respectively (in collaboration with seven medical research institutes across the world, see page 230).

DNDi continues to build its portfolio by proactively identifying projects and sending out calls for

letters of interest to the scientific community. The second call for letters is currently being evaluated and it is hoped that 4–6 new projects will be added to the portfolio by the end of the year. DNDi will lead any successful projects through the R&D process to achieve its final objective of giving neglected patients access to new therapies. The initiative is also pushing for registration of the drug paromomycin for use against visceral leishmaniasis in Africa, and assessing the value of combining existing drugs to treat sleeping sickness. For the longer haul, DNDi is conducting basic discovery work to identify compounds that can block enzymes essential to parasite metabolism.

By pooling resources and know-how, promising projects can be identified and moved forward quickly and at low cost. Besides providing patients with treatments, the initiative is also promoting collaboration and technology transfer between academic research institutes and drug developers across the world.

Malaria patients enter DNDi clinical trials

A year after its launch, the Drugs for Neglected Diseases Initiative (DNDi) is starting clinical trials of two fixed-dose drug combinations against malaria. To ensure a balanced portfolio of drugs in the pipeline, DNDi mixes quick-fix with long-term projects. In the short term, DNDi is developing fixed-dose combinations for uncomplicated malaria: artesunate/amodiaquine for use in Africa and artesunate/mefloquine for use in Asia and Latin America.

Many antimalarials have become virtually useless because of resistance and most countries are now switching to the more effective artemisinin-based combination therapy (ACT). The challenge is now to provide ACT as fixed-dose combinations that are simple to use rather than separate tablets: it helps to ensure patients take their treatment properly and to prevent future resistance.

DNDi has started clinical trials for the two new drug combinations in adult and child strengths in Burkina Faso and Thailand. The new drug combinations will be registered at the end of next year and available to patients as of 2006.

Corrigendum for alcuronium: WHO Model Formulary 2004

The WHO Model Formulary is an indispensable source of independent information on essential medicines for policy makers and prescribers. It describes how to make effective use of medicines on the WHO Model List of Essential Medicines and for each medicine it provides information on use, dosage, adverse effects, contraindications and warnings with guidance on selecting medicines.

A n error has been made concerning the dosage for the muscle relaxant, alcuronium chloride (section 1.4; page 29). This should be expressed in MICROGRAMS. The dosage statement should thus read as follows:

Dosage:
Muscle relaxation, *by intravenous injection,*
ADULT initially 200–250 micrograms/kg, then 50 micrograms/kg as required for maintenance;
CHILD initially 125–200 micrograms/kg, then 50 micrograms/kg for maintenance

The editors are grateful to colleagues from the Vietnamese Pharmacopoeia Commission for pointing out the error. The Model Formulary (2004) is available from the World Health Organization, Marketing and Dissemination, 1211 Geneva 27, Switzerland, or publications@who.int

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Consultation Document

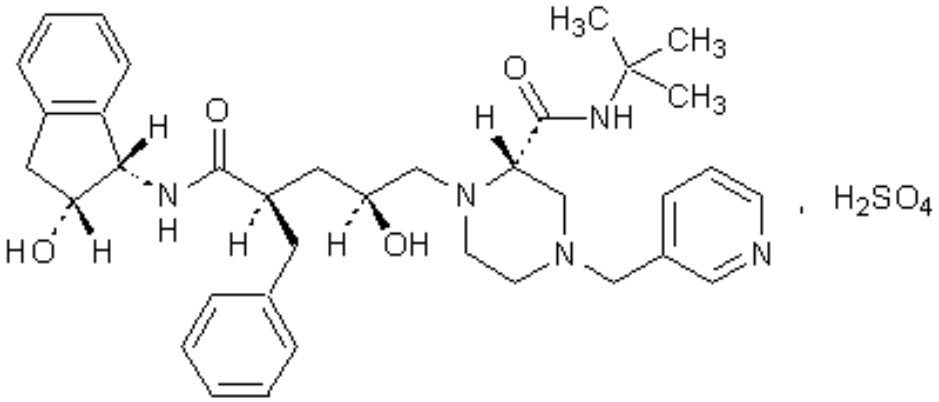
The International Pharmacopoeia — monographs for antiretrovirals

Within the framework of the Pilot Procurement Project for Quality and Sourcing of HIV Drugs (http://www.who.int/medicines), *The International Pharmacopoeia* is collaborating with manufacturers, independent analytical drug quality control laboratories, national and regional pharmacopoeial bodies, research, governments, and regulatory bodies to provide specifications and monographs for the following antiretroviral agents:

abacavir, didanosine, efavirenz, indinavir, lamivudine, nelfinavir, nevirapine, ritonavir, saquinavir, stavudine, zidovudine

Specifications for the respective dosage forms are now being developed and a second draft monograph for indinavir sulfate is now being circulated for consultation following comments received on the first draft published in *WHO Drug Information*, Vol. 18, No. 1, 2004. Please forward any comments to: Quality and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland or kopps@who.int.

Indinaviri sulfas (2nd draft)
Indinavir sulfate



$C_{36}H_{47}N_5O_4,H_2O_4S$

Relative molecular mass: 711.9

Chemical name: (2*S*)-1-[(2*S*,4*R*)-4-benzyl-2-hydroxy-5-[[(1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl]amino]-5-oxopentyl]-*N*-(1,1-dimethylethyl)-4-(pyridin-3-ylmethyl)piperazine-2-carboxamide sulfate; CAS Reg. No. 157810-81-6.

Description: A white or almost white powder.

Solubility: Freely soluble in water, soluble in methanol.

Category: Antiretroviral (protease inhibitor).

Storage: Indinavir sulfate should be kept in a tightly closed container, protected from light.

Additional information: Indinavir sulfate occurs as the monoethanolate which is hygroscopic. It converts to hydrate upon loss of ethanol and exposure to moist air.

REQUIREMENTS

Indinavir sulfate contains not less than 98.5% and not more than 101.0% of $C_{36}H_{47}N_5O_4,H_2O_4S$ calculated on anhydrous, ethanol free basis.

Identity tests

Either tests A, B and D, or tests C and D may be applied.

A. Choice between two alternatives A.1. (UV detection) or A.2. (spraying reagent).
Note: UV detection is preferred due to its higher sensitivity.

A.1. Carry out the test as described under ''Thin-layer chromatography'' (Vol. 1, p. 83*), using silica gel R6 as the coating substance and a mixture of 8 volumes of dichloromethane R and 2 volumes of 2-propanol as the mobile phase. Apply separately to the plate 10 µl of each of the following 2 solutions in methanol (A) 1 mg of Indinavir sulfate per ml and (B) 1 mg of indinavir sulfate RS per ml. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or with a hair-dryer with cold air. Examine the chromatogram in ultraviolet light (254 nm).

The principal spot obtained with solution A corresponds in position, appearance, and intensity with that obtained with solution B.

A.2. Carry out the test as described under ''Thin-layer chromatography'' (Vol. 1, p. 83*), using silica gel R5 as the coating substance and a mixture of 8 volumes of dichloromethane R and 2 volumes of 2-propanol as the mobile phase. Apply separately to the plate 10 µl of each of the following 2 solutions in methanol (A) 1 mg of Indinavir sulfate per ml and (B) 1 mg of indinavir sulfate RS per ml. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or with a hair-dryer with cold air. Spray with vanillin/sulfuric acid TS2. Heat the plate for a few minutes at 120 °C. Examine the chromatogram in daylight.

The principal spot obtained with solution A corresponds in position, appearance, and intensity with that obtained with solution B.

B. The absorption spectrum of a 0.100 mg/ml solution in water, when observed between 220 nm and 280 nm, exhibits one maximum at about 260 nm; the specific absorbance ($A^{1\%}_{1cm}$) is between 56 and 62.

C. Carry out the examination as described under ''Spectrophotometry in the infrared region'' (Vol. 1, p.40*). The infrared absorption spectrum is concordant with the spectrum obtained from indinavir sulfate RS or with the *reference spectrum* of indinavir sulfate.

** Refers to The International Pharmacopoeia*

D. A 20 mg/ml solution yields reaction A described under “General identification tests” as characteristic of sulfates (Vol. 1, p. 115*).

Specific optical rotation: Use a 10.0 mg/ml solution in water and calculate with reference to the anhydrous and ethanol free substance; $[\alpha]_D^{20\,^\circ C}$ = +27 ° to +31 °.

Heavy metals: Use 1.0 g for the preparation of the test solution as described under “Limit test for heavy metals”, Procedure 1 (Vol. 1, p. 118*); determine the heavy metals content according to Method A (Vol. 1, p. 119*); not more than 10 μg/g.

Sulfated ash: Not more than 1.0 mg/g.

Water: Determine as described under ‘‘Determination of water by the Karl Fischer method’’, Method A (Vol. 1, p. 135*), using 0.50 g of the substance; the water content is not more than 15 mg/g.

pH value: pH of a 10 mg/ml solution in carbon-dioxide-free water R, 2.8–3.2.

Ethanol content: Determine by “Gas chromatography with static head-space injection”. Use a fused-silica capillary or wide bore column 30 m long and 0.32 mm or 0.53 mm in internal diameter coated with macrogol 20 000 R (film thickness: 0.25 μm).

As detector use a flame ionization detector.

Use nitrogen for chromatography R or helium for chromatography R as the carrier gas at an appropriate pressure and a split ratio 1:5 with a linear velocity of about 35 cm/sec.

The following head-space injection conditions may be used:

Equilibration temperature (°C)	80
Equilibration time (min)	60
Transfer line temperature (°C)	85
Pressurization time (s)	30
Injection volume (ml)	1

Maintain the temperature of the column at 30 °C for 7 min, then raise the temperature at a rate of 35 °C per min to 180 °C and maintain for 10 min, maintaining the temperature of the injection port at 140 °C and that of the flame ionization detector at 250 °C.

Test solution: Dissolve 0.200 g of Indinavir sulfate in purified water and dilute to 20.0 ml with the same solvent. Introduce 5.0 ml of this solution and 1.0 ml of purified water into a headspace vial. Prepare two more vials.

Reference solutions: Add 0.200 g of ethanol R to purified water and dilute to 200.0 ml with the same solvent. Transfer respectively 2.0 ml, 3.0 ml and 4.0 ml in separate injection vials and bring the volume to 6.0 ml with purified water.

Blank solution: Introduce 6.0 ml of purified water into a headspace vial.

Analyse the blank solution and then alternatively three times the test solution and the three reference solutions.

The test is not valid unless the relative standard deviation on the areas of the peaks obtained from the test solutions is not more than 5%.

** Refers to The International Pharmacopoeia*

Calculate the ethanol content by using the results obtained with the test solution and with the reference solutions; the ethanol content is not less than 50 mg/g and not more than 80 mg/g.

Related substances: Carry out the test as described under "High–performance liquid chromatography" (Vol. 5, p. 257*), using a stainless steel column (25 cm x 4.6 mm) packed with base-deactivated octadecylsilyl silica gel for chromatography R (5 μm).

Use the following conditions for gradient elution:

Mobile phase A: 30 volumes of acetonitrile, 5 volumes of phosphate buffer pH 7.5 and 65 volumes of purified water.

Mobile phase B: 70 volumes of acetonitrile, 5 volumes of phosphate buffer pH 7.5 and 25 volumes of purified water.

Prepare the phosphate buffer pH 7.5 by dissolving 1.4 g of disodium hydrogen phosphate in 50 ml of purified water, adjust the pH to 7.5 by adding phosphoric acid (105 g/l) and dilute it to 100 ml with purified water.

Time (min)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0–5	93	7	Isocratic
5–25	93 to 20	7 to 80	Linear gradient
25–30	20	80	Isocratic
30–35	20 to 93	80 to 7	Return to the initial conditions
35–45	93	7	Isocratic re-equilibration

Prepare the following solutions. For solution (1) use 2.0 mg of Indinavir sulfate per ml. For solution (2) dilute a suitable volume of solution (1) to obtain a concentration equivalent to 2 μg of Indinavir sulfate per ml.

For the system suitability test: prepare solution (3) using 2 ml of solution (1) and 2 ml of sulfuric acid (190 g/l), heat carefully in a water bath at 80 °C for 60 minutes.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 220 nm.

Maintain the column temperature at 40 °C, preferably using a water-bath.

Inject 20 μl of solution (3). The test is not valid unless the resolution factor between the two major peaks, with a retention time between 15 and 20 min, is not less than 3.5. If necessary adjust the amount of acetonitrile in mobile phase A, or adjust the gradient programme.

Inject alternatively 20 μl each of solutions (1) and (2).

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2). In the chromatograms obtained with solution (1), the area of any peak, other than the principal peak, is not greater than that obtained with solution (2) (0.1 %). The sum of the areas of all peaks, other than the principal peak, is not greater than five times the area of the principal peak obtained with solution (2) (0.5 %). Disregard any peak with an area less than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.03%).

** Refers to The International Pharmacopoeia*

Assay: Dissolve 0.300 g, accurately weighed, in 50 ml of water and titrate with sodium hydroxide (0.1 mol/l) VS, determine the end point potentiometrically. Each ml of sodium hydroxide (0.1 mol/l) VS is equivalent to 35.59 mg of $C_{36}H_{47}N_5O_4,H_2O_4S$; calculate with reference to the anhydrous and ethanol free substance.

Reagents

Silica gel for chromatography, octadecylsilyl, base deactivated
A very finely divided silica gel, pretreated before the bonding of octadecylsilyl groups to minimize the interaction with basic compounds.

Macrogol 20 000 R. Polyethyleneglycol 20 000
Description. White or almost white solid with a waxy or paraffin-like appearance.

Solubility: Very soluble in water and methylene chloride R. Practically insoluble in alcohol and in fatty oils and mineral oils.

Nitrogen for chromatography.
Contains not less than 99.95% v/v of N_2.

Helium for chromatography.
Contains not less than 99.995% v/v of He.

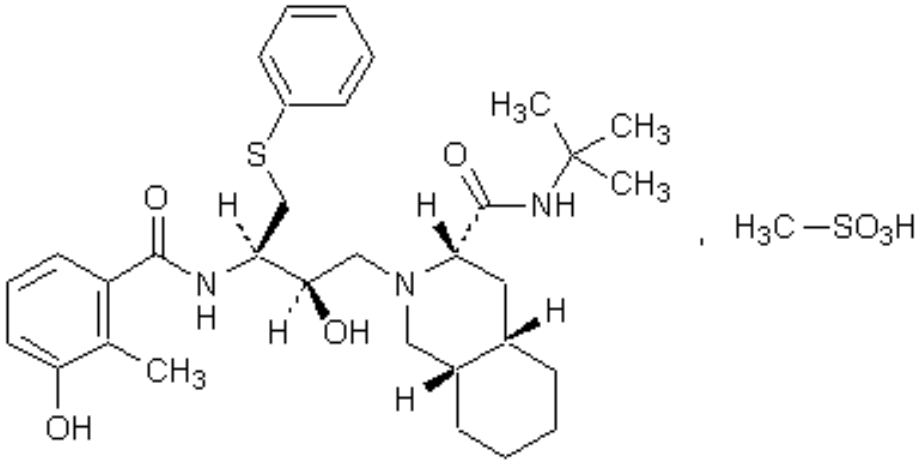
The International Pharmacopoeia — monographs for antiretrovirals

Within the framework of the Pilot Procurement Project for Quality and Sourcing of HIV Drugs (http://www.who.int/medicines), *The International Pharmacopoeia* is collaborating with manufacturers, independent analytical drug quality control laboratories, national and regional pharmacopoeial bodies, research, governments, and regulatory bodies to provide specifications and monographs for the following antiretroviral agents:

abacavir, didanosine, efavirenz, indinavir, lamivudine, nelfinavir, nevirapine, ritonavir, saquinavir, stavudine, zidovudine

Specifications for the respective dosage forms are now being developed and a second draft monograph for nelfinavir mesilate is now being circulated for consultation following comments received on the first draft published in *WHO Drug Information*, Vol. 18, No. 1, 2004. Please forward any comments to: Quality and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland or kopps@who.int.

Nelfinaviri mesilas (2nd draft)
Nelfinavir mesilate



$C_{32}H_{45}N_3O_4S,CH_4O_3S$

Relative molecular mass: 663.9

Chemical name: (3*S*,4a*S*,8a*S*)-*N*-(1,1-dimethylethyl)-2-[(2*R*,3*R*)-2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-(phenylsulfanyl)butyl]decahydroisoquinoline-3-carboxamide methanesulfonate; CAS reg. No. 159989-65-8.

Description: A white or almost white powder.

Solubility: Practically insoluble in water and soluble in methanol R.

Category: Antiretroviral (protease inhibitor).

Storage: Nelfinavir mesilate should be kept in a tightly closed container, protected from light.

Additional information: Nelfinavir mesilate is hygroscopic.

REQUIREMENTS

Nelfinavir mesilate contains not less than 98.5% and not more than 101.0% of $C_{32}H_{45}N_3O_4S,CH_4O_3S$, calculated with reference to the dried substance.

Identity tests

Either tests A and B or test C may be applied.

A. Choice between two alternatives A.1. (UV detection) or A.2. (spraying reagent)
Note: UV detection is preferred due to its higher sensitivity.

A.1. Carry out the test as described under ''Thin-layer chromatography'' (Vol. 1, p. 83*), using silica gel R6 as the coating substance and a mixture of 67 volumes of dichloromethane R, 20 volumes of acetonitrile R, 10 volumes of methanol R and 3 volumes of ammonia (~260 g/l) TS as the mobile phase. Apply separately to the plate 5 μl of each of the following 2 solutions in methanol (A) 1 mg of nelfinavir mesilate per ml and (B) 1 mg of nelfinavir mesilate RS per ml. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or with a hair-dryer with cold air. Examine the chromatogram in ultraviolet light (254 nm).

The principal spot obtained with solution A corresponds in position, appearance, and intensity with that obtained with solution B.

A.2. Carry out the test as described under ''Thin-layer chromatography'' (Vol. 1, p. 83*), using silica gel R5 as the coating substance and a mixture of 67 volumes of dichloromethane R, 20 volumes of acetonitrile R, 10 volumes of methanol R and 3 volumes of ammonia (~260 g/l) TS as the mobile phase. Apply separately to the plate 5 μl of each of the following 2 solutions in methanol (A) 1 mg of nelfinavir mesilate per ml and (B) 1 mg of nelfinavir mesilate RS per ml. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or with a hair-dryer with cold air. Spray with basic potassium permanganate (5 g/l) TS. Examine the chromatogram in daylight.

The principal spot obtained with solution A corresponds in position, appearance, and intensity with that obtained with solution B.

B. The absorption spectrum of a 40 μg/ml solution in methanol R, when observed between 220 nm and 280 nm, exhibits a maximum at about 253 nm; the specific absorbance ($A^{1\%}_{1cm}$) is 124 to136.

C. Carry out the examination as described under ''Spectrophotometry in the infrared region'' (Vol. 1, p. 40*). The infrared absorption spectrum is concordant with the spectrum obtained from nelfinavir mesilate RS or with the *reference spectrum* of nelfinavir mesilate.

Specific optical rotation: Use a 10.0 mg/ml solution in methanol R and calculate with reference to the dried substance; $[\alpha]_D^{20\,^\circ C}$ = -105 ° to -125 °.

** Refers to The International Pharmacopoeia*

Heavy metals: Use 1.0 g in 30 ml of methanol R for the preparation of the test solution as described under ''Limit test for heavy metals'', Procedure 2, (Vol. 1, p.118*); determine the heavy metals content according to Method A (Vol. 1, p.119*); not more than 20 μg/g.

Sulfated ash: Not more than 1.0 mg/g.

Loss on drying: Dry to constant mass at 100 °C; it loses not more than 30 mg/g.

Related substances: Carry out the test as described under "High–performance liquid chromatography" (Vol. 5, p. 257*), using a stainless steel column (25 cm x 4.6 mm) packed with base-deactivated octadecylsilyl silica gel for chromatography R (5μm). (Note: Hypersil BDS C18 is suitable.)

Use the following conditions for gradient elution:

Mobile phase A: 27 volumes of acetonitrile R, 20 volumes of methanol R, 28 volumes of phosphate buffer pH 3.4 and 25 volumes of purified water.

Mobile phase B: 41 volumes of acetonitrile R, 31 volumes of methanol R and 28 volumes of phosphate buffer pH 3.4.

Prepare the phosphate buffer pH 3.4 by dissolving 4.88 g of anhydrous sodium dihydrogen phosphate in 800 ml of purified water, adjust the pH to 3.4 by adding phosphoric acid (105 g/l) and dilute it to 1000 ml with purified water.

Time (min)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0–27	100	0	Isocratic
27–60	100 to 0	0 to 100	Linear gradient
60–75	0	100	Isocratic
75–80	0 to 100	100 to 0	Return to the initial conditions
80–90	100	0	Isocratic re-equilibration

Prepare the following solutions using mobile phase A as diluent. For solution (1) use 2.0 mg of nelfinavir mesilate per ml. For solution (2) dilute a suitable volume of solution (1) to obtain a concentration equivalent to 10.0 μg of nelfinavir mesilate per ml. For solution (3) use 100 μg of methanesulfonic acid R per ml.

For the system suitability test: prepare solution (4) using 2 ml of solution (1) and 5 ml of sulfuric acid (475 g/l), heat carefully in a boiling water bath for 30 minutes.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 225 nm.

Maintain the column at 35 °C.

Inject 20 μl of solution (4). The test is not valid unless the resolution factor between the principal peak and the peak with a retention time relative to the principal peak of about 0.2 is not less than 15. The test is also not valid unless the resolution factor between the last two peaks out of three peaks, which increase during the decomposition process, is not less than 4.0. The ratio of the retention times of these two peaks relative to the principal peak is about 1.8 and 1.9 respectively. If necessary adjust the amount of acetonitrile in both mobile phases A and B, or adjust the gradient programme.

** Refers to The International Pharmacopoeia*

Inject 20 µl of solution (3).

Inject alternatively 20 µl each of solutions (1) and (2).

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2) and calculate the content of related substances as a percentage. In the chromatograms obtained with solution (1), the area of any peak, other than the principal peak, is not greater than that obtained with solution (2) (0.5 %). The sum of the areas of all peaks, other than the principal peak, is not greater than two times the area of the principal peak obtained with solution (2) (1.0 %). Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%). Ignore any peak due to methanesulfonic acid, corresponding to the principal peak in the chromatogram obtained with solution (3).

Assay: Dissolve about 0.50 g, accurately weighed, in 50 ml of methanol R and titrate with sodium hydroxide (0.1 mol/l) VS, determine the end point potentiometrically. Perform a blank determination and make the necessary correction. Each ml of sodium hydroxide (0.1 mol/l) VS is equivalent to 66.39 mg of $C_{32}H_{45}N_3O_4S.CH_4O_3S$.

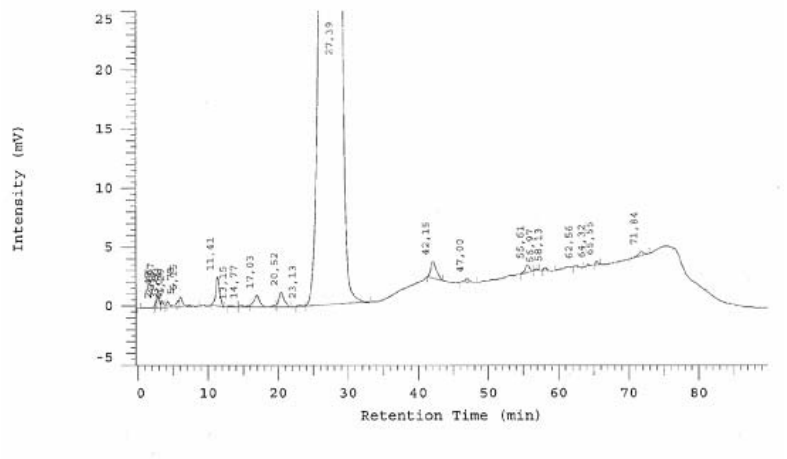
Reagents

Silica gel for chromatography, octadecylsilyl, base-deactivated
A very finely divided silica gel, pre-treated before the bonding of octadecylsilyl groups to minimise the interaction with basic compounds.

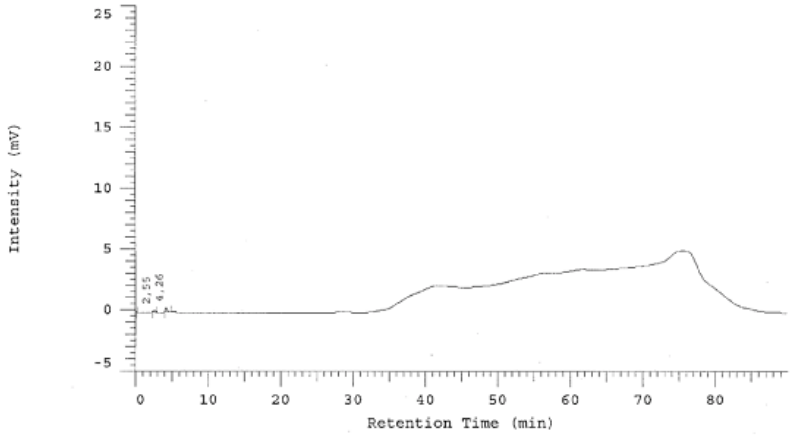
Methanesulfonic acid R
Molecular formula. CH_4O_3S
Description. Colourless and corrosive liquid, strong irritant.
Solubility. Miscible with water.
Density (d). ~1.48.
Melting point. About 20 °C.

Potassium permanganate, basic (5 g/l) TS
A solution of potassium permanganate R containing about 5 g of $KMnO_4$ per litre of sodium hydroxide (1 mol/l).

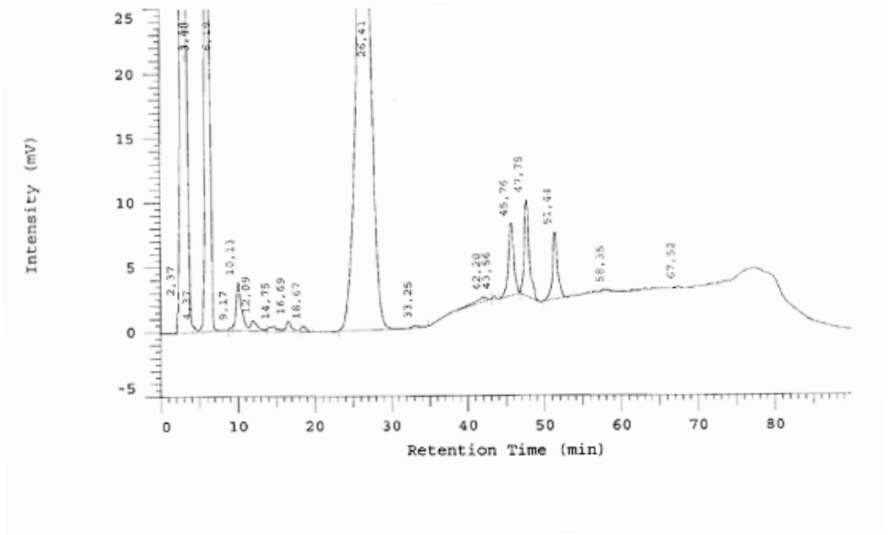
A typical chromatogram obtained for nelfinavir mesilate (Refer to the monograph text for chromatographic conditions in “Related substances”)



A typical chromatogram obtained for blank (Refer to the monograph text for chromatographic conditions in “Related substances”)



A typical chromatogram obtained for system suitability (Refer to the monograph text for system suitability conditions in “Related substances”)



Recent Publications and Sources of Information

Increased recognition needed for benefits of palliative care

There is strong evidence to suggest that palliative care, through the early identification and treatment of pain and other health problems, can make a dramatic difference in the quality of life of the dying and those who care for them. Nevertheless, according to two recent WHO publications, most European health systems offer little training for health professionals, few care options for patients, and minuscule research budgets to support palliative care. Studies in Europe and the United States reveal that while 75% of people would like to die at home, few have that opportunity.

The two publications, *Palliative care: the solid facts* and *Better palliative care for older people,* review the implications of the ageing of the world's population and changing patterns of disease (1). It is estimated that, by 2050, the number of people over 60 years of age will double to 20% in developing countries and to 35% in developed countries. By 2020, the top five causes of death for those over 60 are predicted to be heart disease, cerebrovascular disease, chronic respiratory disease, lower respiratory infections and lung cancer. Although there are differences between individuals, many symptoms and problems in the last year of life are similar.

Common concerns include the need to communicate with family members and health professionals and to cope with disability, pain, anxiety and depression. Family members and caregivers often report the need for support in caring for the ill person and in coping with anxiety and depression.

The publications call for urgent policy action to:

- better meet the care needs of ageing populations that are living with and dying from a range of serious illnesses;
- make palliative care a core part of the health care services and not just an add-on component;
- acknowledge people's right to high-quality palliative care, including concerns for the place of care and death;
- promote training in palliative care across all settings, especially in pain and symptom control and communication;
- ensure equity of access to palliative care;
- raise public awareness of palliative care options; and
- recognize the work of families and caregivers and support them.

The purpose of the studies is to support decision-makers and those who are making the case for realigning health budgets with the real needs of those living with chronic illnesses, and to ensure that all individuals and families have the opportunity to be appropriately supported towards the end of their lives and not to die in unnecessary pain.

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1. *Palliative care: the solid facts* and *Better palliative care for older people* are available on-line at: http://www.euro.who.int/document/E82933.pdf http://www.euro.who.int/document/E82931.pdf

2. World health Organization. Note for the press EURO/11/04, 22 July 2004

Guidance for drug and therapeutics committees

Inefficient and irrational use of medicine is a widespread problem at all levels of the health care system and particularly in hospitals. Many sources of waste can be reduced through application of simple principles of drug management. A drug and therapeutics committee provides a forum where the relevant disciplines can be represented to address drug use problems.

Drug and Therapeutics Committees: A Practical Guide provides guidance to professionals who may be serving on drug and therapeutics committees and who are concerned with how to improve the quality and cost efficiency of therapeutic care

in public or private hospitals at district or tertiary referral level. The manual covers committee functions and structure, the medicines formulary process and how to assess new medicines. Information is provided on tools to investigate drug use and strategies to promote rational use, followed by a discussion of antimicrobial resistance and infection control. Finally, the guide explains in detail how to establish a committee or improve the effectiveness of an existing one.

Drug and Therapeutics Committees: A Practical Guide. WHO/EDM/PAR/2004.3. Available from: Marketing and Dissemination, World Health Organization, 1211 Geneva, 27, Switzerland or publications@who.int

Use of traditional, complementary and alternative medicine

The use of traditional, complementary and alternative medicine continues to grow in line with the trend for patients to take a more proactive approach to their own health and seek out different forms of self care. However, in addition to the many benefits that traditional medicines can offer, there are also associated risks. Many products are unregulated and safety and quality cannot be assured. Reported problems include sales of incorrect plant species and contamination and adulteration of therapies. Heavy metals, fumigation agents, microbial toxins and pharmaceutical substances have been found in toxic concentrations.

Although consumer information cannot compensate for poor products or inadequate practices, it can help consumers gain increased knowledge about the benefits and potential risks and where to find reliable sources of information on correct use. The aim of *Guidelines on Developing Consumer Information on Proper Use of Traditional, Complementary and Alternative Medicine* is to provide an overview of the general principles and activities necessary for the development of reliable consumer information. The document will also be a useful reference for consumers wishing to choose a suitable therapy that is safe and effective and also provides a section on "Things to know about evaluating medical resources on the Internet".

Guidelines on Developing Consumer Information on Proper Use of Traditional, Complementary and Alternative Medicine. Available from: Marketing and Dissemination, World Health Organization, 1211 Geneva, 27, Switzerland or publications@ who.int

Antiretroviral treatment for women and infants: WHO guidelines

The latest *WHO Guidelines on Care, Treatment and Support for Women Living with HIV/AIDS and their Children in Resource-Constrained Settings* contain specific recommendations for the most frequently encountered clinical situations and may be of special use for health service providers. By addressing issues of efficacy, safety, drug resistance and feasibility, the document is intended to guide the selection of antiretroviral regimens to be included in programmes to prevent mother-to-child transmission of HIV. Moreover, it is also intended to support and facilitate antiretroviral treatment for pregnant women and women of reproductive age who have indications for treatment.

An increasing burden is being placed on women and children with AIDS-related illness. Currently, 2.5 million children are HIV positive and a total of 700 000 children were newly infected in 2003 alone. Guidelines on use of antiretroviral drugs for treating pregnant women and preventing HIV infection in infants were last issued in 2000. Since then, considerable experience has accumulated in implementing programmes to prevent mother-to-child transmission of HIV as well as the safety and effectiveness of various antiretroviral regimens.

Guidelines on care, treatment and support for women living with HIV/AIDS and their children in resource-constrained settings ISBN 92 4 159209 5. *Available from: Marketing and Dissemination, World Health Organization, 1211 Geneva, 27, Switzerland or publications@ who.int*

Malaria on–line project

A malaria educational website is provided by the Royal Perth Hospital, Australia, for clinicians, scientists, healthcare professionals and students. The site contains sections on malaria diagnosis, prophylaxis, treatment and history as well as an innovative interactive "test and teach" self assessment module. A trilingual version of the components is available on CD/ROM. All requests for the CD should be sent to sandy.treadgold@health.wa.gov.au.

Information available at http://www.rph.wa.gov. au/labs/haem/malaria/index.html

Non-clinical safety testing: WHO handbook

WHO has released a handbook on nonclinical safety testing to serve as an aid for regulatory purposes during product development. A Scientific Working Group – composed of independent scientific specialists from around the world – was convened to produce the handbook by the UNICEF/UNDP/World Bank/WHO Special Programme for Research & Training in Tropical Diseases.

The handbook is broadly based on current safety testing guidelines including those of the Organization for Economic Cooperation and Development (OECD) and the International Conference on Harmonization (ICH). The handbook will provide scientists and laboratories in disease endemic countries with the necessary technical aid for planning and implementing non/clinical safety testing programmes.

Handbook on nonclinical safety testing. TDR/PRD/NCT/04.1. Available from: Marketing and Dissemination, World Health Organization, 1211 Geneva, 27, Switzerland or publications@ who.int

Global Forum for Health Research: 10/90 Report

The Global Forum for Health Research has launched its fourth report on the state of world health research. The 10/90 Report on Health Research 2003–2004 reviews the recommendations made since 1990 to help correct the 10/90 gap and action taken since then. It leads with two strong messages to ministers of finance: health research pays big dividends and research is needed to meet the Millennium Development Goals (MDGs).

The 10/90 Report on Health Research 2003-2004: available on the website http:/www.globalforumhealth.org where orders can be placed for a printed copy (English only) or CD-ROM,

UN consolidated list of products

The United Nations regularly publishes a consolidated list of chemical and pharmaceutical products whose consumption and/or sale have been banned, withdrawn, severely restricted or not approved by governments. It serves as a tool for governments to remain up to date with regulatory action taken worldwide. The information concerning pharmaceutical products is provided by the World Health Organization.

The Eighth issue of the consolidated list has now been published and contains information on pharmaceuticals up to the end of 2002. For more up-to-date information, however, WHO regularly publishes a booklet entitled *Pharmaceuticals: restrictions in use and availability.* Information includes references to relevant legal or statutory documents to enable the user to verify the legal context and scope of regulations.

United nations. Consolidated list of products whose consumption and/or sale have been banned, withdrawn, severely restricted or not approved by governments. ST/ESA/282. New York, 2003, & World Health Organization. Pharmaceuticals: restrictions in use and availability. WHO/EDM/QSM/2003.5 April 2003. Available from: Marketing and Dissemination, World Health Organization, 1211 Geneva, 27, Switzerland or publications@ who.int

Conflict of interest and research

The United States Office of Public Health and Science has announced publication of a guidance document on financial relationships and interests in research. The document raises points to consider in determining whether specific financial interests in research could affect the rights and welfare of human subjects, and the actions which could be considered to protect those subjects.

The guidance is targeted to institutional review boards, investigators, and research institutions. Other guidance regulates institutional management of financial interests of investigators who conduct public health services research and Food and Drug Administration requirements on sponsor responsibility to disclose certain financial interests in marketing applications. These regulations can be found on http://www.fda.gov/oc/guidance/finan and http://grants.nihgov/grants.

Office for Human Research Protections. Financial relationships and interests in research involving human subject: guidance for human subject protection. http://ohrp.osophs.dhhs.go. *Federal Register*, **69**(02): 26393–26397 (2004).

Access and use of psychotropic medicines

Mental and behavioural disorders account for a large proportion of the global burden of disease, but only a minority of those suffering from such disorders receive basic treatment and in many developing countries, health systems are often not able to provide even the most essential mental care. Psychotropic medicines can effectively be used for a variety of mental disorders in conjunction with psychosocial interventions. However, their use needs special consideration with regard to access.

Improving Access and Use of Psychotropic Medicines, is a guidance package consisting of a series of interrelated user-friendly modules that are designed to address a wide variety of needs and priorities in policy development and service planning. The topic of each module represents a core aspect of mental health and they may be used individually or as a package. The modules will be of interest to policy makers and health planners as well as groups representing people with mental disorders in order to develop policies and strategies for improving mental health, and to use existing resources to achieve the greatest possible benefits.

Improving Access and Use of Psychotropic Medicines. Available from: Marketing and Dissemination, World Health Organization, 1211 Geneva, 27, Switzerland or publications@who.int

Medical devices guidelines

A series of guidelines concerning medical devices has been developed to provide information on particular aspects of the new regulatory system for medical devices, which was introduced in Australia in October 2002.

A medical device is defined as any instrument, apparatus, appliance, material or other article ... for human beings ... which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means. A key part of the definition is the intended purpose, as specified by the manufacturer.

The new medical devices legislation incorporates accepted best practice relating to safety, quality and risk management procedures, as well as providing flexibility and capacity to regulate new and changing technology.

Australian Medical Devices Guidelines. Available from TGA Therapeutic Goods Administration, http://tga.gov.au