

# WHO PHARMACEUTICALS NEWSLETTER



prepared in collaboration with the  
WHO Collaborating Centre for  
International Drug Monitoring,  
Uppsala, Sweden

*The aim of this Newsletter is to disseminate information on the safety and efficacy of pharmaceutical products, based on communications received from our network of "drug information officers" and other sources such as specialized bulletins and journals, as well as partners in WHO. The information is produced in the form of résumés in English, full texts of which may be obtained on request from:*

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## **News & Issues**

The recently concluded twenty-ninth meeting of the National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring was, as always, an incredible event, bringing together over a hundred participants from 43 countries. Those of you who attended this meeting in Liège, Belgium will remember the sessions moving on well-oiled wheels, thanks to the excellent organization by Thierry Roisin and his team. This meeting will stay with us for many reasons. The topics were very relevant with several outstanding presentations. We learnt much but have become even more aware of all that needs to be done, in global networking for information sharing, towards improving patient safety, about special safety monitoring needs in pandemics, the need to build an evidence base for pharmacovigilance in resource-poor countries as well as in many other areas. We shall be reporting on these issues in the next editions of this newsletter. But things have never looked this promising; more and more countries are recognizing pharmacovigilance as an important tool towards rational use of medicines, with an ultimate impact on patient safety. With growing awareness, the resources too will follow. There is cause for optimism.

Earlier this year, WHO took the lead in establishing the International Medical Product Anti-Counterfeiting Taskforce, IMPACT. The feature article in this issue provides an overview of why this was needed and what countries can do to protect public health from this menace.

As usual, we also bring you sections covering new global drug regulatory and safety information on medicines.

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## Bevacizumab Reports of reversible posterior leukoencephalopathy syndrome (RPLS)

**USA.** Genentech Inc. is informing health-care providers that some cases of confirmed and possible RPLS have been reported in patients treated with bevacizumab (Avastin, an immunosuppressant) in clinical studies and in post-marketing experience at a rate of <0.1 %. RPLS is a rare brain-capillary leak syndrome associated with hypertension, fluid retention, and the cytotoxic effects of immunosuppressive drugs on the vascular endothelium. The syndrome can present as headache, seizures, visual disturbance and altered mental function and is characterized by its reversibility upon control of hypertension or other instigating factors. Magnetic Resonance Imaging is needed to confirm RPLS. And if RPLS is confirmed, bevacizumab (Avastin) should be discontinued and hypertension, if present, should be treated. The prescribing information for bevacizumab (Avastin) has been updated accordingly.

### Reference:

'Dear Health-care Provider' letter from Genentech Inc., September 2006 (<http://www.fad.gov>).

## Dexamfetamine sulfate

### Label to warn of sudden death from misuse

**USA.** The labelling for dexamfetamine sulfate (Dexedrine Spansule) sustained-release capsules and tablets has been updated in the US in response to a United States Food and Drug Administration (US FDA) request. The updated Boxed Warning section states that misuse of amfetamines may lead to serious cardiovascular adverse events and sudden death. The

updated Warning section states the following:

- CNS stimulants have been linked with sudden death in children and adolescents with structural cardiac abnormalities or other serious heart disorders. Sudden death, stroke and myocardial infarction have been reported in adults receiving stimulants for attention-deficit hyperactivity disorder (ADHD). Stimulant drugs should not be given to patients with structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease or other serious heart disorders.
- Stimulant drugs can modestly increase mean heart rate (HR) and blood pressure (BP). Patients should be monitored for larger changes in BP and HR; caution is indicated in treating those with conditions that might be compromised by HR or BP increases. Cardiovascular (CV) status should also be assessed in patients being considered for treatment with stimulants.
- Stimulant drugs may worsen thought disorders and behaviour disturbances in patients with a pre-existing psychotic disorder. Care should also be taken when using stimulants for ADHD in patients with bipolar disorder due to concern for possible induction of mixed/manic episodes in such patients.
- Stimulant drugs may cause treatment-emergent psychotic or manic symptoms, and may lower the convulsive threshold. In addition, hostility or behavioural disorders have been reported in clinical trials, and in the post-marketing experience of some ADHD drugs, so

patients starting ADHD treatment should be monitored for such symptoms.

- Consistent methylphenidate use was associated with a slowing growth rate in a study in children. It has been anticipated that chronic use of amfetamines may cause a similar growth suppression; therefore, growth should be monitored during stimulant therapy.
- Stimulant treatment has also been linked to visual disturbances.

(Reports in WHO database: Death - 9  
Myocardial infarction - 9).

### Reference:

*Advisories, Warnings & Recalls. United States Food and Drug Administration, 4 August 2006 (<http://www.fda.gov>).*

## Dietary supplement Adulterated with estazolam

**Canada.** Canadian consumers have been warned by Health Canada not to use Salt Spring Herbs Sleep Well Dietary Supplement, as a sample has been found to contain estazolam. Health Canada advises that although there have been no reports of adverse reactions suspected of being associated with the supplement, estazolam is a sedative that can be habit-forming after only a few months of use, and serious adverse effects associated with the drug include memory loss, hallucinations, depression and confusion; other common adverse effects include dizziness and drowsiness. The agency also warns that people with a benzodiazepine allergy, or who have myasthenia gravis, sleep apnoea, are pregnant or elderly or have a history of substance abuse, should not use estazolam. Health Canada

says that consumers taking the supplement should talk to a health-care professional before they stop using it, as withdrawal symptoms are possible. Although the product is not authorized for sale in Canada, the agency advises that the product has been found on the Canadian market. The Canadian distributor has initiated a recall.

**Reference:**

*Advisories, Warnings & Recalls. Health Canada, 30 August 2006 (<http://www.hc-sc.gc.ca>).*

## Diethylene glycol Detected in cough syrup; fatalities reported

**Republic of Panama.** Several cases of acute renal failure, many of them fatal, were recently reported in Panama in patients treated with lisinopril. The Panama Ministry of Health investigated these cases and has concluded that these reactions resulted from the concomitant use of a cough syrup that contained diethylene glycol (DEG) and were not due to lisinopril as previously feared (1). DEG is a highly toxic organic solvent that causes acute renal failure and death when ingested. DEG-associated fatalities have been reported also in the past, in 1938 in the USA, when DEG had been used as a diluent for sulfanilamide and in 1998 in India, where contaminated cough syrup caused the deaths of a number of children (2). The United States Congress passed the Federal Food, Medicines & Cosmetic Act in 1938 in reaction to the DEG incident. WHO issued an Alert in 1996 (3) when several children died in Haiti after consuming DEG-contaminated paracetamol syrup. The Panama Ministry of Health is currently performing a root cause analysis of events leading to the presence of a poisonous substance such as DEG in a pharmaceutical preparation for human consumption.

**References:**

1. *Comunicado N° 15. Ministerio de Salud, República de Panama,*

17 October 2006

(<http://www.minsa.gob.pa>).

2. *The Safety of Medicines in Public Health Programmes; pharmacovigilance an essential tool. WHO, 2006.*  
3. *DRS Information Exchange Service Alert No. 50. WHO, 28 June 2006.*

## Hydrogen peroxide High strength peroxide not a medical product

**USA.** The US FDA is warning consumers against drinking high-strength hydrogen peroxide products for medicinal purposes, including a product marketed as "35 Percent Food Grade Hydrogen Peroxide," because ingestion may lead to serious health risks or death. The FDA advises consumers of these products to immediately discontinue them and to consult their health-care provider. The FDA says that high-strength hydrogen peroxide is not approved by the FDA and is therefore being illegally sold for medical indications without proven clinical value. The Agency says that it is working to prevent companies that sell these products from making illegal claims about their products, and that it has issued warning letters to two firms who are illegally selling "35 percent hydrogen peroxide" products on websites. The FDA states that this high-strength hydrogen peroxide is highly corrosive, and that hydrogen peroxide at a strength of 35% is dangerous even if handled according to manufacturer directions. Hydrogen peroxide ingestion can lead to GI ulceration or irritation, and IV administration can lead to air embolisms, blood vessel inflammation at the injection site and potential life-threatening allergies, says the FDA.  
(Reports in WHO database: Total 76  
Conjunctivitis - 16  
Application site reaction - 7

Vomiting - 8  
Abdominal pain - 4).

**Reference:**

*FDA News Release. United States Food and Drug Administration, 27 July 2006 (<http://www.fda.gov>).*

## Neophase Formula Presence of undeclared active ingredient

**Canada.** Health Canada is advising consumers not to use Neophase Formula for Men, which is manufactured in the US by Vigor Nutraceutical Healthcare Inc, because it has been found to contain homosildenafil, a modified version of sildenafil. The Agency says that the use of this product can lead to serious health risks, particularly in patients with heart disorders, those at risk for stroke, and those using heart medications, and that the use of sildenafil-containing products has been linked with serious adverse effects including penile tissue damage, sudden loss of vision and urinary tract infections. The product is being recalled by its Canadian distributor, and consumers who may have purchased Neophase Formula for Men are advised to not use it and to consult a health-care professional if they have used it and have health concerns, says the Agency.

**Reference:**

*Advisories, Warnings & Recalls. Health Canada, 4 August 2006 (<http://www.hc-sc.gc.ca>).*

(Reports in WHO database: Cardiomyopathy - 27).

## Antidepressants

### Update on adverse reaction reports

**Finland.** From 1998 to 2005, Finland's National Agency for Medicines (NAM) received 396 reports of adverse reactions (ARs) associated with antidepressants, including tricyclic antidepressants (7 reports), SSRIs (170) and other antidepressants (227). NAM advises that the reports received on SSRIs involved sertraline (51 reports), citalopram (44), paroxetine (27), fluoxetine (22), escitalopram (18) and fluvoxamine (8); about one-third of the reports involved neurological disorders, whereas other reports were related to skin disorders, digestive system disorders, oedema, serotonin syndrome, drug interactions, withdrawal symptoms and intentional overdoses. The Agency added that, among other antidepressants, the majority of AR reports were related to mirtazapine (106), venlafaxine (53) and reboxetine (20), and involved neurological disorders. Mirtazapine-related ARs also included skin disorders, oedema, leucopenia and stomatitis. Venlafaxine-associated reports included serotonin syndrome, withdrawal symptoms and QT-interval prolongation. According to NAM, seven adverse reaction reports involved neonates and all of them involved SSRIs, whereas 21 reports involved adolescents aged 15–19 years. Adverse symptoms in the neonates included seizures, somnolence, and breathing and eating difficulties.

#### Reference:

TABU, 4: 56, 2006. National Agency for Medicines, Finland.

## Bismacine

### Warning against use

**USA.** The US FDA is warning consumers and health-care providers against using bismacine, also known as chromacine. The Agency is investigating one report of death and several reports of injury associated with bismacine use. According to the US FDA, injectable bismacine is not a pharmaceutical, is not approved for anything, and contains high amounts of bismuth, which is not approved for use by injection. The FDA says that one person has died, one was hospitalised and others experienced serious adverse events after receiving bismacine. The Agency also states that possible effects of bismuth poisoning include renal failure and cardiovascular collapse.

#### Reference:

FDA News. United States Food and Drug Administration, 21 July 2006 (<http://www.fda.gov>).

## Bisphosphonates

### Additional cases of osteonecrosis of the jaw

**Australia.** Since the Australian Adverse Drug Reactions Advisory Committee (ADRAC) drew attention to the issue of osteonecrosis of the jaw (ONJ) associated with bisphosphonates in 2005, further Australian cases have been published. ADRAC advises that, up to June 2006, it has received 106 reports of ONJ associated with bisphosphonates; these reports involved IV zoledronic acid (n = 69), IV pamidronic acid (33), oral alendronic acid (19), oral risedronic acid (2), IV ibandronic acid (1) and IV and oral clodronic acid (1). According to ADRAC, a review of 368 published case reports of ONJ found that 94% involved patients with bony metastasis

or multiple myeloma receiving IV bisphosphonates, and 60% of cases were preceded by a dental procedure.

#### Reference:

Australian Adverse Drug Reactions Bulletin 25(4): 14, August 2006.

## CFC-free beclometasone inhalers

### Dose adjustments needed with different brands

**UK.** The Medicines and Healthcare products Regulatory Agency (MHRA) has advised health professionals that two chlorofluorocarbon (CFC)-free beclometasone inhalers, Clenil Modulite and Qvar provide different amounts of the active drug to the lungs; Qvar is approximately twice as potent as Clenil Modulite. The Agency says that this difference should be taken into account and dosages adjusted according to the type of brand chosen. The MHRA is asking prescribers to state clearly on prescriptions which product should be dispensed by using the brand name rather than the generic name. Furthermore, pharmacists who receive a prescription with the generic name should establish whether a (CFC)-free product is required, and if so, which of the two brands should be dispensed.

#### Reference:

Press release. Medicines and Healthcare products Regulatory Agency, 8 August 2006 (<http://www.mhra.gov.uk>).

## Enoxaparin

### To decrease dose in renal disease

**Australia.** ADRAC has received 10 reports of death associated with haemorrhage after enoxaparin use in

2005–2006, giving a total of 46 since 1997. In three of the reports received in 2005, patients with chronic renal disease received inappropriate doses; two reports also implicated an incorrect dose for the patient's weight.

The Australian ADRAC advises that since the clearance of enoxaparin sodium is decreased in patients with chronic renal disease, the dosage should be decreased in such patients. ADRAC warns that low molecular weight heparins such as enoxaparin have a longer half-life than unfractionated heparins, their anticoagulant effect is not routinely monitored and, in cases of haemorrhage, their effects are harder to reverse.

ADRAC says that patients' renal function should be assessed before starting low molecular weight heparins; for those with severe chronic renal disease (glomerular filtration rate < 30 mL/min) requiring therapeutic dosages, the dosage of enoxaparin should be decreased from 1 mg/kg twice daily or 1.5 mg/kg once daily to 1 mg/kg once daily. An alternative is to use unfractionated heparin with dose monitoring by activated partial thromboplastin time. Also, unfractionated heparin is preferred in patients with unstable or deteriorating renal function. Where there is a high risk of haemorrhage, unfractionated heparin is preferred, since rapid and complete reversal of anticoagulation can be attained.

(Reports in WHO database: Death - 85).

**Reference:**

*Australian Adverse Drug Reactions Bulletin* 25(4): 14-15, August 2006.

## Ibuprofen

### Interaction with low-dose, non-coated aspirin

**USA.** The US FDA has warned health-care providers that ibuprofen can interfere with the anti-platelet effect of low dose aspirin (81 mg per day), potentially rendering aspirin less effective when used for cardioprotection and stroke prevention. It has been demonstrated in published and unpublished human *ex vivo* studies, that ibuprofen interferes with the antiplatelet activity of low dose aspirin (81 mg, immediate release) when they are ingested concurrently. The mechanism by which this occurs may be through competitive inhibition of the acetylation site of cyclooxygenase (COX) in the platelet. Both ibuprofen (reversible inhibition) and aspirin (irreversible inhibition) occupy nearby sites on COX, such that the presence of ibuprofen interferes with aspirin binding. Once the ibuprofen releases from the binding site, COX will not be inhibited because some aspirin available to bind will have been excreted. This ibuprofen interference attenuates the expected aspirin-mediated irreversible inhibition of thromboxane B2 (TXB2) production and the expected inhibition of platelet aggregation.

Health-care professionals should advise consumers and patients regarding the appropriate concomitant use of ibuprofen and aspirin. They should consider:

- counselling patients about the appropriate timing of ibuprofen dosing if they are also taking aspirin for cardioprotective effects.
- with occasional use of ibuprofen, there is likely to be minimal risk from any attenuation of the antiplatelet effect of low dose aspirin, because of the

long-lasting effect of aspirin on platelets.

- patients who use immediate release aspirin (not enteric coated) and take a single dose of ibuprofen 400 mg should dose the ibuprofen at least 30 minutes or longer after aspirin ingestion, or more than 8 hours before aspirin ingestion to avoid attenuation of aspirin's effect.
- recommendations about the timing of concomitant use of ibuprofen and enteric-coated low dose aspirin cannot be made based upon available data.
- other nonselective OTC NSAIDs should be viewed as having the potential to interfere with the antiplatelet effect of low-dose aspirin unless proven otherwise.
- prescribing analgesics that do not interfere with the antiplatelet effect of low dose aspirin for high risk populations.

**Reference:**

*Healthcare Professional Sheet. United States Food and Drug Administration, 8 September 2006 (<http://www.fda.gov>).*

## Infliximab

### Reports of hepatosplenic non-hodgkin's lymphoma

**Canada, Switzerland.**

Schering Canada Inc. and Schering Plough / Essex Chemie AG (Switzerland) are advising that infliximab (Remicade) may be associated with hepatosplenic non-Hodgkin's lymphoma in paediatrics and young adults with Crohn's disease (CD). According to the companies there have been six post-marketing reports of hepatosplenic non-Hodgkin's lymphoma in paediatric and young adult patients\* receiving infliximab (Remicade) for CD in

the US; five of the cases were fatal. They say that exposure to infliximab (Remicade) in these cases ranged from 1–2 infusions to more than four years of maintenance therapy. The companies advise that, in all cases, other immunosuppressants (including mercaptopurine or azathioprine) had been used in the past or concomitantly, so a clear causal relationship between infliximab (Remicade) and the development of hepatosplenic non-Hodgkin's lymphoma has not been established; however, they cannot exclude that infliximab (Remicade) may play a role in causing or exacerbating the disease. The companies note that infliximab is not authorized for use in paediatric patients, in Canada (1) or in Switzerland (2).

\*aged 12–19 years (five cases) and 31 years (one case).

(Reports in WHO database: Non-Hodgkin's lymphoma - 85).

#### References:

1. *Advisories, Warnings & Recalls. Health Canada, 14 September 2006* (<http://www.hc-sc.gc.ca>).
2. *Informations: Pharmacovigilance: Surveillance du marché. Swissmedic, 17 July 2006* (<http://www.swissmedic.ch>).

## Jambrulin

### High lead content

**Canada.** Health Canada has issued an advisory to consumers warning against the use of Jambrulin, an Ayurvedic medicinal product, due to high lead content. The Agency says that Jambrulin tablets are not authorized for sale in Canada and have not been found on the country's market. However, according to Health Canada, they can be purchased over the Internet, and travellers may have brought them into the country for personal use. Heavy metal consumption, including

lead, can have potentially serious health risks due to accumulation in vital organs. Pregnant women, children and infants are particularly susceptible to lead's toxic effects.

#### Reference:

*Advisories, Warnings & Recalls. Health Canada, 14 September 2006* (<http://www.hc-sc.gc.ca>).

## Lamotrigine

### In utero exposure and risk of cleft lip and/or palate

#### Canada, Denmark, USA.

Regulatory Agencies in Denmark, Canada and the USA have all issued warnings that data from the North American Antiepileptic Drug Registry suggest a possible association between exposure to lamotrigine monotherapy during the first trimester of pregnancy and cleft lip and / or cleft palate in the new born (1-3). Cleft palate/cleft lip was found in five out of 564 infants exposed to lamotrigine in the first trimester of pregnancy, (total prevalence of 8.9 per 1000); prevalence of non-syndromic oral clefts among infants of nonepileptic mothers not taking lamotrigine in other studies from the US, Australia and Europe range from 0.50 to 2.16 per 1000. The agencies say that other pregnancy registries of similar size have not replicated this observation and that the clinical significance of this preliminary report is uncertain at the moment. GlaxoSmithKline (GSK), the manufacturer of lamotrigine (Lamictal) is also administering a pregnancy registry to learn more about this possible association. At this time, women who take lamotrigine and are pregnant or are thinking of becoming pregnant should discuss with their doctor. Patients should not start or stop using lamotrigine without talking to their doctor.

(Reports in WHO database: Cleft palate - 14).

#### References:

1. *'Advisories, Warnings & Recalls'. Health Canada, 1 August 2006* (<http://www.hc-sc.gc.ca>).
2. *Media Release. Danish Medicines Agency, 30 June 2006* (<http://www.dkma.dk>).
3. *FDA Alert. United States Food and Drug Administration, 28 September 2006* (<http://www.fda.gov>).

## Norelgestromin/ ethinyl estradiol contraceptive patch

### New study shows increased risk of VTE

**USA.** Two separate epidemiological studies evaluated the risk of developing a serious blood clot in women using norelgestromin/ethinyl estradiol transdermal (Ortho Evra) contraceptive patch compared to women using a different oral contraceptive. The first study found that the risk of non-fatal venous thromboembolism (VTE) associated with the use of the contraceptive patch (Ortho Evra) is similar to the risk with the use of oral contraceptive pills containing 35 micrograms of ethinyl estradiol and norgestimate. However the second study found an approximate two-fold increase in the risk of medically verified VTE events in users of the patch (Ortho Evra). The second study results support earlier concerns of increase in the risk of blood clots with norelgestromin/ ethinyl estradiol (Ortho Evra) contraceptive patch. The US Agency advises that according to prescribing recommendations (for Ortho Evra) women with concerns or risk factors for thromboembolic disease should discuss various contraceptive

options with their health professionals.

**Reference:**

*MedWatch - Ortho Evra. United States Food and Drug Administration, September 2006 (<http://www.fda.gov>).*

## Sirolimus High rate of renal transplant rejection

**Canada.** The use of sirolimus (Rapamune), mycophenolate mofetil (MMF) and corticosteroids (ST), in combination with interleukin-2 receptor antibody (IL2R Ab, basiliximab) induction, appears to be associated with an increased risk of acute rejection in renal transplant recipients if the regimen is used from the time of transplantation. Wyeth Pharmaceuticals has stopped an investigational clinical trial, as interim results showed that the rate of acute rejection was higher than expected, and that a renal function benefit was not supported in renal transplant recipients who received the above immunosuppressant regimen (Rapamune, MMF and corticosteroids), relative to the control group (cyclosporine + MMF + corticosteroids); all patients (control and treated group) received basiliximab. The reported rate of biopsy-confirmed acute rejection was significantly higher in the sirolimus (Rapamune) group than in the control (cyclosporine) group (17.5% vs 2.5%); the respective reported death rates were 2.9% and 0.6%. One arm of another study (daclizumab + Rapamune + MMF) has also been stopped, as interim data also revealed an increased acute rejection rate and a numerically higher death rate.

Wyeth recommends that:

- The combination (Rapamune, MMF and corticosteroids), together with interleukin-2 receptor antagonists, should not be used in the *de novo* organ transplant setting.

- Initial use of sirolimus (Rapamune) should be in combination with cyclosporine and corticosteroids.
- Patients should not stop taking sirolimus (Rapamune) or change their medication without consulting their transplant physician.

(Reports in WHO database: Transplant rejection - 149).

**Reference:**

*Advisories, Warnings & Recalls. Health Canada, 18 August 2006 (<http://www.hc-sc.gc.ca>).*

### Medication Errors

According to a report from the Institute of Medicine of the National Academies, medication errors harm at least 1.5 million people annually in the US; the conservative estimate of the extra medical costs of treating drug-related injuries that occur in hospitals alone is \$3.5 billion annually. Linda R. Cronenwett, co-chair of the committee that wrote the report, says "the frequency of medication errors and preventable adverse drug events is cause for serious concern." The report recommends the creation of new information resources through which patients can access objective and easy-to-understand drug information, and that all prescriptions should be written electronically by 2010.

**Reference:**

*National Academies Press, 20 July 2006 (<http://www.national-academies.org>).*

### US Senate bill to improve safety of medications

A bill has been introduced in the US Senate to increase the safety of prescription medications. The bill includes a 2-year moratorium on direct-to-consumer advertising for some drugs that have been newly approved. It also calls for better safety planning by pharmaceutical manufacturers before a drug receives FDA approval, and for an improvement in the FDA's postmarketing surveillance.

**Reference:** *JAMA, 296(10): 1225, 13 September 2006.*

### Counterfeit Lipitor: detected again

Health Canada has warned consumers about a batch of counterfeit atorvastatin (Lipitor) found on the UK market. The drug is used to treat high cholesterol. The counterfeit Lipitor, lot number 004405K1, was originally removed from the UK market but was found there again in a pharmacy.

**Reference:** *Information Update. Health Canada, 2 August 2006. [www.hc-sc.gc.ca](http://www.hc-sc.gc.ca).*

## Counterfeit medicines: an intent to deceive

Valerio Reggi, IMPACT, WHO

It has been said that imitation is the highest form of flattery. However, we can do without this type of flattery if it harms our health. 'Brand name' goods such as watches and clothes have always attracted the attention of unscrupulous counterfeiters everywhere in the world. Unfortunately, this menace has also spread to the world of medicines, putting hundreds and thousands of unsuspecting lives into serious danger. Counterfeiting is deceptive and immoral in any field. But in healthcare, it is criminal and simply unacceptable.

### What are counterfeit medicines?

According to WHO, a counterfeit medicine is a product which is '*deliberately and fraudulently mislabelled with respect to identity and/or source*'. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging. It is important to make a distinction between counterfeit medicines and other kinds of substandard medicines: all counterfeit medicines are substandard because they are manufactured and distributed outside of regulatory control and their composition is unpredictable. On the other hand, not all substandard medicines are counterfeit because not all of them have been '*deliberately and fraudulently mislabelled*'. Experience has shown that there are 'many kinds' of counterfeit medicines. Counterfeiters have targeted well known as well as unbranded products, expensive as well as inexpensive products. They have even produced fake medicines that do not refer to any existing brand or manufacturer.

### What are the consequences of counterfeit medicines?

Therapeutic failures and adverse effects would be the more serious consequences. In fact many cases of counterfeiting have been uncovered while investigating therapeutic failure or adverse events observed in patients. But a serious if not fatal consequence is the erosion of confidence in health-care systems.

### Where do we find counterfeit medicines?

Everywhere. No country is outside the counterfeiters' reach, the problem is truly global. Counterfeit medicines are increasingly detected in European and North-American countries. This suggests that even countries with advanced regulatory systems are seriously challenged by this menace. Nor are some medicines free from this disgrace; if widely used medicines such as atorvastatin and paracetamol are counterfeited, so are other, less commonly used products such as growth hormone, paclitaxel and filgrastim. Stated differently, counterfeits can surface in community pharmacies and in hospitals alike.

Nobody knows the precise extent of the problem. Counterfeits are difficult to detect, investigate or quantify. Rough estimates, mainly based on unpublished reports, suggest that up to 10% of the medicines circulating in the world could be counterfeit. It is very likely that this estimate is not a realistic description of the situation of the best regulated countries of the world. Yet, even a few dozen cases in a year mean many thousands of tablets and ampoules and therefore many thousands of patients at risk!

### Who are the counterfeiters?

Counterfeiting medicines has attracted organized crime, but it also requires the cooperation of people with some experience in pharmaceutical manufacturing and distribution. In addition to organized crime, there are small-scale counterfeiting activities. And individuals indulge in it as well, as in the case of Robert Courtney, a Kansas City pharmacist who, in ten years, accumulated at least US\$19 million by diluting injections, often prepared for patients he personally knew. He got a 30-year prison sentence.

Counterfeiting is 'easy business' because:

- it is relatively easy to hide and smuggle medicines: very few countries have customs control that is specialized in detecting counterfeit medicines;
- most users are not able to distinguish between real and counterfeit;
- manufacturing bad quality medicines does not require huge investment and the equipment is easy to move from one 'counterfeit' site to another;
- in many countries, regulatory and control systems, especially oversight on distribution channels, are ineffective;
- in addition, in most countries, punishment is not sufficiently strong to deter criminals.

And governments face considerable challenges in fighting the menace because of:

- a lack of willingness to recognize the existence or the seriousness of the problem;

- inadequate legal framework and ineffective punishment: counterfeiting medicines is not properly defined and is dealt with in the same way as all other types of counterfeiting;
- weak administrative and coordination measures;
- ineffective control on pharmaceutical manufacturing, importation and, especially, distribution.

Additional factors include national drug policies that prioritize export activities over compliance with good manufacturing practices; ineffective collaboration among authorities and institutions involved in regulation, control, investigation and prosecution (e.g. Drug regulatory authorities, police, customs and the judiciary); an extremely fragmented distribution channel that increases the opportunities for counterfeiters to infiltrate the system; wide price gaps or extremely high prices in countries that cause patients to 'wander' in search of 'affordable' versions of the medicines; internet vending of medicines; and third-party manufacturing, which, if not properly and carefully organized, may lead to unauthorized and substandard use of manufacturing techniques and packaging materials.

### **How to protect public health?**

Combating counterfeit medicines requires collaboration, at national, regional and international levels involving all stakeholders of the public sector and the civil society including health professionals, patients, manufacturers, distributors, as well as communication professionals and the media. But the first step is to sensitize and obtain the commitment of law-makers to introduce adequate legislative measures that clearly define and recognize counterfeiting of medicines as a crime that is different and far more serious than the counterfeiting of other kinds of goods.

Efficient coordination mechanisms should be put in place for rapid and effective anti-counterfeit measures without bureaucratic delay. While regulations and controls should not unnecessarily hinder the exportation of medicines, it is necessary to ensure that both exporting and importing countries can apply measures that permit to effectively identify the actual origin of exported medicines. Liberalization and intensification of international trade offer opportunities for trading in medicines of unclear origin, including counterfeits. It is necessary that national authorities improve border control and develop appropriate international collaboration and exchange of information through international legal and administrative agreements. Essential stakeholders in these efforts should include Interpol, the Organisation for Economic Co-operation and Development, the World Customs Organization, the World Intellectual Property Organization, the World Trade Organization, and the World Health Organization.

Pharmaceutical manufacturers and their associations are also key players in combating counterfeit medicines. In the past, many companies kept quiet on the cases that were detected, probably fearing negative publicity for the company products. However, this attitude has now changed. Industry has an important role in providing information as well as in developing technologies that help detect and deter the manufacture of counterfeit medicines. In a similar vein, distributors, wholesalers, importers and exporters should develop and effectively implement business practices that make the distribution chain impermeable to counterfeits and open to appropriate verification by national authorities. Purchasing organizations and NGOs should similarly develop appropriate procurement procedures. Other players in this important battle are the health professionals; nurses and pharmacists should stay vigilant to the presence of counterfeits and report suspicious products. Similarly, physicians should rule out counterfeits as a possible cause of adverse reactions or therapeutic failure. To complete the cycle of protection, the public must do their bit as well: patients must report to their pharmacists and doctors if they sense any irregularity with their medication, if they experience a side effect or a decrease in beneficial effect.

The International Medical Product Anti-Counterfeiting Taskforce, IMPACT was established by WHO with the aim of bringing together all key stakeholders at the international, regional and national level, to effectively combat counterfeit medicines. The Declaration of Rome, included on the next page describes the background and captures the remit of the task force.

**DECLARATION OF ROME**

18 FEB 2006

The participants of the WHO International Conference  
'Combating Counterfeit Drugs: Building Effective International Collaboration',  
gathered in Rome on 18 February 2006

**DECLARE**

1. Counterfeiting medicines, including the entire range of activities from manufacturing to providing them to patients, is a vile and serious criminal offence that puts human lives at risk and undermines the credibility of health systems.
2. Because of its direct impact on health, counterfeiting medicines should be combated and punished accordingly.
3. Combating counterfeit medicines requires the coordinated effort of all the different public and private stakeholders that are affected and are competent for addressing the different aspects of the problem.
4. Counterfeiting medicines is widespread and has escalated to such an extent that effective coordination and cooperation at the international level are necessary for regional and national strategies to be more effective.
5. National, regional and international strategies aimed at combating counterfeit medicines should be based on:
  - a) political will, adequate legal framework, and implementation commensurate to the impact of this type of counterfeiting on public health and providing the necessary tools for a coordinated and effective law enforcement,
  - b) inter-sectoral coordination based on written procedures, clearly defined roles, adequate resources, and effective administrative and operational tools,
  - c) creating an awareness about the severity of the problem among all stakeholders and providing information to all levels of the health system and the public,
  - d) development of technical competence and skills in all required areas,
  - e) appropriate mechanisms for ensuring vigilance and input from healthcare professionals and the public.
6. The WHO should lead the establishment of an International Medical Products Anti-Counterfeiting Taskforce (IMPACT) of governmental, non-governmental and international institutions aimed at:
  - a) raising awareness among international organizations and other stakeholders at the international level in order to improve cooperation in combating counterfeit medicines, taking into account its global dimensions
  - b) raising awareness among national authorities and decision-makers and calling for effective legislative measures in order to combat counterfeit medicines
  - c) establishing effective exchange of information and providing assistance on specific issues that concern combating counterfeit medicines
  - d) developing technical and administrative tools to support the establishment or strengthening of international, regional and national strategies
  - e) encouraging coordination among different anti-counterfeiting initiatives.

The IMPACT shall function on the basis of existing structures/institutions and will in the long term explore further mechanisms, including an international convention, for strengthening international action against counterfeit medicines.