# WHO Drug Information

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### General Information



### Recommended International Nonproprietary Names: List 55

# Counterfeit Medicines

## Combating counterfeit medicines

Counterfeit medicines are part of a broader phenomenon of substandard pharmaceuticals. They are deliberately and fraudulently mislabelled with respect to identity and/or source. Counterfeiting can involve both branded and generic products and may include products with the correct ingredients but fake packaging, with the wrong ingredients, without active ingredients or with insufficient active ingredients. The regular use of substandard or counterfeit medicines by the population can lead to therapeutic failure or drug resistance; and in some cases it can lead to death.

Until recently, the most frequently counterfeited medicines in wealthy countries were new, expensive lifestyle medicines. In developing countries the most counterfeited medicines have been those used to treat life-threatening conditions such as malaria, tuberculosis and HIV/AIDS. As the phenomenon develops, more and more medicines are counterfeited, including anticancer drugs and those in high demand such as antivirals. Although it is difficult to obtain precise figures, estimates put counterfeits at more than 10% of the global medicines market. They are present in all regions but developing countries bear the brunt of the problem. An estimated 25% of the medicines consumed in developing countries are believed to be counterfeit. In some countries, the figure is thought to be as high as 50%. In industrialized countries, Internet-based sales remain a major source of counterfeit medicines and are a threat to those seeking cheaper, stigmatized or unauthorized treatments.

Where there is a lack of regulation and enforcement, the quality, safety and efficacy of both imported and locally manufactured medicines cannot be guaranteed. Trade in counterfeit products is more prevalent in countries with weak drug regulatory control and enforcement, scarcity and/or erratic supply of basic medicines, unregulated markets and unaffordable prices. However, as counterfeiting methods become more sophisticated, counterfeits are found to be increasingly present in better-controlled markets.

## Strengthening global cooperation through IMPACT

Since 1992, the World Health Organization (WHO) has been calling for action against the growing epidemic of counterfeit medicines. In a bid to accelerate the war on fake drugs, WHO is pushing for stronger global cooperation, political commitment and creative solutions. During a conference it recently organized in Rome, Italy, WHO has called on stakeholders to find global solutions to this health threat.

The conference was attended by 160 participants representing 57 national drug regulatory authorities, 7 international organizations, 12 international associations of patients, health professionals, pharmaceutical manufacturers and organizations including the International Narcotics Control Board, Organization for Economic Cooperation and Development, World Customs Organization, International Pharmaceutical Federation, International Federation of Pharmaceutical Manufacturers and Associations, World Medical Association, International Council of Nurses, and the International Federation of Pharmaceutical Wholesalers.

It was constructive in providing a consensus on many issues. Two major outputs of the event involved the Declaration of Rome (see page 4) and creation of a global task force (IMPACT) based in WHO. The task force will focus on creating partnerships and improved cooperation among all major interested parties in the areas of legislation and law enforcement, trade, risk communication and innovative solutions, including new technologies for the detection of counterfeits and technology transfer to developing countries. Further information is available at http://www.who.int/medicines/counterfeit.

## WHO International Conference on Combating Counterfeit Medicines

# DECLARATION OF ROME

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:

    - 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.
    - Intersectoral coordination based on written procedures, clearly defined roles, adequate resources, and effective administrative and operational tools.
    - 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.
    - Development of technical competence and skills in all required areas.
    - Appropriate mechanisms for ensuring vigilance and input from healthcare professionals and the public.

6. WHO should lead the establishment of an International Medical Products Anti-Counterfeiting Task force (IMPACT) of governmental, nongovernmental and international institutions aimed at:

    - 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.
    - Raising awareness among national authorities and decision-makers and calling for effective legislative measures in order to combat counterfeit medicines.
    - Establishing effective exchange of information and providing assistance on specific issues that concern combating counterfeit medicines.
    - Developing technical and administrative tools to support the establishment or strengthening of international, regional and national strategies.
    - Encouraging coordination among different anti-counterfeiting initiatives.

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.

# Biological Medicines

## Supply of life-saving antisera: a growing need for concern

Antisera represent the only therapy for the treatment of envenomation and are essential, in combination with vaccination, for post-exposure rabies treatment. Antisera are produced by the fractionation of plasma obtained from horses immunized against the infectious agent or its toxin. No alternative specific therapeutic treatment is available to treat these diseases. Now, production of effective equine-derived antisera in developed countries is being halted before affected countries have developed the capacity to manufacture enough quality products themselves. As a result, the world is now at imminent risk of lacking effective treatment for rabies and envenomation due to snake or scorpion bites.

Rabies is the tenth most common cause of death due to infections in humans. Although one hundred percent fatal, it is none the less a preventable disease if post-exposure treatment with antisera is readily available. An estimated 3 to 4 million people would need to receive equine rabies antisera each year after being exposed to animals suspected of carrying rabies. Almost half of those requiring the antisera and those dying of rabies are children less than 15 years of age. More than 99% of all human deaths from rabies occur in Africa, Asia and South America. Six to 8 million vials of equine rabies antisera is required to cover these needs.

There are close to 5 million snake bites each year in Africa, Asia, and South America; 50 to 75% necessitating treatment by equine antivenoms to avoid deaths, amputation, or severe neurological disorders. Unfortunately, equine antivenoms are largely unavailable. Over 2.5 millions vials of antivenoms would be needed to treat envenomation worldwide. Deaths or disability resulting from these accidents and diseases could be avoided if a sufficient supply of antisera of controlled and assessed quality could be ensured, the logistics of distribution improved, and education on clinical use provided.

The shortage of antisera has become a very critical health issue at global level. Most manufacturers in the developed world have abandoned production due to reduced clinical needs in industrialized countries. Most remaining producers are located in developing countries, where the application of quality and safety standards needs to be improved. The decreasing number of producers and the fragility of the production systems in developing countries dramatically jeopardize the availability of antisera in Asia, Africa, the Middle East, and South America.

In October 2005, the WHO Expert Committee for Biological Standardization (ECBS) recognized the extent of the problem and endorsed, as a priority, the role that WHO must play in supporting and strengthening world capacity to ensure long-term and sufficient supply of safe antisera. The Interagency Pharmaceutical Coordination Group, meeting in November 2005, also endorsed WHO action.

### Prequalification of antisera

WHO is proposing to strengthen existing local production of antisera by building the technical capacity and expertise of regulatory authorities and also to develop a prequalification system for these products that will ensure quality and facilitate the procurement of antisera products through procurement schemes. The WHO project would inherently facilitate transfer of technologies to developing countries. WHO proposes to take the following action to guarantee the production capacity of antisera and improve the supply of safe products:

- Define a global standard for the production, quality control, and regulation of equine-derived antisera to be used as a guidance by local regulatory authorities and manufacturers.
- Conduct educational workshops at regional level to help in the implementation of quality and safety requirements for antisera production following the principles of good manufacturing practices (GMP).

- Train regulators, pharmaceutical inspectors and local manufacturers on the critical parameters of the production of antisera and GMP implementation.

- Facilitate transfer of technology to developing countries.

- In the framework of the WHO prequalification project, initiate prequalification of antisera producers.

**References**

1. Burnouf, Th., Griffiths, E., Padilla, A. et al. Assessment of the viral safety of antivenoms fractionated from equine plasma. *Biologicals,* **32**: 115–128 (2004).

2. Theakston, R.D., Warrell, D.A,, Griffiths, E. Report of WHO workshop on the standardization and control of antivenoms. *Toxicon*, **41**(5): 541–557 (2003).

3. European Medicines Agency. *Note for Guidance on Production and Quality Control of Animal Immunoglobulins and Immunosera for Human Use.* EMEA (2002).

4. Chippaux, J. P. Snake-bites: appraisal of the global situation. *WHO Bulletin*, **76**(5): 515–524 (1998).

5. World Health Organization. http://www.who.int/biologicals

# Latest developments in biological standardization

WHO's biological standardization programme provides, promotes and implements global norms and standards for biological medicines, and strives to provide the most relevant products for the improvement of global health.

The WHO Expert Committee on Biological Standardization (ECBS) was set up to develop, establish and promote technical standards to assure the quality, safety and efficacy of vaccines, biological therapeutics, blood products and selected in vitro diagnostic devices (IVDs). This is one of the longest standing WHO Committees and has been operating since 1947. Among its activities, the WHO biological reference preparations are important tools that allow the comparability of data worldwide in diverse fields of medical practice.

The latest meeting of the ECBS was convened in Geneva from 24 to 28 October 2005. Experts were invited from Belgium, Brazil, France, Germany, Japan, Russian Federation, United Kingdom, and United States of America. Other participants and observers represented the Council of Europe, European Department for the Quality of Medicines, France; European Pharmacopoeia Commission, France; Developing Country Vaccine Manufacturer's Network, Serum Institute of India; European Diagnostic Manufacturers Association, Germany; Eye Bank Association of America, USA; International Association of Biologicals, Switzerland; International Federation of Clinical Chemistry and Laboratory Medicine, Canada; International Federation of Pharmaceutical Manufacturers Associations, Switzerland; GlaxoSmithKline Biologicals, Belgium; International Society of Blood Transfusion/European Plasma Fractionation Association, Netherlands; International Society on Thrombosis and Haemostasis, United Kingdom; Plasma Protein Therapeutics Association, Belgium; and the United States Pharmacopeia.

## Current issues of regulatory concern

The means for preventing and controlling most chronic diseases are well established, and include biotechnological interventions. The number of approved innovative biotherapeutic products is expected to increase substantially over the coming years (e.g. some 500 monoclonal antibody-based products are currently in the pipeline in the European Union and USA alone). In addition, the imminent patent expiration of many biotechnology products will result in a substantial increase in "follow-on" or "biosimiliar" products

WHO is receiving requests from countries for advice on appropriate regulatory oversight for biological therapeutics, since the potential for success of therapeutic biological products used in treatment of a wide variety of chronic diseases is being tempered by concerns over quality, safety and availability of such products. Inappropriate assay methods or poor potency determinations can lead to life or death clinical problems; and adverse drug reactions — for example, unwanted antibody development in some individuals — could occur with a variety of products. Increased risks of infections have been seen with blockers of tumour necrosis factor $\alpha$ and the potential for substandard and counterfeit biotech products represents an important matter of concern.

The Committee proposed that WHO should organize a meeting of interested parties to review these issues in depth and help WHO develop consensus on the global needs, priorities and potential role for global standardization in the area

of biotherapeutics for the major chronic diseases. The Committee also recommended that WHO should facilitate the strengthening of technical capacity in national regulatory authorities for biological therapeutics and also collate information on substandard or counterfeit biological medicines for chronic diseases.

Documents that were considered and approved by the Committee during its meeting included:

- Guidelines For Assuring The Quality And Nonclinical Safety Evaluation Of DNA Vaccines.
- Recommendations For Inactivated Rabies Vaccine for Human Use Produced In Cell Substrates And Embryonated Eggs.
- Guidelines to assure the quality, safety and efficacy of live attenuated rotavirus vaccines (oral).
- Recommendations for the production. control and regulation of human plasma for fractionation.
- WHO biosafety risk assessment and guidelines for the production and quality control of human influenza pandemic vaccines.
- Recommendations for whole cell pertussis Vaccine.
- Biological Substances: International Standards and reference reagents.
- Recommendations and guidelines for biological substances used in medicine and other documents.

**Reference**: World Health Organization. http://www.who.int/biologicals

## Biological substances: International standards and reference reagents

| Preparation | Activity | Status |
|---|---|---|
| **Antigens and related substances** | | |
| Haemophilus influenza type b capsular polysaccharide | 4.933 ± 0.267 mg/ampoule of polyribosyl ribitol phosphate (PRP) | First International Standard |
| **Blood products and related substances** | | |
| Prothrombin Mutation G20210A | No assigned activity | First International Genetic Reference Panel |
| Folate in human serum | 12.1 nmol/l of folate per ampoule | First International Standard |
| Vitamin B12 in human serum | 480 pg/mL of vitamin B12 per ampoule | Second International Standard |
| Coagulation factor V, plasma, human | 0.74 International Units of Factor V:C per ampoule | First International Standard |
| Coagulation factor XI, plasma, human | 0.86 International Units per ampoule | First International Standard |
| Thromboplastin, rabbit, plain | International Sensitivity Index (ISI) value of 1.15 | Third International Standard |

| Preparation | Activity | Status |
|---|---|---|
| ***Antisera*** | | |
| Anti-dengue virus types 1,2, 3 and 4 serum | 100 units per serotype per ampoule | First WHO reference reagent |
| Anti-Human platelet antigen-1a | 100 International Units per ampoule | First International Standard |
| Anti-A blood grouping minimum potency reagent | No assigned activity; however a 1 in 8 dilution should define the recommended minimum potency specification for anti-A blood grouping reagents | First International Standard |
| Anti-B blood grouping minimum potency reagent | No assigned activity; however a 1 in 4 dilution should define the recommended minimum potency specification for anti-B blood grouping reagents | First International Standard |
| **Cytokines, growth factors and endocrinological substances** | | |
| Vascular endothelial growth factor, human | 13000 units per ampoule | First WHO reference reagent |
| Keratinocyte growth factor, human | 4000 units per ampoule | First WHO reference reagent |
| Karatinocyte growth factor, (24–163), human | 9000 units per ampoule | First WHO reference reagent |
| **Diagnostic reagents** | | |
| HIV–1 RNA | 5.56log10 International Units per vial | Second International Standard |

*These substances are held and distributed by the International Laboratory for Biological Standards, National Institute for Biological Standards and Control, Potters Bar, Herts., EN6 3QG, England.*

# Safety and Efficacy Issues

## Suicidality risk associated with atomoxetine

**Singapore** — Atomoxetine (Strattera®) a norepinephrine re-uptake inhibitor, is licensed for the treatment of attention deficit hyperactivity disorder in children 6 years of age and older, in adolescents and adults. It was registered in Singapore in April 2005.

The manufacturer has alerted healthcare professionals to an increased risk of suicidal thinking in children and adolescents associated with the use of atomoxetine. This new finding emerges as part of a larger evaluation of psychiatric drugs and suicidality following the US Food and Drug Administration's request to manufacturers to conduct a review of their database and clinical trials.

Physicians are advised to carefully monitor patients on atomoxetine for possible clinical worsening, as well as agitation, irritability, suicidal thinking or behaviours, and unusual changes in behaviour, especially during the initial few months of therapy or when the dose is increased or decreased. Patients, their families and caregivers should be informed of this risk.

**Reference**: Health Sciences Agency, Product Safety Alert, 12 December 2005 on http://www.hsa.gov.sg/cda/safetyalerts

## Drug interaction between capecitabine and warfarin

**Singapore** — Capecitabine (Xeloda®) is a cytostatic agent indicated for metastatic breast cancer when used as an adjunct to docetaxel, and for metastatic colorectal cancer. The co-administration of capecitabine and warfarin may predispose a patient to an increased risk of bleeding. The probable mechanism for the interaction is the down-regulation of CYP 2C9 isoenzyme by which warfarin is principally metabolised (1).

Postmarketing reports have revealed clinically significant increases in prothrombin time (PT) and the international normalized ratio (INR) in patients who were stabilized on anticoagulants when capecitabine therapy was initiated. These events occurred within several days to several months after concurrent therapy (1).

Patients being prescribed warfarin and capecitabine concurrently should be closely and regularly monitored for alterations in the PT or INR; the dose of warfarin should be retitrated if necessary.

**References**

1. Klasco RK (Ed): DRUGDEX® System (electronic version). Thomson Micromedex, Greenwood Village, Colorado, USA. Available at: http://www.thomsonhc.com (cited: 09/06/2005).

2. Product Info Xeloda®, 15/06/2005.

3. Health Sciences Agency, Product Safety Information on http://www.hsa.gov.sg/cda/safetyalerts

## Fluoroquinolone antibiotics and interaction with warfarin

**Australia** — The potential interaction between warfarin and fluoroquinolones (ciprofloxacin, norfloxacin, moxifloxacin, gatifloxacin) was reported in a 1993 review (1). The Australian Adverse Drug Reactions Committee (ADRAC) has received 20 reports of this interaction, implicating ciprofloxacin (9 reports), norfloxacin (11) and moxifloxacin (1). One of the reports involves both ciprofloxacin and norfloxacin. As yet, no reports have been received with gatifloxacin, which has had little use.

Health Canada has reported 57 cases of this interaction up to January 2004 (2). Gatifloxacin was also implicated in the Canadian series. In 16 of the 57 cases the patient was hospitalized and four patients aged 70–90 years with complex medical conditions died.

Although significant pharmacokinetic interactions have not been demonstrated in interaction studies, the product information for each of the fluoroquinolones and for warfarin warn that an increased effect of warfarin is possible, and that the INR should be closely monitored when a

fluoroquinolone and warfarin are administered concomitantly.

Possible mechanisms of this interaction include decreased warfarin cytochrome P450-mediated metabolism, and reduction in gut flora that produce vitamin K.

ADRAC advises health professionals to consider the possibility of this interaction and monitor the INR when fluoroquinolones and warfarin are used concomitantly.

*Extracted from Australian Adverse Drug Reactions Bulletin, Volume 25, Number 1, February 2006.*

**References**

1. Marchbanks, C.R. Drug-drug interactions with fluoroquinolones. *Pharmacotherapy,* 1993;**13**: 23S–28S.

2. Morawiecka, I. Fluoroquinolones and warfarin: suspected interactions. *Canadian Adv Reaction Newsletter,* 2004;**14**: 1–2.

## Clozapine: revised monitoring frequency

**United States of America** — After reviewing recommendations provided by the Psychopharmacological Drugs Advisory Committee (PDAC) of June 2003 regarding the white blood cell monitoring schedule required for all clozapine users, the Food and Drug Administration (FDA) concluded that the current monitoring schedule should be modified. The changes to monitoring frequency have resulted in revisions to the boxed warning concerning.

- The absolute neutrophil count (ANC) to be determined and reported along with each WBC count.
- New parameters for initiation of clozapine treatment.
- Initiation of monthly monitoring schedule after one year (six months weekly, six months every two weeks) of WBC counts and ANCs in the normal range (WBC t 3500/mm3 and ANC t 2000/mm3).
- Addition of cautionary language to prescribers describing the increased risk of agranulocytosis in patients who are rechallenged with clozapine following recovery from an initial episode of moderate leukopenia(3000/mm3 > WBC t 2000/mm3 and/or 1500/mm3 >ANC t 1000/mm3). After recovering from such an episode, these patients are now required to undergo weekly monitoring for 12 months if they are re-challenged.

**References**

1. Revised prescribing information is available at http://www.clozaril.com/index.jsp.

2. http://www.fda.gov/medwatch.

## Hepatitis B reactivation and anti–TNFα products

**Canada** — The manufacturers of anti-TNFα products, in consultation with Health Canada, have updated safety information regarding anti-TNFα therapy. There are three such products authorized for sale in Canada, and a summary of these products and their general indications follows:

| INN | Indication(s) |
|---|---|
| etanercept | Rheumatoid arthritis<br>Juvenile rheumatoid arthritis<br>Psoriatic arthritis<br>Anchylosing spondylitis<br>Chronic plaque psoriasis |
| adalimumab | Rheumatoid arthritis |
| infliximab | Rheumatoid arthritis<br>Crohn disease<br>Anchylosing spondylitis |

Hepatitis B virus (HBV) reactivation has been reported very rarely in patients with chronic hepatitis B infection receiving anti-TNFα agents.

Patients at risk should be evaluated for prior evidence of HBV infection before initiating anti-TNFα therapy. Those identified as chronic HBV carriers (i.e. surface antigen positive) should be monitored for signs and symptoms of active HBV infection throughout the course of therapy and for several months following discontinuation. Reactivation of HBV is not unique to anti-TNFα agents and has been reported with other immunosuppressive drugs.

Very rare cases of HBV reactivation associated with anti-TNFa therapy have been reported cumulatively, with one report originating from Canada. Clinically-active HBV infections occurred following a latency period ranging from 3 weeks to 20 months after initiation of therapy. In the majority of cases, patients were also being treated with other immunosuppressive drugs, including methotrexate, azathioprine, and/or corticosteroids. Hence, establishing a direct causal relationship to anti-TNFa agents is confounded by the presence of these other medications.

Where outcome information was provided, most patients were reported to have improved after antiviral treatment and/or discontinuation of the anti-TNFα agent. However, fatal outcomes have also occurred in reported cases.

**Reference**: Health Canada alert, 13 January 2006 at http://www.hc-sc

## Clinical trials of gatifloxacin: shorter tuberculosis treatment regimen?

**World Health Organization** — Clinical results on a new combination treatment that could dramatically shorten the length of tuberculosis (TB) treatment were recently presented at the 45th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy, in Washington, D.C.

The phase II trial results of a gatifloxacin-containing regimen have demonstrated good potential. The regimen is significantly more potent than the currently recommended six-month regimen of isoniazid, rifampicin, pyrazinamide and ethambutol, and suggests that when gatifloxacin is used instead of ethambutol, the standard six-month regimen may be shortened to four months. This is the most advanced shorter TB treatment regimen presently in development, and could be available to the public by the end of 2009 if positive results continue.

The phase II trial was conducted by the South African Medical Research Council in patients with newly diagnosed pulmonary tuberculosis with and without HIV co-infection. It was designed to measure the anti-tuberculosis activity of the treatment in the first two months of therapy when compared to standard WHO recommended treatment and two other similar regimens which contained either ofloxacin or moxifloxacin.

Treatment with either the gatifloxacin or moxifloxacin containing regimen was shown to be significantly more active than either the standard regimen or the ofloxacin containing regimen after two months of treatment. A multicentre Phase III clinical trial is planned to definitely assess whether the four-month gatifloxacin containing regimen is equivalent to the current standard six-month short course regimen. Study sites are in Benin, Guinea, Kenya, Senegal and South Africa. The clinical trial sites are the result of an EC funded Consortium of ten European and African institutions (OFLOTUB) that are in the process of finalizing the terms of a proposed collaboration with WHO to develop a new short-course treatment regimen.

Research is planned to continue as part of an international collaboration which is being developed between the World Health Organization-based Special Programme for Research and Training in Tropical Diseases (TDR), the European Commission (EU), the OFLOTUB Consortium that is coordinated by the French Institut de Recherche pour le Développement (IRD), and Lupin Pharmaceuticals Ltd.

**Reference:** WHO Special Programme for Research and Training in Tropical Diseases (TDR). WHO Press Release, 16 December 2005. http://www.who.int

## Update on safety of oseltamivir

**European Union —** A potential influenza pandemic remains currently of high public interest and the European Medicines Agency (EMEA) has provided the following update on oseltamivir (Tamiflu®).

Oseltamivir is an antiviral approved in the European Union for the treatment of influenza in children between 1 and 13 years of age and for the prevention and treatment of influenza in adolescents over 13 years and adults. Two cases of alleged suicide associated with treatment of influenza (involving a 17-year-old boy in February 2004 and a 14-year-old boy in February 2005) were reported to EMEA. In both cases the adolescents exhibited abnormal/disturbed behaviour which led to their deaths. So far, no causal relationship has been identified between the use of oseltamivir and psychiatric symptoms (such as hallucination and abnormal behaviour). EMEA stresses that the assessment of psychiatric events during oseltamivir treatment is difficult because:

- Other medicines are often taken at the same time as oseltamivir.

- Patients with influenza and a high fever can show psychiatric symptoms. This is particularly relevant for children and elderly patients.

All adverse reactions are monitored and assessed by the Committee for Medicinal Products for Human Use (CHMP) on a continuous basis. The CHMP, at its meeting of 14–17 November 2005, decided to request the Marketing Authorization Holder of Tamiflu® to provide a cumulative safety review of all available data on serious psychiatric disorders, including all case reports with a fatal outcome where oseltamivir was involved. The EMEA will make a statement on the outcome

**Reference**: Press release. EMEA/385013/2005. London, 17 November 2005 http://www.emea.eu.int

## Paroxetine: possible risk of teratogenicity

**Singapore** — The manufacturer of paroxetine has notified healthcare professionals of preliminary findings of a retrospective epidemiological study which showed a 2-fold increase in the risk of congenital malformations in infants born to mothers who took paroxetine during the first trimester compared to other antidepressants. Paroxetine (Seroxat®) is indicated for the treatment of depression, obsessive-compulsive disorder, panic disorder, social anxiety disorder, generalized anxiety disorder and post-traumatic stress disorder. Seroxat CR® is approved for the treatment of major depressive disorder. The company has updated the package inserts of both Seroxat® and Seroxat CR® to reflect this risk under the Pregnancy subsection.

Physicians are advised to carefully weigh the potential risks and benefits of using paroxetine therapy in women during pregnancy and to discuss the risks and benefits as well as treatment alternatives with their patients. Paroxetine should be used during pregnancy only if the potential benefit outweighs the possible risk to the foetus.

**References**

1. HSA Product Safety Alert, 12 December 2005. http://www.hsa.gov.sg/cda/safetyalerts

2. GSK Clinical Trial Register; http://ctr.gsk.co.uk/Summary/paroxetine/epip083.pdf

3. Ministry of Health, Singapore. MOH Clinical Practice Guidelines 3/2004: Depression. http://www.moh.gov.sg

## Restrictions on use of promethazine in children

**Singapore** — The Health Sciences Authority (HSA) and its Pharmacovigilance Advisory Committee (PVAC) have recently reviewed the safety profile of promethazine in children following action taken by the US Food and Drug Administration (FDA) to contraindicate the use of promethazine hydrochloride preparations (e.g. Phenergan®) in children younger than 2 years old.

From a review of the risks versus benefits of promethazine, it was concluded that the risk of serious adverse drug reactions outweighs the potential benefits of the drug in young children. To reflect this safety concern, HSA is currently working with pharmaceutical companies to include the following information in the affected package inserts/patient information leaflets:

- Promethazine is contraindicated in children less than 6 months old;

- It is not recommended for use in children less than 2 years old;

- Caution should be exercised when used in children 2 years of age and older.

Although there have been no local reports of fatal ADRs associated with promethazine, HSA is aware of cases of apnoea occurring in very young children. In view of the unpredictable nature of the adverse events and their serious outcomes, healthcare professionals should exercise caution when prescribing promethazine to young children.

**Reference**: HSA Product Safety Alert. 12 December 2005 http://www.hsa.gov.sg/cda/safetyalerts

## Rosiglitazone and diabetic macular oedema

**United States of America** — The Food and Drug Administration (FDA) and the manufacturer of products containing rosiglitazone (Avandia®, Avandamet®, and Avandaryl™) have received

very rare postmarketing reports of new onset and worsening diabetic macular oedema. In the majority of these cases, the patients also reported concurrent peripheral oedema. In some cases, the macular oedema resolved or improved following discontinuation of therapy and in one case resolved after dose reduction.

Macular oedema typically occurs in association with diabetic retinopathy, although it is more likely to occur as retinopathy progresses. Risk factors for macular oedema include duration of diabetes, presence of retinopathy, hypertension, and poor glycaemic control. Symptoms suggestive of macular oedema include blurred or distorted vision, decreased colour sensitivity, and decreased dark adaptation.

**Reference**: Communication from GlaxoSmithKline available at: http://www.fda.gov/medwatch. December 2005.

## Topical immunomodulators : carcinogenic potential?

**Singapore** — Pimecrolimus cream (Elidel®) and tacrolimus ointment (Protopic®) are topical immunomodulators granted local marketing approval in January 2003 and March 2004 respectively.

Elidel® (1%) is licensed for short-term and intermittent long-term treatment of mild to moderate atopic dermatitis in non-immunocompromised patients who are 2 years and older in whom the use of alternative, conventional therapies is deemed inadvisable because of potential risks, or in the treatment of patients who are not adequately responsive to or intolerant of conventional therapies.

Protopic® (0.1%; 0.03%) is licensed for the treatment of moderate to severe atopic dermatitis in adults (0.1%) and children aged 2 years and above (0.03%) who are not adequately responsive to or are intolerant of conventional therapies.

Topical immunomodulators are increasingly being used in the US as first-line therapy in atopic dermatitis because they are perceived to be safer than steroid preparations. This perception by physicians and patients has been attributed to aggressive promotion of the drugs in the US market.

Prompted by concern over the increasing use of these products especially in very young children and findings of carcinogenicity in some of the animal studies as well as postmarketing reports of malignancies, the US Food and Drug Administration (FDA) issued a public advisory in March 2005.

**HSA's assessment**
The HSA Pharmacovigilance Advisory Committee (PVAC) have reviewed the following safety information.

*(i) Animal studies*
Carcinogenicity findings were not uniformly detected in all animal studies. Although some animal studies revealed no carcinogenic potential, others demonstrated some signals. For studies with positive findings, the data showed that the risk of cancer increased with increasing dose and duration of treatment. It was noted that in general the doses used in these animal studies were higher than the maximum recommended human dose (MRHD). For example, lymphoma formation in mice was reported with dermal application of tacrolimus and pimecrolimus dissolved in ethanol, at 26 times and 47 times MRHD, respectively.

*(ii) Postmarketing reports*
As of December 2004, the US FDA reported that it received 10 and 20 cases of postmarketing reports of malignancy-related events (e.g. lymphoma) with pimecrolimus and tacrolimus, respectively. For many of these cases, the causality could not be established due to the presence of other confounding factors. To-date, HSA has not received any reports of malignancy associated with pimecrolimus or tacrolimus.

**Recommendations**
HSA and its PVAC advise physicians to weigh the risks and benefits of the drugs for individual patients and to take into consideration the following:

- Pimecrolimus and tacrolimus are approved for short-term and intermittent treatment of atopic dermatitis in patients unresponsive to, or intolerant of other treatments
- They are not approved for use in children younger than 2 years old. The long term effect of these drugs on the developing immune system is not known
- They should not be used continuously for a prolonged period of time as their long-term safety has yet to be determined.

• Patients who are immunocompromised should not be prescribed pimecrolimus or tacrolimus.

**References**

1. FDA Paediatric Advisory Committee Meeting. http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4089b2.htm

2. *FDA Talk Paper on Elidel® and Protopic®.* http://www.fda.gov/bbs/topics/ANSWERS/2005/ANS01343.html

3. HSA Product Safety Alert. 12 December 2005. http://www.hsa.gov.sg/cda/safetyalerts

## Telithromycin: serious liver toxicity

**United States of America** — An article reporting three patients who experienced serious liver toxicity following administration of telithromycin (Ketek®) has recently been published. The cases have also been reported to the Food and Drug Administration (FDA).

FDA is continuing its investigation of this issue, and is providing the following recommendations to healthcare providers and patients:

• Healthcare providers should monitor patients taking telithromycin for signs or symptoms of liver problems. Telithromycin should be stopped in patients who develop signs or symptoms of liver problems.

• Patients who have been prescribed telithromycin and are not experiencing side effects such as jaundice should continue taking their medicine as prescribed unless otherwise directed by their healthcare provider.

• Patients who notice any yellowing of their eyes or skin or other problems like blurry vision should contact their healthcare provider immediately.

• As with all antibiotics, telithromycin should only be used for infections caused by a susceptible microorganism. Telithromycin is not effective in treating viral infections, so a patient with a viral infection should not receive telithromycin since they would be exposed to the risk of side effects without any benefit.

A case review of the reports shows serious adverse events following administration of telithromycin. All three patients developed jaundice and abnormal liver function. One patient recovered, one required a transplant, and one died. When the livers of the latter two patients were examined in the laboratory, they showed massive tissue death. These two patients had reported some alcohol use. All three patients had previously been healthy and were not using other prescription drugs. The FDA is also aware that these patients were all treated by physicians in the same geographic area. The significance of this observation is not clear at the present time.

In pre-marketing clinical studies, including a large safety trial and data from other countries, the occurrence of liver problems was infrequent and usually reversible. Based on the pre-marketing clinical data, it appeared that the risk of liver injury with telithromycin was similar to that of other marketed antibiotics. Nonetheless, the product label advises doctors about the potential for liver-related adverse events associated with the use of telithromycin.

Telithromycin is an antibiotic of the ketolide class. It was the first antibiotic of this class to be approved by the FDA in April, 2004 for the treatment of respiratory infections in adults caused by several types of susceptible microorganisms including *Streptococcus pneumoniae* and *Haemophilus influenzae*.

**Reference**.

1. FDA Public Health Advisory. 20 January 2006. http://www.fda.gov/medwatch/

2. Clay, K.D., Hanson, J.S., Pope, S.D. Brief communication: severe hepatotoxicity of telithromycim: three case reports and literature review. *Annals of Internal Medicine* (on-line edition), January 20, 2006, http://www.acponline.org

## Deaths with galantamine in mild cognitive impairment studies

**Australia** — Galantamine (Reminyl®), donepezil (Aricept®) and rivastigmine (Exelon®) are approved for the treatment of mild to moderately severe Alzheimer dementia. Cardiac arrhythmias with these cholinesterase inhibitors have been reported (1).

Galantamine has also been investigated in patients with mild cognitive impairment, an indication which is not approved in Australia. In two placebo controlled trials, there was a higher mortality with galantamine than placebo, and galantamine was not effective (2). The deaths

were due to various causes which could be expected in an elderly population.

The precautions' section of the Australian Product Information for Reminyl® has been updated, along with further advice to use with caution in patients with cardiovascular and pulmonary conditions, particularly immediately after myocardial infarction and with new onset atrial fibrillation, second or third degree heart block, unstable angina and pneumonia.

It is recommended that galantamine should only be used for the approved indication of mild to moderately severe Alzheimer dementia. The safety and efficacy in other indications have not been established and the risks may outweigh benefits.

*Extracted from the Australian Adverse Drug Reactions Bulletin, Volume 25, Number 1, February 2006.*

**References**

1. Australian Adverse Drug Reactions Committee (ADRAC). Cholinesterase Inhibitors and Cardiac Arrhythmias. *Australian Adverse Drug Reactions Bulletin*, 2004; **23**:5.

2. http://www. clinicalstudyresults.org/drugdetails/

## Fluoroquinolone antibiotics and tendon disorders

**Australia** — Since the beginning of 2005, the Australian Adverse Drug Reactions Committee (ADRAC) has received 16 cases of tendon disorders, predominantly Achilles tendinitis. Eleven of these cases have involved the fluoroquinolones ciprofloxacin, norfloxacin, and gatifloxacin.

ADRAC reminds prescribers that there is an increased risk of tendinitis or even tendon rupture with all fluoroquinolones (1). Of the 213 cases of tendinitis or tendon rupture reported to ADRAC, over 80% have involved fluoroquinolones. In addition to fluoroquinolone use, increasing age and concomitant corticosteroid use are established risk factors.

Patients should be advised to be alert for pain or discomfort in the Achilles tendon or calf and to inform their doctors and cease taking the medicine if this occurs.

*Extracted from the Australian Adverse Drug Reactions Bulletin, Volume 25, Number 1, February 2006.*

**Reference**

1. Australian Adverse Drug Reactions Committee (ADRAC). Fluoroquinolones and tendon disorders. *Australian Adverse Drug Reactions Bulletin,* 2002; **21**:15

## Ergot derivatives and fibrotic reactions

**Australia** — Ergot derivatives are now the most commonly used dopamine agonists in the treatment of Parkinson disease in Australia.

Important potential adverse reactions associated with ergot derivatives such as cabergoline, bromocriptine and pergolide are fibrotic complications, including pericarditis and retroperitoneal or pleural fibrosis. From marketing in 1997 to December 2005, the Australian Adverse Drug Reactions Committee (ADRAC) has received 86 reports of suspected adverse reactions in association with cabergoline. Of these, 15 have described pleural or pulmonary fibrosis/effusion or pneumonitis. Time to onset varied but apart from one report which indicated a few days, the onset time was from 1 month to over 3 years.

Most of the reports described either pleural fibrosis or pleural effusion or both and this was demonstrated by biopsy or chest X-ray in over half of the cases. Eight of the patients had recovered, two were improving but the remaining five had not recovered at the time the report was submitted.

As cabergoline has a long half-life (65 hours), recovery may be slow or the fibrotic changes may progress after drug withdrawal (1).

There have been no reports of fibrotic complications in association with low-dose cabergoline (Dostinex®) for the treatment of lactation suppression and hyperprolactinaemia. All ergot derivatives can induce fibrotic changes.

Prescribers should be aware of the possibility of fibrotic changes associated with long-term administration of ergot derivatives such as cabergoline, bromocriptine and pergolide, and should instruct the patient to report dyspnoea or cough.

*Extracted from the Australian Adverse Drug Reactions Bulletin, Volume 25, Number 1, February 2006.*

**Reference**

1. Frans E, Dom R, Demedts M. Pleuropulmonary changes during treatment of Parkinson's disease with a long-acting ergot derivative, cabergoline. *Eur Respir J* 1992; **5**: 263-265.

## Immune globulin: possible intravascular haemolysis

**United States of America** — The Food and Drug Administration (FDA) has requested the manufacturer of an immune globulin product (WinRho® SDF) to address two safety concerns and alert patients to the early signs and symptoms of intravascular haemolysis. Symptoms include back pain, shaking chills, fever, discoloured urine, decreased urine output, sudden weight gain, fluid retention/oedema, and/or shortness of breath. Rare, but severe and sometimes fatal, intravascular haemolysis and its potentially serious complications, including disseminated intravascular coagulation have been observed. Analysis of these events indicates that the aetiology is complex and the potential associations are not clearly understood.

*Important safety information on potential interference with blood glucose.*
Healthcare professionals are also alerted to the potential for falsely elevated glucose readings when using certain blood glucose testing systems that are not glucose-specific in patients who have received maltose-containing parenteral products.

**Reference**: Communication from Cangene Corporation, Baxter Healthcare Corporation on https://www.accessdata.fda.gov/scripts/medwatch/

## Aprotinin injection: renal toxicity and ischaemic events

**United States of America** — Recently published articles (1, 2) have associated aprotinin injection with serious renal toxicity and ischaemic events (myocardial infarction and stroke) in patients undergoing coronary artery bypass grafting surgery (CABG) or undergoing cardiac surgery with cardiopulmonary bypass. The Food and Drug Administration (FDA) is evaluating these studies to determine if labelling changes or other actions are warranted.

In the meantime, the following recommendations have been issued to healthcare providers and patients:

Physicians who use aprotinin injection should carefully monitor patients for the occurrence of toxicity, particularly to the kidneys, heart, or central nervous system and promptly report adverse event information.

Physicians should consider limiting aprotinin injection use to those situations where the clinical benefit of reduced blood loss is essential to medical management of the patient and outweighs the potential risks.

**Reference**: *FDA Public Health Advisory,* 26 January 2006. http://www.fda.go

## Benzocaine sprays and methaemoglobinaemia

**United States of America** — Benzocaine sprays are used in medical practice for locally numbing mucous membranes of the mouth and throat for minor surgical procedures or when a tube must be inserted into the stomach or airways. Their use is known to be occasionally associated with methemoglobinemia. On February 8, 2006, the Veterans Health Administration (VA) announced the decision to stop using benzocaine sprays for these purposes.

The Food and Drug Administration (FDA) is aware of the reported adverse events and is reviewing all available safety data, but at this time is not planning action to remove the drugs from the market. Up until now, the FDA has concluded that the number of reported adverse events with these sprays has been low and, when properly used, these products can help make important procedures less uncomfortable for patients.

Benzocaine sprays used in the mouth and throat can result in potentially dangerous levels of methemoglobinemia. Patients who have breathing problems such as asthma, bronchitis, or emphysema, patients with heart disease, and patients who smoke are at greater risk for complications related to methemoglobinemia and may be candidates for other forms of therapy.

Patients who may have greater tendency for elevated levels of methemoglobinemia, such as all children less than 4 months of age and older patients with certain inborn defects (such as

glucose-6-phosphodiesterase deficiency, haemoglobin-M disease, NADH-methaemoglobin reductase (diaphorase 1) deficiency, and pyruvate-kinase deficiency may benefit from products with different active ingredients such as lidocaine.

Patients who receive benzocaine sprays should be given the minimum amount needed, to reduce the risks associated with methemoglobinemia. Patients who receive benzocaine sprays should be carefully observed for signs of methaemoglobinaemia including pale, gray or blue coloured skin, headache, light-headedness, shortness of breath, anxiety, fatigue and tachycardia.

**Reference**: *FDA Public Health Advisory*. 10 February 2006. http://www.fda.gov

## Quetiapine and urinary disorders

**Netherlands** — Four reports of urinary retention and three reports of urinary incontinence associated with the use of quetiapine were received by the Pharmacovigilance Centre, Lareb, prior to mid June 2005. The time to urinary incontinence onset ranged from four weeks to four months, the time to urinary retention onset ranged from three days to six months, and most patients recovered from the disorders. According to Lareb, urinary incontinence and urinary retention were disproportionately associated with the use of quetiapine in reports in both the WHO and Lareb databases.

**Reference**: Lareb, August 2005. http://www.lareb.nl

## Hydroxyurea and risk of cutaneous vasculitic toxicities

**Canada** — Postmarketing case reports of cutaneous vasculitic toxicities, including vasculitic ulcerations and gangrene, have been received concerning patients with myeloproliferative disorders during therapy with hydroxyurea (Hydrea®). In response, Health Canada is revising the product monograph to include the following statements:

Cutaneous vasculitic toxicities, including vasculitic ulcerations and gangrene, have occurred in patients with myeloproliferative disorders during therapy with hydroxyurea. These vasculitic toxicities were reported most often in patients with a history of, or currently receiving, interferon therapy. Hydroxyurea should be discontinued if cutaneous vasculitic ulcerations develop and alternative cytoreductive agents should be initiated as indicated.

To minimize the risk of exposure, impervious gloves should be worn. This includes handling activities in clinical settings, pharmacies, storerooms, and home healthcare settings, including during unpacking and inspections, transport within a facility, and dose preparation and administration.

**Reference**: Bristol-Myers Squibb Canada 1 March 2006. http://www.hc-sc.ca

## Proton pump inhibitors and reduced testosterone levels

**Netherlands** — Prior to 30 June 2005, the Pharmacovigilance Centre, Lareb, received 28 reports of gynaecomastia associated with the use of proton pump inhibitors (PPIs), including omeprazole, lansoprazole, pantoprazole, esomeprazole and rabeprazole; in most reports there was a latency period of several weeks to months from start of treatment, and all reports were in men. In addition, Lareb has also received several reports of impotence, erectile dysfunction and decreased libido that may also be associated with reduced testosterone levels. According to Lareb, most of the gynaecomastia reports were associated with the use of omeprazole, and according to reports in the WHO database there was also a disproportionate association with gynaecomastia and the use of PPIs, suggesting that gynaecomastia may be a class effect.

**Reference**: Internet document. Lareb, August 2005. http://www.lareb.nl

## Colchicine and toxicity

**New Zealand** — The Medicines and Medical Devices Safety Authority, Medsafe, has revised the dosage advice for colchicine following reports of dose-related serious adverse effects. This advice coincides with the introduction of a colchicine 0.5 mg tablet (Colgout®).

Medsafe also advises that:

- colchicine is now limited to second-line treatment for acute gout, when nonsteroidal anti-inflammatory drugs (NSAIDs) are contraindicated, lack efficacy or have unacceptable adverse drug effects;

- the dosing interval has increased from two-three hourly to six hourly, the maximum daily colchicine dose is 2.5 mg in the first 24 hours and the

maximum cumulative dose should not exceed 6 mg over four days;

- other treatments should be considered in elderly patients and, if using colchicine, prescribers should observe a maximum cumulative dose of 3 mg over four days;
- colchicine is contraindicated in severe renal or hepatic impairment, and concomitant renal and hepatic disease, and doses should be reduced in patients with less severe impairment or who weigh < 50 kg;
- at least three days must elapse between colchicine courses.

Patients should be warned that the initial symptoms of colchicine-associated toxicity include nausea, vomiting and diarrhoea, and usually occur approximately 12 hours after ingestion; if toxicity does occur, patients should discontinue colchicine immediately and seek medical advice.

**Reference**: *Prescriber Update*, **26**(2), December 2005. http://www.medsafe.govt.nz

## Topical corticosteroids and skin damage

**New Zealand** — The Centre for Adverse Reactions Monitoring has received 14 reports of facial skin damage associated with the use of potent topical corticosteroids. The reports included telangiectasia, abnormal pigmentation, rosacea, perioral dermatitis, skin atrophy and striae, and were primarily associated with mometasone (Elocon®), although all topical corticosteroids used on the face carry a risk of facial skin damage. Prescribers and patients are reminded that the use of topical corticosteroids on the face should not exceed two weeks and prescribers are advised to give clear instructions to patients about where, and how often to apply the medication.

**Reference**: *Prescriber Update*, **26**(2), December 2005. http://www.medsafe.govt.nz

## Pegaptanib sodium injection and hypersensitivity reactions

**Canada** — Health Canada has issued safety information for pegaptanib sodium injection (Macugen®), following postmarketing reports of hypersensitivity reactions including anaphylaxis/anaphylactoid reactions. Ophthalmologists should be aware of the potential for hypersensitivity reactions and should monitor their patients accordingly. Appropriate procedures should be followed to treat anaphylaxis/anaphylactoid reactions if necessary.

Macugen® is indicated for the treatment of subfoveal choroidal neovascularization secondary to age-related macular degeneration, and is administered once every six weeks by intravitreous injection. Since the aseptic injection preparation procedure consists of various components (e.g., anaesthesia, broad-spectrum microbicide, or possibly latex gloves), a direct relationship has not been established .

**Reference**: http://www.hc-sc.ca and http://www.pfizer.ca

*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.*

# Access to Medicines

## European Union initiative to evaluate medicines for developing countries

*The European Medicines Agency (EMEA)* is a decentralized body of the European Union located in London, United Kingdom. Its main responsibility is the protection and promotion of public and animal health through the evaluation and supervision of medicines for human and veterinary use. EMEA coordinates the evaluation and supervision of medicinal products throughout the European Union and brings together the scientific resources of Member States of the European Economic Area (EEA) in a network of 42 national competent authorities. A network of some 3500 European experts supports the scientific work of EMEA and its committees. EMEA cooperates closely with international partners, reinforcing the EU contribution to global harmonization.

EMEA began activities in 1995, when the European system for authorizing medicinal products was introduced, providing for a centralized and mutual recognition procedure. EMEA is primarily involved in the centralized procedure. Where this procedure is used, companies submit one single marketing authorization application to EMEA. A single evaluation is carried out through the Committee for Medicinal Products for Human Use (CHMP) or the Committee for Medicinal Products for Veterinary Use (CVMP). If the relevant Committee concludes that quality, safety and efficacy of the medicinal product is sufficiently proven, it adopts a positive opinion. This is sent to the Commission to be transformed into a single market authorization valid for the whole of the European Union.

*The Committee for Medicinal Products for Human Use (CHMP)* is a scientific body that is part of EMEA and consists of representatives from all the EU Member States plus Iceland, Liechtenstein and Norway. The CHMP meets monthly and is responsible for drawing up the opinion of EMEA on any matter concerning the admissibility of the files submitted in accordance with the centralized procedure, the granting, variation, suspension or revocation of an authorization to place a medicinal product for human use on the market, and pharmacovigilance.

### Article 58 procedure allows scientific assistance to non-Member countries

Many developing countries with limited regulatory capacity rely on prior assessment of a medicinal product by a developed country as an indicator for marketing suitability. However, many products needed by developing countries may have no marketing authorization in a developed country. This may happen for those diseases that have no, or low, prevalence in developed countries and which are not economically viable. In an effort to facilitate access to these often life-saving medicines, the European Commission included in its proposal for Regulation (EC) No 726/2004 (1) an article establishing a mechanism whereby:

*"The Agency [EMEA] may give a scientific opinion, in the context of cooperation with the World Health Organization, for the evaluation of certain medicinal products for human use intended exclusively for markets outside the Community. For this purpose, an application shall be submitted to the Agency in accordance with the provisions of Article 6. The Committee for Medicinal Products for Human Use [CHMP] may, after consulting the World Health Organization, draw up a scientific opinion in accordance with Articles 6 to 9. The provisions of Article 10 [Commission Decision granting a marketing authorization] shall not apply".*

This mechanism is now formalized as Article 58 of Regulation (EC) No 726/2004, which was adopted on 31 March 2004. Part of the Regulation, including Article 58, entered into force on 20 May

*Article prepared by Dr Antoon Gijsens, Pre-Authorization Unit of Medicines for Human Use, European Medicines Agency (EMEA), London.*

2004. Article 58 thus responds to the need to protect public health and to give scientific assistance to non-member countries in the context of cooperation with WHO, whilst at the same time allowing rapid access to those countries for important medicinal products.

For the implementation of Article 58, the EMEA developed, in cooperation with WHO, a procedure (2) with the objective of delivering a CHMP scientific opinion of **equal standing** to the opinions provided for medicinal products intended to be marketed in the EU. In order to achieve this objective, the procedure mirrors the EU centralized evaluation procedure in line with the legislation.

## Eligibility for the procedure

In order to have access to the Article 58 procedure, eligibility of the medicinal product needs to be confirmed. After having consulted WHO, EMEA will inform the applicant whether the product is eligible. To be eligible, the medicinal product for human use intended exclusively for markets outside the Community should be intended to prevent or treat diseases of major public health interest. A non-exhaustive list of such products includes

- vaccines used, or of possible use, in the WHO Expanded Programme on Immunization (EPI);
- vaccines for protection against a WHO public health priority disease;
- vaccines that are part of a WHO managed stockpile for emergency response; and
- medicinal products for WHO target diseases such as HIV/AIDS, malaria, tuberculosis, lymphatic filariasis (elephantiasis), trachoma, leishmaniasis, schistosomiasis, African trypanosomiasis (sleeping sickness), onchocerciasis (river blindness), dengue fever, Chagas disease, leprosy.

## Scientific advice

When developing a medicinal product, pharmaceutical companies are often confronted with critical choices on how to demonstrate the quality, safety and efficacy of the product. In order to confirm whether CHMP agrees with certain approaches in the development of a medicinal product, applicants are encouraged to apply for scientific advice, whether it is in the initial development, before an application for a CHMP scientific opinion or in the post-opinion phase. In the request for scientific advice, applicants can ask questions or seek CHMP agreement with regard to quality, safety or efficacy related aspects in the development of their medicinal product. The scientific advice procedure is the result of the input of coordinators preparing assessment reports, experts and the different CHMP Working Parties providing comments, the Scientific Advice Working Group where the assessment reports and comments are discussed and a common position is adopted and forwarded to CHMP for formal adoption. The standard scientific advice procedure takes 70 days.

## Application for a CHMP scientific opinion

The evaluation procedure for applications for a CHMP scientific opinion mirrors the procedure for applications for a medicinal product intended to be marketed in the EU. The same data requirements and evaluation standards will be adhered to, taking into account possible adjustments as appropriate (e.g. stability). The evaluation procedure will be an EMEA/WHO partnership, with input from WHO experts as needed. In addition, observers from WHO and observers from authorities of developing countries (recommended by WHO) may attend CHMP plenary discussions on products under the CHMP scientific opinion procedure in cooperation with WHO. All experts and observers involved will be bound by the EMEA rules on public declaration of interest and confidentiality undertaking.

Where CHMP considers it necessary in order to complete its evaluation of the application, CHMP may require the applicant to undergo a good manufacturing practices (GMP), good clinical practices (GCP) or good laboratory practices (GLP) inspection with regard to the medicinal product concerned.

A CHMP scientific opinion is given within 210 days, excluding clock stops during which the applicant prepares the responses to questions adopted by CHMP. Taking account of the full scientific debate within CHMP and the conclusions reached, the final assessment report is prepared, which, once adopted by CHMP, becomes the CHMP assessment report and is appended to the CHMP scientific opinion. The CHMP assessment report contains the conclusions on the quality, safety and efficacy of the medicinal product and will take into account appropriate benefit/risk scenarios on the populations and conditions of use as documented within clinical data supplied by the applicant.

The CHMP assessment report of the medicinal product and the reasons for the favourable CHMP scientific opinion will be made available on the EMEA website (http://www.emea.eu.int), after consulting the applicant on deletion of any information of a commercially confidential nature. This document is called the European Public Assessment Report (EPAR) on a scientific opinion in cooperation with WHO.

## Certification

Before issuing a marketing authorization to a medicinal product, some countries require a certificate that the product has a valid marketing authorization in a country or region with recognised regulatory capacity. The current WHO Certification Scheme (http://who.int/medicines) accommodates the issuing of Certificates of a Medicinal Product (CMPs) for products having received a positive CHMP scientific opinion in cooperation with WHO. EMEA will issue these CMPs upon request from the Opinion Holder, in the same way as it does for medicinal products that have a marketing authorisation in the EU.

## CHMP scientific opinions reflecting the current status of the medicinal product

Countries relying on CMPs as part of their process to issue a marketing authorization, rightfully expect that the CMPs are based on CHMP Opinions that truly reflect the *current* status of the medicinal product. Therefore, the Opinion Holder shall be held responsible to update the CHMP scientific opinion through post-opinion follow-up, variations and extension applications, before implementing any changes, in analogy to medicinal products authorized in the European Union. Updates to the CHMP scientific opinion will be reflected in updates to the EPAR.

## Pharmacovigilance

Together with the countries where products evaluated via this procedure have received a marketing authorization, the EMEA endeavours to review any new relevant data to ensure continued safe and effective use.

Therefore, the Opinion Holder will have to ensure that all serious adverse reactions to a medicinal product are recorded and reported promptly to the competent authorities of the countries where the product is marketed and to the EMEA.
In addition, detailed records of all suspected adverse reactions will have to be submitted for evaluation to the EMEA, immediately upon request or periodically in the form of a periodic safety update report. Any other information relevant to the evaluation of the risks and benefits of a medicinal product should also be submitted, particularly information concerning post-authorization safety studies.

CHMP can perform a benefit/risk review at any time. In some cases and taking into account the pharmacovigilance reporting received, CHMP can, after having consulted WHO, revise its opinion based on the reassessment of the benefit/risk profile of the product. Such revisions will be reflected in updates to the EPAR.
The EMEA will collaborate with WHO and may exchange any information related to the pharmacovigilance of medicinal products evaluated under this procedure.

## Recognition of CHMP scientific opinions in cooperation with WHO

To inform drug regulatory authorities worldwide, this article will be complemented with presentations at international fora such as the International Conference of Drug Regulatory Authorities (ICDRA) and the Drug Information Association (DIA). The websites of EMEA and WHO will also feature Questions & Answers sections, addressing frequent questions from both pharmaceutical industry and drug regulatory authorities worldwide.

### References

1. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, OJ L 136, 30.4.2004, p. 1-33.

2. Guideline on procedural aspects regarding a CHMP scientific opinion in the context of cooperation with the World Health Organization (WHO) for the evaluation of medicinal products intended exclusively for markets outside the Community (EMEA/CHMP/5579/04). http://www.emea.eu.int/pdfs/human/regaffair/557904en.pdf

# Production and export of generic medicines under the TRIPS Agreement

At the WTO Ministerial Conference in Doha, November 2001, WTO Members adopted the Ministerial Declaration on the TRIPS Agreement and Public Health (the Doha Declaration). The Doha Declaration confirmed, amongst others, the right of WTO Members to use safeguard measures, such as compulsory licensing and parallel imports, to protect public health and promote access to medicines.

However, WTO Members failed to resolve a key issue at Doha: how countries which have insufficient or no manufacturing capacity in the pharmaceutical sector can effectively exercise the right to use compulsory licensing? The TRIPS Agreement permits the grant of compulsory licences for local production of generic versions of patented medicines in the interest of facilitating access to affordable medicines. But countries with insufficient or no manufacturing capacity cannot take advantage of this measure.

One option for these countries is to grant a compulsory licence to enable the import of generic medicines produced by foreign manufacturers. The problem is that where generic versions of patented drugs are produced under a compulsory licence, the TRIPS Agreement (Article 31f) requires that such production shall be predominantly for the supply of the domestic market. This has raised concerns that exporting countries may have difficulties exporting sufficient quantities to meet the needs of those countries with insufficient or no manufacturing capacity. The Doha Declaration highlighted this problem in Paragraph 6 and WTO Members were instructed to find an expeditious solution.

On 30 August 2003, the WTO General Council established, as an interim measure, a system to permit the export of pharmaceutical products manufactured under compulsory licence. This system was finally adopted on 6 December 2005 as an amendment (subject to ratification) to the TRIPS Agreement.

## Can the system work?

Whilst the proposed amendment has been hailed by some as an important breakthrough in the debate on patents and access to medicines, this optimism may be a little premature. No country has yet to make use of the system even though it was adopted in 2003. Since the final 2005 amendment will essentially incorporate the same system (and the same conditions), the workability of the system remains to be proven.

The system permits countries wishing to import generic medicines to do so from a foreign producer. Whilst least-developed countries are automatically eligible, developing countries have to establish either that they have no manufacturing capacity or the current capacity is insufficient to meet their needs. Countries make the determination themselves; and the WHO guide on implementing the Decision observes that this is a matter of self-assessment that is not challengeable by other Members. The system requires the importing country to notify the TRIPS Council. Where the needed medicine is patent protected in the importing country, the government will have to grant a compulsory licence for the import of the generic version of the medicine. Where no patent is in force, the importing country has to provide notification of its intention to use the system.

Whilst much has been made about the amendment allowing least-developed countries to import generic medicines, the most significant aspect of the system is the ability of generic-producing countries to export generic medicines without the quantitative restrictions. The generic manufacturer has to obtain a compulsory licence to produce and export, which will only permit the production and export of the quantity required by the importing country. The compulsory licence will also require the manufacturer to make the products clearly identifiable through labelling or marking, and notify the TRIPS Council of the quantities supplied to the importing countries and the distinguishing features of product. But will generic manufacturers be willing and able to produce and export the needed medicines under the system?

**TRIPS Amendment**

TheTRIPS Amendment agreed on 6 December 2005 essentially converts the interim system adopted on 30 August 2003 into a new Article of the TRIPS Agreement —Article 31*bis*. It is agreed that this amendment will come into force when it is ratified by two-thirds of WTO Members by 1 December 2007. It can be expected that the amendment will come into force on or before this date.

The first component of the system is the lifting of the requirement that pharmaceutical products manufactured under a compulsory licence shall be "predominantly for the supply of the domestic market". The second is elimination of the need to pay remuneration to the patent holder in the importing country if remuneration has already been paid to the patent holder in the exporting country. This prevents double remuneration to the patent holder.

Other components of the system include: definition of products covered under the system; criteria for eligibility of Members to import or export; measures to prevent re-exportation (or anti-diversion measures); and requirements to notify the WTO when use is made of the system. WHO has published a guide on how to implement the system.

## How to make it work

In order to ensure that countries can make effective use of the system adopted in the decision on Paragraph 6 and the amendment, it will be important for national laws to be reviewed and amended where necessary, in order to put the system into effect. A list of required changes to national laws is set out on page 24. The workability of the system will depend, in large part, on how the demand-and-supply chain can be linked up. On the demand side, importing countries must be able to indicate their needs. Procurement agencies in these countries must be able to forecast and quantify needed medicines, so that this information can be notified to the TRIPS Council.

This notification will be the trigger for necessary measures to be taken on the supply side. Without this indication of demand, it is difficult to see how generic manufacturers will be moved to offer their products for export. In Canada, India and China — where national legislation has been amended to permit the production and export of generic medicines under compulsory licence — the law generally requires some indication from an importing country of its intention to permit the import of products manufactured under compulsory licences, before the compulsory licence may be granted.

## Pooled procurement

Generic manufacturers will have to respond by making the necessary applications for compulsory licences. They will have to evaluate the economic feasibility of applying for a compulsory licence. It has been said that the system is a "drug-by-drug, country-by-country, case-by-case system", so that manufacturers will be forced to produce limited quantities under each compulsory licence. However, it should be possible for a number of the purchasing countries to coordinate their orders in order for the manufacturers to use a single compulsory licence for production and export to more than one country. This method of pooled procurement should be explored in order to take advantage of the significant cost and other efficiency savings that can accrue. But it requires a degree of cooperation between participants and shared purchasing needs.

**Exporting country governments** will have to respond by enabling the granting of compulsory licences for production and export by their generic manufacturers. This may involve amendments to patent legislation. The initiative taken by Canada, India and most recently, by China, to provide for the granting of compulsory licences under the system is welcome; given that the concentration of generic manufacturers is in these countries. Governments should demonstrate their good faith by enacting simple and speedy procedures for the granting of compulsory licences without unnecessary requirements that may delay the grant of the licences, or restrictions on the types of pharmaceutical products or diseases.

**Importing country governments** may have to take the necessary first step by notifying their intention to use the system. Where the product is patent protected in the importing country, a compulsory licence or government use authorization will be required. Where no patent exists, or where a least-developed country has opted not to grant or enforce pharmaceutical patents until

**Changes required in national laws for effective implementation of the system**

1. National laws should allow export of pharmaceutical products produced under compulsory licence to another country, for example, by explicitly stating that the supply of an export market is a possible ground for a compulsory licence.

2. To be able to make the best use of the system as an importer, national laws should explicitly permit compulsory licences for import and also include specific provisions for government use or public, non-commercial use of patents.

3. Where a compulsory licence is granted to enable import of pharmaceutical products produced abroad under the system, payment of remuneration or royalties to the patent holder should be waived, i.e. payment of remuneration or royalties is waived in the importing country.

4. In granting a compulsory licence, prior negotiations for a voluntary license with the patent holder may be required. If so, a defined time limit, preferably short, should be set for such negotiations so that where the negotiations are unsuccessful within that period of time the issuing of a compulsory licence can proceed).

5. Where a compulsory licence is granted on grounds of national emergency, other circumstances of extreme urgency, public non-commercial use/government use, or to remedy anticompetitive behaviour, the requirement for prior negotiation with the patent holder may be waived.

6. A compulsory licence may be granted for the lifetime of the patent.

7. There should be a definition of "pharmaceutical products" for which the system be used, and this definition should be a broad one. Countries should consider explicitly including diagnostics, vaccines and medical devices used for treatment, within the definition.

8. National laws should not limit the implementation of the Decision to a restricted list of products or diseases;

9. Least-developed countries may wish to make necessary changes to their legislation in order to make use of Paragraph 7 of the Doha Declaration, which allows them to defer the implementation and enforcement of pharmaceutical patents until at least 2016.

10. Any litigation or appeal by the patent holder should not suspend the implementation of a compulsory license (CL).

2016, a notification to the TRIPS Council of intention to use the system would be sufficient.

What may also be needed is an intermediary to link up the various actors in the demand and supply chain. In this regard, the United Nations agencies such as WHO, UNAIDS and UNICEF, and the Global Fund for the Fight Against AIDS, TB and Malaria may have an important role to play. These agencies are well-placed to assist countries in forecasting demand for medicines, identifying the potential suppliers of quality assured medicines and have as part of their mandate the public health objective of access to medicines.

## Making it happen

It is now time for governments and international organizations to make a concerted effort to implement the system. There are several good reasons to put the system to the test.

One reason for not using the Paragraph 6 Decision was that developing countries did not have sufficient assurance that the interim waiver system was "permanent" enough. Where changes to national law were required, governments were reluctant to take such action if more changes seemed imminent. With an amendment that is substantially the same as the Paragraph 6 Decision, this should no longer be a concern.

Secondly, the post–2005 environment should provide another impetus for countries to test the system. As all new medicines come under the requirement for the 20-year patent protection in all but the least-developed countries, generic suppliers, including those in India, will not be able

to reproduce patented medicines, without compulsory licensing. This is already the case of medicines such as second-line HIV treatments.

Global efforts, such as WHO's 3 by 5 Strategy may have helped to put more people on treatment, but it has also increased the need — as resistance inevitably develops — for a switch to second-line or third-line treatments. The generic competition that resulted in the price plunge for first-line antiretrovirals (ARV) does not yet exist for the second-line medicines. Current prices of the typical second-line treatments can be 6 to 12 times higher than those of the older first-line medicines. Governments and international organizations will have to develop alternative strategies to ensure the future sustainability of ARV treatment, particularly in low-income countries. Compulsory licensing to permit imports (and local production) of generic second-line ARVs is an obvious option to introduce market competition and reduce prices.

Third, the seemingly imminent avian flu pandemic demonstrates that it is neither easy nor possible to predict the future need for medicines, or the quantities in which they may be required. In the event of another public health emergency or pandemic, countries will want to ensure their ability to obtain the necessary treatments in sufficient quantities, at affordable prices. The global debate about access to oseltamivir and the ability of countries to fill national stockpiles have raised questions about the need to ensure multiple suppliers to guarantee availability and affordability.

The amendment proposing this solution is expected to come into force 1 December 2007. WTO Members have set this deadline to have the amendment ratified by the required two-thirds of the membership. It would appear that this system will be the permanent solution to the Paragraph 6 problem. WTO Members have been congratulated for their unprecedented decision to amend the TRIPS Agreement, which demonstrates their willingness and flexibility to take concrete steps to improve intellectual property rules to ensure the primacy of health.

**References**

1. World Health Organization. Implementation of the WTO General Council Decision on Paragraph 6 of the Doha Declaration on the TRIPS Agreement and Public Health (2004). *Health Economics and Drugs*. EDM Series No. 16.

2. Médicins Sans Frontières. Untangling the web of price reductions: A pricing guide for the purchase of ARVs for developing countries. (2005) http://www.accessmed-msf.org/index.asp

3. Sources and prices of selected medicines and diagnostics for people living with HIV/AIDS at: http://www.who.int/medicines/

4. World Health Organization. Implementation of the WTO General Council Decision on Paragraph 6 of the Doha Declaration on the TRIPS Agreement and Public Health, at: http://www.who.int/medicines/

5. World Health Organization. Statement on the TRIPS Amendment for the WTO Ministerial Conference in Hong Kong, 13–18 December 2005 at: http://www.who.int/medicines/areas/policy/WHO_Statement_Hong_Kong.pdf

6. Will the TRIPS Amendment on compulsory licensing work? *Bridges Monthly Review*, **10**(1): 22 (2006) at: http://www.ictsd.org

7. World Health Organization. Determining the patent staus of essential medicines in developing countries. (2004). *Health Economics and Drugs*. EDM Series No. 17

8. World Health Organization. Remuneration guidelines for non-voluntary use of a patent on medical technologies. (2005). *Health Economics and Drugs*. EDM Series No. 18

# Regulatory Action and News

## New requirements for prescribing information

**United States of America** — The Food and Drug Administration (FDA) is issuing final regulations amending the content and format of prescribing information for human drug and biological products. The final rule revises the current regulations to require that the prescribing information of new and recently approved products includes highlights of the prescribing information and a table of contents for the full prescribing information. *Requirements on the Content and Format of Labelling for Human Prescription Drug and Biological Products*, come into effect on 30 June 2006.

The goal is to provide more informative and accessible prescribing information, resulting in a better risk communication and management tool. These revisions will make it easier for healthcare professionals to access, read, and use prescribing information, and will enhance the safe and effective use of prescription drug products.

**Reference**: *FDA News, P06-08.* 18 January 2006. http://www.fda.gov/cder/regulatory/physLabel/default.htm

## Paediatric hepatitis A vaccine approval extended

**United States of America** — The Food and Drug Administration (FDA) has approved an application to allow use of the paediatric/adolescent formulation of hepatitis A vaccine, inactivated (Havrix®) for persons 1—18 years of age. Previously, paediatric use of hepatitis A vaccine was approved for use in persons aged 2—18 years.

The formulation, dosage, and schedule for Havrix have not been changed. Each 0.5-mL dose of paediatric/adolescent the vaccine contains 720 enzyme-linked immunosorbent assay units of formalin-inactivated hepatitis A viral antigen adsorbed onto aluminium hydroxide. The formulation contains 0.5% 2–phenoxyethanol as a preservative.

The primary vaccination schedule is unchanged and consists of 2 doses, administered on a 0, 6—12–month schedule. Hepatitis A vaccine is contraindicated in persons with known hypersensitivity to any component of the vaccine.

**References**

1. Notice to Readers: FDA Approval of Havrix (Hepatitis A Vaccine, Inactivated) for Persons Aged 1-18. *MMWR: posted on line* 12/22/2005

2. CDC. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morbidity and Mortality Weekly Report,* No. 48**,** (RR-12) 1999.

## Electronic individual case safety reports: testing has begun

**United Kingdom** — The Medicines and Healthcare Products Regulatory Agency (MHRA) is preparing the introduction of mandatory electronic transmission of an individual case safety report (ICSR) between marketing authorization holders (MAHs) and the MHRA.

All MAHs will be required to successfully test electronic transmission with the MHRA prior to switching from paper to electronic reporting. Testing will be conducted within a dedicated testing environment at the MHRA. Paper reporting of real reports in fulfilment of reporting obligations should continue in parallel during the testing period. Once testing has been completed to the satisfaction of the MHRA and the MAH, paper reporting can stop and electronic reporting of real reports can begin. It is not intended to have a transition period of parallel paper and electronic reporting of real reports.

If an MAH has already successfully tested electronic reporting with the EMEA EudraVigilance system or intends to submit reports via the EMEA EVWEB tool, then it is envisaged that a truncated testing process can be followed. Registering requests should be sent to ICSRTesting@mhra.gsi.gov.uk

Until testing is completed, paper reporting should continue in line with reporting obligations.

**Reference**: http://www.mhra.gov.uk

## First biosimilar medicinal product approval

**European Union** — The European Medicines Agency (EMEA) has adopted the first positive opinion for a similar biological medicinal product. The product, Omnitrope®, contains somatropin, a recombinant-DNA growth hormone. It is intended for the treatment of growth disturbance and growth hormone deficiency in children and adults.

EMEA's scientific committee, the Committee for Medicinal Products for Human Use (CHMP) considered that, in accordance with European Union requirements, Omnitrope® has been shown by studies demonstrating comparable quality, safety and efficacy to be similar to a reference medicinal product already authorized in the EU, namely Genotropin®.

The European Commission and European Medicines Agency have worked actively over a number of years to put in place a legal and regulatory framework for similar biological medicinal products. The first guidelines on quality, nonclinical and clinical issues were adopted by the CHMP in December 2003. A general regulatory guideline on similar biological medicinal products was adopted in September 2005. Further guidelines, including guidance on specific classes of products, are planned for adoption during the first quarter of 2006. A conference was held in Paris in December 2005 as part of the public consultation process.

**Reference**: *European Medicines Agency adopts first positive opinion for a similar biological medicinal product*. EMEA/31797/2006. Press release, 27 January 2006 http://www.emea.eu.int

## Tenecteplase withdrawn for commercial reasons

**European Union** — Tenecteplase is not marketed anywhere in the European Union. On 28 June 2005, the manufacturer notified the European Commission of its decision to withdraw the Community Marketing Authorization for Tenecteplase Boehringer Ingelheim Pharma KG® for commercial reasons. There is still one Community Marketing Authorization valid throughout the European Union for medicinal products containing tenecteplase, namely Metalyse®.

On 9 August 2005, the European Commission issued a decision to withdraw the Marketing Authorization for Tenecteplase Boehringer Ingelheim Pharma KG®. Consequently, the European Public Assessment Report has been removed from the EMEA website.

**Reference**: European Medicines Agency. *Public statement on tenecteplase Noehringer Ingelheim Pharma. Withdrawal of the marketing authorization in the European Union.* CHMP/343408/2005. London, 1 December 2005. http://www.emea.eu.int

## Immune globulin approved for primary immune deficiency disease

**United States of America** — The Food and Drug Administration has approved the first immune globulin product for subcutaneous injection for the prevention of serious infections in patients with primary immune deficiency diseases (PIDD). Vivaglobin®, manufactured from human plasma collected at US licensed plasma centres, provides new delivery options for PIDD patients. It is given under the skin (subcutaneously) on a weekly basis using an infusion pump, which means patients can self-administer the product at home. Some patients develop problems that make chronic intravenous administration of needed medicines difficult.

PIDD are inherited disorders that affect an estimated 50 000 people in the United States. These patients require regular treatment with immune globulin in order to fight off or prevent potentially serious or life-threatening infections. Other immune globulin products are administered either intravenously or intramuscularly. In clinical studies, the most common side effect is mild or moderate injection site reaction such as swelling, redness and itching.

As for all immune globulin preparations, plasma is tested and found to be nonreactive for HIV and hepatitis viruses prior to its use, and the manufacturing process includes steps that further reduce the risk of transmission of viruses.

**Reference**. FDA Approves First Immune Globulin for Subcutaneous Use.. *FDA Talk Paper*, P06-03, 9 January 2006. http://www.fda.gov

## Cetuximab approved for head and neck cancer

**United States of America** —The Food and Drug Administration (FDA) has announced approval of cetuximab (Erbitux®) for use in combination with radiation therapy to treat patients with squamous cell cancer of the head and neck (SCCHN) that can not be removed by surgery (unresectable SCCHN). This is the first drug approved for head and neck cancer that has shown a survival benefit in this population. Cetuximab was also approved for monotherapy to treat patients whose head and neck cancer has metastasized despite the use of standard chemotherapy.

Cetuximab received a priority review and approval was based on a study that showed it prolonged survival by 20 months compared to treatment with radiation alone. Approval of monotherapy was based on evidence of tumor shrinkage in 13 percent of patients, lasting on average of 6 months.

Commonly reported side effects of cetuximab were infusion reactions (fever, chills), skin rash, fatigue/malaise, nausea. The common side effects associated with radiation such as sore mouth, trouble swallowing, and radiation skin changes were similar in frequency in patients receiving cetuximab plus radiation and those receiving radiation alone.

**Reference**: *FDA News*, P06-34. 1 March 2006.

## Selegiline patch for depression

**United States of America** — The Food and Drug Administration has approved the first transdermal patch (Emsam®) for use in treating major depression. The once a day patch works by delivering the monoamine oxidase inhibitor (MAOI) selegiline. At its lowest strength, the patch can be used without the dietary restrictions that are needed for all oral MAO inhibitors that are approved for treating major depression.

MAO inhibitors usually require specific dietary restrictions because when combined with certain foods they can cause hypertensive crisis which can lead to a stroke and death.

The only common side effect of Emsam® detected in placebo-controlled trials was a mild skin reaction where the patch is placed. There may be mild redness at the site when a patch is removed. If the redness does not go away within several hours after removing the patch or if irritation or itching continues, patients are advised to contact their doctor. Another side effect that was seen less commonly was light-headedness related to a drop in blood pressure. Like all approved antidepressants, this product carries a warning of increased suicidality in children and adolescents.

Although the effects of heat on the patch are not known, the drug labelling advises health care professionals and patients about the possible effects of direct heat applied to the Emsam® patch. Direct heat may result in an increased amount of the drug absorbed from the patch. Patients should avoid exposing the patch to heating pads, electric blankets, heat lamps, saunas, hot tubs, or prolonged sunlight.

**Reference**: *FDA News*, P06-31, 28 February 2006.

## Ketamine now a classified drug

**United Kingdom —** As of 1 January 2006, Ketamine has become a controlled drug in the United Kingdom. This step has been taken because of its increasing misuse within the country. It is now a Class C drug, in Schedule 4 part 1, under the United Kingdom Misuse of Drugs Act, which places it alongside benzodiazepines, such as diazepam, etc.

**Reference:** *News & Updates.* National electronic Library for Medicines, 3 January 2006. http://www.nelm.nhs.uk

# Recent Publications, Information and Events

## The importance of independent drug bulletins

Using medicines safely and effectively requires that information is available to prescribers and others who give advice about medicines. Providing information in an impartial, objective and accessible way is a challenge and one effective approach is the local production of a drug bulletin.

In collaboration with the International Society of Drug Bulletins (ISDB), the World Health Organization (WHO) has published a comprehansive manual entitled *Starting or Strengthening a Drug Bulletin.* Bulletins provide reliable comparative information on drugs and therapeutics and can be a key means of improving health. Impartial, clear, reliable and up-to-date advice and information about treatments is invaluable and bulletins have an added advantage if the information is delivered in a local context by local experts. By strengthening the provision of advice at local level, the manual will benefit health workers, patients and community members alike.

In recent years the concept of the empowered patient and the informed community has grown. This development has been mirrored by drug bulletins, which initially focused on prescribers and pharmacists but have since broadened to producing materials for patients and consumers.

**Reference**: World Health Organization, International Society of Drug Bulletins, European Community. *Starting or Strengthening a Drug Bulletin. A Practical Manual.* WHO/PSM/PAR/2005.1 (2005). http://www.who.int/medicnes

## Patient–centred healthcare and safety

The International Alliance of Patients' Organizations (IAPO) organized the second Global Patients Congress in Barcelona, Spain from 22–24 February 2006. The congress brought together over 120 patient leaders from around the world, together with global health professional associations and the World Health Organization (WHO). The aim was to develop strategies to bring patients to the centre of healthcare systems. Over 150 participants attended from more than 25 countries.

A key event was the launch of IAPO's Declaration on Patient-Centred Healthcare as the first globally accepted definition developed by and representing the global patients movement. The Declaration contains five principles which, if followed, will result in patient-centred healthcare:

- Respect.
- Choice and empowerment.
- Patient involvement in health policy.
- Access and support.
- Information.

IAPO is calling for the support and collaboration of policy-makers, health professionals, service providers, and health-related industries to endorse and commit to these five principles and make them the core of their policies and practice.

A second policy focus responds to the global problem of patient safety. The World Health Organization estimates that in developed countries, up to one in every 10 hospital patients experiences an adverse event. In developing countries, over 50% of medical equipment is faulty (1). An international panel of policy-makers, patient advocates, industry and health professional representatives considered the global challenges to improving patient safety. The panel discussion raised awareness of patient safety issues such as medical errors, the importance of communication and information to patients, and how risks and benefits of medicines are considered.

IAPO is particularly concerned about the specific patient safety issues related to counterfeit medicines and supported the proposal to establish an International Medical Products Anti-Counterfeiting Taskforce (IMPACT) during the

recent WHO International Conference on Combating Counterfeit Drugs held in Rome (see page 4).

IAPO is a global alliance representing patients of all nationalities across all disease areas and promoting patient-centred healthcare worldwide. Members are patient organizations working at the local, national, regional and international levels to represent and support patients, their families and carers. Through its membership, IAPO represents nearly 370 million patients worldwide.

**References**

1. WHO World Alliance for Patient Safety. A Year of Living less Dangerously. Progress Report 2005. http://www.who.int

2. International Alliance of Patients Organizations. Together we can. Press release, 28 February 2006. http://www.patientsorganizations.org

## Boletín Fármacos: medicines information in Spanish

In April 1997, during the First international conference on improving use of medicines, a network was created entitled Researchers and promoters of the appropriate use of medicines in Latin America (RUAMAL). Publication of an electronic bulletin in Spanish was considered the best way to facilitate communication and, in1998, the first issue of Boletín Fármacos was published.

The main objective is to collect information on appropriate use of medicines. The staff of the Boletín Fármacos is composed of physicians, pharmacists, and social scientists. It has an Advisory Council and Editorial Board made up of experts in the field.

The content includes research articles and briefs, news about drug policies and regulations, pharmaceutical industries, intellectual property right and trade agreements, ethics and law, drug prices and access, safety and adverse drug reactions, drug interactions, recommended therapies, and dispensation and pharmacy. A section includes abstracts of articles on the above issues published in the leading journals in the field.

Boletín Fármacos is pleased to receive research papers, news and articles on any topic related to the use and promotion of drugs, drug policies, ethics and drugs, controversial drugs, recommended practices and questioned practices for the use and promotion of drugs. It also publishes news about conferences and workshops that are going to be held or have been held on the appropriate use of drugs.

There are three sections on its website :

- Presentaciòn: where the main goals are set .
- Boletín Fármacos: containing all the bulletins published so far (with acess in html, Word, PDF or Zip).
- Otras paginas de interès: with hundreds of links classified by topics.

**Reference**: Boletín Fármacos is available on http://www.boltinfamacos.org

## Antiretroviral programmes in low resource settings

The promise of improved funding through international initiatives has meant that HIV infection is treatable in developing and transitional countries. Resources such as antiretroviral medicines (ARV) and diagnostics are increasingly becoming available. Notwithstanding this progres, rapid scale-up of HIV treatment programmes has not been as fast as expected, in part, due to management issues such as difficulties with pharmaceutical supply systems and logistics, insufficient human resources and problems of compliance.

The WHO Collaborationg Centre for Pharmaceutical Policy at Boston University will be organizing a training seminar from 7–18 August 2006 for policy makers, ARV program managers, and nongovernmental organization officials responsible for national and local programmes. Social scientists, pharmacists, and other public health professionals interested in ARV management and adherence are also welcome.

The seminar will cover:

- Drug management issues, evidence-based selection of medications, quantification, procurement, pricing, quality assurance, pre-qualification of suppliers and monitoring and evaluation.
- Approaches to improve adherence to AIDS and other chronic diseases.

The format will be highly interactive with presentations by international experts followed by facilitated group exercises and discussion. Case

studies and guided readings will be provided and substantial preparation is required for each session.

**Reference**: WHO Collaborationg Centre for Pharmaceutical Policy, Boston University. Sarah Petty at spetty@bu.edu

## Developing countries and paediatric drug information

The British National Formulary has published a *British National Formulary for Children* (BNFC) which is available online. The website is accessible free of charge for certain countries. (To find out which countries can access BNFC see http://www.who.int/hinari/eligibility/en/).

Paediatricians often use medicines in children with serious or complicated conditions that have been developed and tested only in adults. The BNFC fills an important gap as there is often no information on off-label or unlicensed pediatric use of medicines from manufacturers if the medicine was licensed to be used only in adults in a country.

**Reference**: BNFC website http://bnfc.org/bnfc/

## Prudent use of antibiotics

The Alliance for the Prudent Use of Antibiotics (APUA) Newsletter has been published quarterly since 1982. The Newsletter contains expert information on antibiotic use and resistance for healthcare practitioners, researchers and policy makers. It is distributed to several thousand individuals, including members, organizations and lbraries worldwide. Newsletters up to year 2005 are available as a PDF at http://www.tufts.edu/med/apua/Newsletter/

**Reference**: Alliance for the Prudent Use of Antibiotics (APUA). http://www.apua.org

## International Network for Rational Use of Drugs now online

The International Network for Rational Use of Drugs (INRUD) was established in 1989 to design, test, and disseminate effective strategies and to improve the way drugs are prescribed, dispensed and used, with particular emphasis on resource poor countries.

The network now comprises 23 groups, 18 from Africa, Asia and Latin America, and other groups from the World Health Organization, Harvard Medical School, the Karolinski Institute in Sweden, the University of Newcastle in Australia, and Management Sciences for Health in the United States.

A key responsibility for any health programme or organization is to ensure that high-quality essential drugs are available, affordable, and used rationally. For both health systems and individuals, pharmaceuticals represent a major expenditure. Misuse of scarce resources, makes a difficult situation even worse. INRUD's mission is to identify the best ways of improving the use of medicines and to disseminate these findings.

The International Network for the Rational Use of Drugs (INRUD) is pleased to announce posting of the first web only edition of the INRUD News is now posted on the INRUD website.

**Reference**: http://www.inrud.org.

## Rational medicines management course for diseases of poverty

Health is an intrinsic human right as well as a central input to poverty reduction and socioeconomic development. Cost-effective interventions including medicines for controlling major diseases exist, but a lack of money for health and a range of system constraints hamper efforts to expand health services to the poor.

Medicines have led to improvements in health worldwide. Yet the main diseases of poverty such as HIV/AIDS, malaria and tuberculosis continue to claim innumerable lives in the developing world. Medicines are an essential and cost-effective tool of health care and an important element of health systems. The number and type of medicines on the world market is constantly increasing, while financial resources for health care services in general remain limited or decrease. Today, for millions of people worldwide essential medicines remain unavailable and unaffordable.

The sixth international training course on rational medicine management for HIV, tuberculosis and malaria will take place from 28 August to 9 September 2006 in Ifakara, Tanzania. The objectives of the course are to enable health professionals to understand and apply the

concepts and principles of essential medicines and rational medicine management with a focus on the diseases of poverty HIV/Aids, malaria and tuberculosis, to recognise the need for a national and international medicine policy environment, to improve knowledge and skills and to gain practical field experience for rational medicine management within different health system contexts.

The target group is health professionals and managers with experience (at least two years) in the health sector and in the pharmaceutical sector.

**Reference**: Swiss Tropical Institute at http:// http://www.sti.ch or courses-sti@unibas.ch

# General Information

## Revised WHO treatment recommendations for malaria

Global malaria control is being threatened on an unprecedented scale by rapidly growing resistance of *Plasmodium falciparum* to conventional monotherapies such as chloroquine, sulfadoxine-pyrimethamine (SP) and amodiaquine. Multidrug-resistant falciparum malaria is widely prevalent in South-East Asia and South America and now Africa, the continent with highest burden of malaria, is also being seriously affected.

In response to this situation, WHO recommends that treatment policies for falciparum malaria in all countries experiencing resistance to monotherapies should be combination therapies, preferably those containing an artemisinin derivative.

The therapeutic options currently recommended by WHO are:

- artemether/lumefantrine
- artesunate plus amodiaquine
- artesunate plus sulfadoxine/pyrimethamine (in areas where SP efficacy remains high)
- amodiaquine plus sulfadoxine/pyrimethamine, in areas where efficacy of both amodiaquine and sulfadoxine/pyrimethamine remains high (mainly limited to West Africa).
- artesunate plus mefloquine, an additional recommended combination treatment which is reserved for areas of low transmission.

### Expanding access to artemisinin combination therapy

Over the last three years around 20 countries (seven in Africa) have updated their treatment policies to include artemisinin combination therapy (ACT) as first or second-line treatment of malaria.

The single non-artemisinin-based combination therapy (amodiaquine plus SP), listed above among WHO recommended options is reserved for countries which, for whatever reason, are unable to move into ACT. However, the limitations of this option should be noted:

- The number of countries where efficacy is high of both amodiaquine and SP is limited and mainly restricted to West Africa.
- As both amodiaquine and SP are currently in wide usage as monotherapies it is unlikely that the adoption of this combination therapy will significantly delay the spread of resistance to either drug. Therefore, the adoption of combination therapy with amodiaquine plus SP is likely to be a short-term solution.
- Even in areas where the efficacy of both amodiaquine and SP remain high, their combined use will compromise the useful therapeutic life of both, and thus endanger their potential use as partner drugs for artesunate in ACT.
- There is currently no replacement for SP as a drug for Intermittent Preventive Treatment (IPT) in pregnancy. Rather than compromise its therapeutic life by using it as a component of a combination therapy, SP should be reserved for IPT.
- As the process of drug policy change and implementation is resource and time intensive (experience shows it to take from one to three years), all efforts for improving access to treatment should be directed towards implementing the most effective and durable treatment policy.

One of the principal reasons for countries wishing to adopt non artemisinin-based combinations is their lower price. However, multiple financial mechanisms are now available in countries, and international support is being mobilized to help countries adopt ACT, and an increasing number of countries are now replacing ineffective monotherapies.

To facilitate access to ACT, WHO will continue to inspect manufacturers of artemisinin derivatives as part of the WHO prequalification project,

negotiate price agreements with manufacturers, engage in international procurement, and set up systems of pharmacovigilance. A service for malaria medicines and supplies has been established by WHO and RBM partners to facilitate access to ACT within a larger facility for improving access to medicines and supplies for HIV-AIDS, TB and Malaria.

Consistent with WHO recommendations, malaria endemic countries which are experiencing resistance to currently used antimalarial drug monotherapies (chloroquine, sulphadoxine/pyrimethamine or amodiaquine) should change treatment policies to the highly effective artemisinin-based combination treatments (ACT).

**References**

1 World Health Organization. *The Use of Antimalarial Drugs. Report of a WHO Informal Consultation.* WHO unpublished report. WHO/CDS/RBM/2001.33.

2 World Health Organization. *Antimalarial Drug Combination Therapy, Report of a WHO Technical Consultation.* WHO unpublished report . WHO/CDS/RBM/2001.35.

3. World Health Organization. New malaria treatment guidelines issued by WHO. *News Release,* WHO/2, 19 January 2006.

## Quality assurance: latest guidance

The purpose of the WHO Expert Committee on Specifications for Pharmaceutical Preparations is to provide guidance to WHO and Member States concerning the quality of medicines. Within this broad mandate, it focuses on good manufacturing practices and provides regulatory guidance texts for interrelated activities on bioequivalence, prequalification, stability testing, fixed-dose combinations, and counterfeit and substandard medicines. Guidelines, specifications and international nomenclature developed under the aegis of this Expert Committee serve all Member States.

During its most recent meeting in Geneva from 24 to 28 October 2005, the Expert Committee made recommendations in various specific work areas related to quality assurance. Quality control issues discussed target essential medicines and those used in the treatment of large populations for which no international quality requirements may be available. The following new standards and guidelines were approved.

1. ICRS, List of available International Chemical Reference Substances.

2. Supplementary guidelines on GMP for heating, ventilation and air-conditioning systems.

3. Good manufacturing practices: supplementary guidelines on GMP for the manufacture of herbal medicines.

4. Good manufacturing practices: Validation.

5. Good distribution practices (GDP) for pharmaceutical products.

6. Model Quality Assurance System for Assessment of Procurement Agencies.

7. Guidelines on registration requirements to establish interchangeability of multisource (generic) pharmaceutical products.

8. Proposal to waive in-vivo bioequivalence requirements for the WHO model List of Essential Medicines, immediate release, solid dosage forms.

9. Guidelines for organizations performing in vivo bioequivalence studies.

10. *International Pharmacopoeia* monographs on:

abacavir sulfate, efavirenz, lamivudine, stavudine, zidovudine, nelfinavir mesilate tablets, nelfinavir mesilate oral powder, and saquinavir mesilate capsules

fixed-dose antituberculosis medicines in their finished dosage forms: rifampicin tablets, rifampicin capsules, rifampicin + isoniazid tablets, rifampicin + isoniazid + pyrazinamide + ethambutol HCl tablets, isoniazid + ethambutol HCl tablets, and rifampicin + isoniazid + pyrazinamide tablets.

In addition, the following revisions were adoped.

- WHO Guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms Annex 5, WHO Technical Report Series 863, 1996, and Update, WHO Technical Report Series 908, 2003. http://www.who.int/medicines

- List of comparator products included in the Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products. Annex 11, WHO Technical Report Series No. 902, 2002, and Annex 11, WHO Technical Report Series No. 902, 2002. http://www.who.int/medicines/areas/quality_safety/quality_assurance/regulatory_standards/en/index.html) to be published on the web in order to ease its regular updates, and

- Several test methods currently published in the publication entitled "Quality control methods for medicinal plant materials", in collaboration with TRM.

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

## WHO clinical trial registry initiative: update

As previously reported (1), a registry platform has been set up within WHO to link registers into a comprehensive network and provide harmonization and information for the initiative. The Scientific Advisory Group (SAG) is composed of international experts who represent key stakeholders involved in clinical trials and advises on the principles and substantive standards for trial registration. The Group met for the first time in Geneva, Switzerland on 17 and 18 November 2005 where participants agreed to key elements of global trial registration policies:

- Registration of all interventional trials is a scientific, ethical, and moral responsibility.

- At a minimum, the 20 item Data Set is required for trial registration (See table below). (1).

- Full disclosure of all 20 items at the time of registration is critical on scientific grounds and is in the public interest.

The SAG also supported the general structure and composition of an international network of registers, and confirmed the importance of detecting multiply-registered trials.

The first meeting of the International Advisory Board (IAB) took place at Imperial College, London, UK on 6 February 2006. The panel of experts endorsed the strategic plan of the Registry Platform and provided a strong vote of support, in particular for the key milestones which includes the launch of a network of qualified trial registers, a unique identification number for tracking trials (Universal Trial Reference Number or UTRN), and a one-stop search portal that will direct users to trial information contained in individual registers worldwide. The IAB also endorsed the Registry Platform's two-tiered approach to the proposed network of Primary and Associate Registers.

### WHO Network of Member Registers

WHO will establish a coordinated, international network of trial registers that will serve global health needs through a web-based platform. Acceptable registers will be approved based on criteria that are being finalized. The WHO has no plans to administer its own trial register.

The composition of the register network has been finalized. It will consist of two types of registers:

- A relatively small number of national, regional, or international Primary Registers, which accept all trials, perform deduplication of entries within their own register, and provide data directly to the WHO;

**20 item Data Set**

1. Primary Register and Trial ID number
2. Date of Registration in Primary Register
3. Secondary ID number(s)
4. Source(s) of Monetary or Material Support
5. Primary Sponsor
6. Secondary Sponsor(s)
7. Contact for Public Queries
8. Contact for Scientific Queries
9. Public Title
10. Scientific Title
11. Countries of Recruitment
12. Health Condition(s) or Problem(s) Studied
13. Intervention(s)
14. Key Inclusion and Exclusion Criteria
15. Study Type
16. Date of First Enrollment
17. Target Sample Size
18. Recruitment Status
19. Primary Outcome(s)
20. Key Secondary Outcomes

• A larger number of Associate Registers, which send their registration data to designated Primary Registers. They can be either broadly-based or restricted in scope, such as a specific disease, company, or institution.

In collaboration with its six regional offices and through other mechanisms, WHO is facilitating the coordination of regional approaches to trial registration worldwide (5).

The Registry Platform Newsletter website is available at: www.who.int/ictrpis and e-mail copies can be requested through: ICTRPinfo@who.int with the word “Subscribe” or “Unsubscribe” in the subject line.

**References**

1. *WHO Drug Information*, **19**(2): 126–129 (2005)

2. World Health Organization. SAG meeting report: http://www.who.int/ictrp/SAG_Report.pdf

3. The minutes of the International Advisory Board (IAB) meeting are available online at: http://www.who.int/ictrp/IAB_report.pdf.

4. Trial Registration Data Set Detailed explanation of each item is available at: http://www.who.int/ictrp/data_set/en/index1.html

5. http://www.who.int/ictrp/registration/member_reg/en/index1.html

## WHO Network of Member Registers